DISABILITY, DEMENTIA AND FRAILTY IN LATER LIFE – MID-LIFE APPROACHES TO PREVENT OR DELAY THE ONSET OF THESE CONDITIONS

REVIEW 2 - Behavioural risk factors in midlife associated with successful ageing and the primary prevention or delay of disability, dementia, frailty, and non-communicable chronic conditions

APPENDICES (v2)

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APPENDIX A – Evidence tables of included primary studies

Study Details: authors, year, citations, country of study, aim of study, study design, quality score [++, +, or -], applicability [++, +, or -]
Source Population
* Country of study * Number of people who participated in original study (or who were initially contacted to participate or selected from register) with sex breakdown, if available (provide study name)
Study (eligible and selected) population
* Number of people who participated in this particular study/wave * Location (city and country) * Recruitment strategies (e.g. media advertisement, birth register, class list, area) * Study time period/ length of follow-up * Sex breakdown (if available, include SES- and ethnicity-breakdown) * Mean age, or age at midlife and late-life examinations, if reported * Response rate and loss to follow-up (% and number) * State if the eligible population is considered by the study authors as representative of the source population. **Excluded populations:** Who and how many were excluded **Attrition:** Details on attrition (n lost to follow-up and why; was loss to follow-up higher in specific sub-groups [e.g. SES], as indicated by study authors)
Exposures at midlife
* Relevant exposures reported at midlife (with units) e.g. PA, diet, alcohol, smoking at baseline * Time period during which the exposures were ascertained * Report how exposures were measured – objective/subjective e.g. self-reported questionnaire or independent objective assessment
Outcomes at 55 years or over
* State all outcomes assessed * Details on outcome measurement/ ascertainment * Report how outcomes were measured – objective/subjective e.g. self-reported questionnaire or independent objective assessment * Time period during which cases were ascertained * Note: indicate that measures have been validated only if this has been explicitly reported by the author
Analysis
* Analysis strategy used for multivariate model, e.g. logistic regression * Report all confounders
Results, limitations, source of funding
* Include number of people who developed relevant outcome (with sex breakdown)

* Include statistically significant relevant effect estimates adjusted for all or as many covariates as possible (e.g. report OR, RR, HR with CI)
* Mention highly significant trends (do not need to report effect estimates for each level; however, state p-value of trend test)
* Include relevant and statistically significant interactions (report effect estimates with CI)

Limitations:

* Include limitations identified by study authors
* State additional study limitations not reported by study authors (only if significant and obvious biases have been omitted)

Source of funding:

Authors: Agahi N, Shaw BA

Year: 2013

Citation: Preventive Medicine 57(2): 107-112

Country of study: Sweden

Aim of study: To assess smoking trajectories from midlife to old age and the development of non-life-threatening health problems in a 34-year time span

Study design: Longitudinal

Quality score: (++, + or -): -

Source population

Data for this study originated from the Swedish Level of Living Survey, a nationally representative study of Swedish people ages 18-75 years, and the Swedish Panel Study of Living Conditions of the Oldest Old, which comprised participants from the first study over the age of 75 years.

Study (eligible and selected) population

- Data from the 1968, 1981, 1991 and 2000 phases of first study merged with data from 2002 phase of second study
- Up to 34 years follow-up of individuals that were 30-50 years of age at baseline in 1968
- Final sample: 1060 people (52% of original sample)

Follow-up: Of the people meeting the inclusion criteria, 655 (32%) died during follow-up. Those who died during follow-up were older, less well educated, more likely to smoke, had more mobility impairment and psychological distress at baseline compared with those included in study

Exclusion: -

Attrition: Of 2051 people meeting the inclusion criteria, 336 (16%) people did not participate in study phases or had missing variable values (and 655 or 32% died)

Exposures at midlife

>Smoking was assessed using structured participant interviews

>Smoking status trajectories assessed in 1968, 1981, 1991, 2000/2002

Smoking categories: current non-smoking, light smoking (< 10 cigarettes/day), heavy smoking (10+ cigarettes/day)

Persistent heavy smokers (n=81): those who smoked throughout the period, with heavy smoking reported for at least 3 study waves

Persistent light smokers (n=63): those who smoked throughout the follow-up period, but with two or fewer episodes of heavy smoking

Former smokers: smoking in the first and/or second study waves

Former heavy smokers (n=107): those who reported mostly heavy smoking

Former light smokers (n=176): light smokers

Persistent non-smokers (n=633): never smoked

Outcomes at 55 years or over

>Three outcomes assessed using structured interviews: mobility impairment, musculoskeletal pain, psychological distress

>Mobility impairment: index measuring ability to walk, run, go up and downstairs without difficulties (0=no mobility problems; 3=mobility in all 3 domains)

>Index of musculoskeletal pain and index of psychological distress based on summary score of health problems in past 12 months ranging from 0 (no pain) to 6 points (severe pain) and from 0 (no symptoms) to 8 points (severe problems in all domains assessed), respectively

Musculoskeletal pain index: assessed perceived pain in hands, elbows, legs or knees, shoulders, back, hips, sciatica

Psychological distress index: assessed anxiety, nervousness, anguish, general fatigue, sleeping problems, depression

Analysis

Analysis strategy: Multivariate, multinomial regression analysis was used to assess smoking trajectories from midlife to old age and the development of non-life-threatening health problems

Confounders: Age, education, sex

Results, limitations, source of funding

- Rate of increase in mobility impairment was steepest among persistent heavy smokers (coeff.=0.01, SE=0.004), and former heavy smokers (coeff.=0.01, SE=0.003) in comparison with non-smokers over 34 years of follow-up
- Compared to non-smokers, former light smokers had statistically significantly steep progression of mobility problems over 34 years of follow-up (coeff.=0.006, SE=0.003)
- Compared to the persistent non-smoking group, faster increases in mobility impairment were observed for all smoking trajectory groups
- Heavy smokers had higher levels of psychological distress at baseline compared to persistent non-smokers, and this difference did not change over the follow-up period

Limitations:

1. Selective survival, leaving healthier individuals in sample
2. Shorter period for observing the development of health problems for younger segments (follow-up until 2000) than for older segments (until 2002) in study; thus number of health problems may be underestimated in younger participants

Source of Funding: none reported

Authors: Agrigoroaei S, Lachman ME

Year: 2011

Citation: Journals of Gerontology Series B-Psychological Sciences & Social Sciences 66 Suppl 1: i130-140

Country of study: United States

Aim of study: To examine combined effect of psychological, social, and physical factors on cognitive functioning (above and beyond the effects of sodiodemographics, risk factors, cognitive activities

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Data used from 1995-96 and 2004-05 national survey called Midlife in the United States (MIDUS), as well as a survey subsample, the Boston Longitudinal Study (BOLOS). BOLOS measurements taken one year after MIDUS measurements.

Overall purpose: are behavioral, social, psychological, biological, neurological factors assessed in MIDUS associated with cognitive performance measured in MIDUS, as well as with subsequent cognitive functioning measured over 10-year-period in BOLOS

Study (eligible and selected) population

Specific study aims:

1. MIDUS Time 2 (2004-05): cross-sectional assessment of influence of psychosocial and behavioural factors on cognitive performance
2. Influence of changes in the number of factors from Time 1 (1995-96) to Time 2 (2004-05) on cognition at Time 2
3. National probability sample of 4,238 non-institutionalised adults from 48 states selected through random-digit dialing

>included 949 siblings of main respondents

1,913 twins selected from national sample of 50,000 households

Time 1: **7,100** participants ages 24-75 years (mean=46.40, SD=13.00)

Time 2: **4,900** participants ages 32-84 years (mean=55.45, SD=12.44) remaining (75% of people from Time1

Overall response rate: 70%

1 year after MIDUS Time 1, **302** people ages 24-74 years (mean=47.89, SD=13.74), living in Boston recruited for BOLOS

1 year after MIDUS Time 2, **151** people who participated in first BOLOS wave participated in second BOLOS wave (68% participation rate); participants ages 34-84 years (mean=59.99, SD=12.81)

Exclusion: -

Attrition:

i) Participants at Time 2 indicated positive selection on variables compared to those who dropped out.
ii) Participants of BOLOS T2 were more education compared to non-participants of this wave

Exposures at midlife

Control beliefs: Perceived control over life outcomes assessed using MIDUS sense of control scale, with scores ranging from 1-7 (higher values = higher sense of control)

Quality of social support: 12 items assessed social strain in relationships, with scores ranging from 1-4 (higher values = higher quality of social support)

Physical exercise: Frequency of engaging in vigorous physical activities, with scores ranging from 1-6 (higher values = more frequent physical exercise)

Psychosocial and behavioural protective composite score of above variables created (scores of aforementioned variables summed and higher values represent greater number of factors present at higher level)

Exposures assessed:

Influence of MIDUS protective composite

Interaction of MIDUS composite with age and education

Influence of Time 1 MIDUS protective composite score and difference in MIDUS protective composite scores between Time 2 and Time 1

Outcomes at 55 years or over

Seven cognitive domains assessed over telephone at Time 2 in MIDUS using the Brief Test of Adult Cognition by Telephone; cognitive factors grouped into episodic memory and executive functioning

Cognitive factors, such as short-term memory, speed of processing, reasoning, and vocabulary, assessed in person at Time 1 and Time 2 in BOLOS

Analysis

Analysis strategy: Hierarchical multiple regression

Confounders:

i) Frequency of engaging in cognitive activities
ii) Age sex, level of education, race, waist circumference, smoking, alcohol or drug problems
iii) Health status including history of diabetes, stroke, lupus, HIV or AIDS, MS, epilepsy or other neurological disorders, cancer, heart disease

Results, limitations, source of funding

<u>MIDUS</u>

- The number of behavioural protective factors were positively associated with memory (b = 0.03, p = 0.032) and executive functioning, (b = 0.06, p < 0.001), and a significant percent of model variance was explained by these factors over and above the confounders assessed (R2 change = 0.001, R2 change = 0.003, respectively)
- The association between education and cognition was reduced by the number of protective factors for episodic memory (b = –0.04, p = 0.015)

<u>BOLUS</u>

- Time 1 protective composite positively associated with change in reasoning (b = .10, p = .045)
- The number of protective factors reduced the association between education and reasoning abilities when the interactions of the protective composite with age and education were entered in the model (b = –.09, p = .045)

Limitations:

1. Small sample size of BOLUS
2. Approach used to compute protective composite cannot provide universal guidelines (method of dividing participants into high and low categories may not be clinically meaningful)
3. Optimization of self-reported measures through use of multiple indicators
4. Residual confounding from unexplored variables such as level of stress, personality profiles, nutrition

Source of funding: National Institute on Aging and the John D. and Catherine T. MacArthur Foundation Research Network on Successful Midlife Development

Authors: Akbaraly T, Sabia S, Hagger-Johnson G, Tabak AG, Shipley MJ, Jokela M… Kivimaki M

Year: 2013

Citation: American Journal of Medicine 126(5): 411-419

Country of study: England

Aim of study: The association between diet at midlife assessed using dietary patterns and adherence to the Alternative Healthy Eating Index (AHEI) and overall health at older ages **Study design:** Longitudinal **Quality score: (++, + or -):** +
Source population
London-based office staff ages 35-55 years and working in civil service departments; recruited for Whitehall II study. Baseline screening of 10,308 participants in 1985-1988.
Study (eligible and selected) population
Baseline: Phase 3 of study took place 1991-1996 and 8815 people included Study comprised 5350 people at least 60 years of age at end of follow-up in phase 9 (2007-2009) 3775 (70.6%) men and **1575** (29.4%) women included **Follow-up:** 16-years **Exclusion:** i) Participants with no history of stroke, myocardial infarction, or cancer (n=7032) in 1991-1996 at phase 3 ii) For this particular study, 1682 excluded (more likely to be women, younger, less likely to have a higher AHEI score) **Attrition:** Included participants were less likely to be younger, to have a higher AHEI score, and better health outcomes compared to excluded participants
Exposures at midlife
>At phase 3, participants completed a semi-quantitative food-frequency questionnaire (hence, self-report): Nutrient intakes of food items were computed by multiplying the consumption frequency for each food by its nutrient content and then summing the nutrient contributions from all foods Validity and reliability of questionnaire has been established Dietary variables (exposure) for each participant included: 1. Dietary patterns: “healthy-foods” diet versus “Western-type” diet (see analysis) 2. AHEI score based on intake of vegetables, fruits, nuts and soy, ratio of white meat (seafood and poultry) to red meat, total fibre, trans fat, ratio of polyunsaturated fat to saturated fat, long-term multivitamin use, alcohol consumption; higher AHEI scores represent healthier diet
Outcomes at 55 years or over
>Five outcomes ascertained from three follow-up screenings in 1997-99, 2002-04, 2008-09: ideal aging, nonfatal cardiovascular disease at follow-up, cardiovascular death, noncardiovascular death, natural or normal aging Records from national health registers (e.g. national cancer registry), self-reported questionnaires and medical records used for case ascertainment Deaths identified through National Health Services Central Registry >Ideal aging at age 60 and older defined as: Being alive Absence of chronic diseases, such as CHD, stroke, cancer (identified through cancer registry), diabetes (identified through self-reported doctor diagnosis, use of anti-diabetic medication, oral

glucose tolerance test)

Absence of mental health problems (>42 in mental health scale of the Short Form General Health Survey)

Good cardiometabolic functioning (based on systolic blood pressure and fasting glucose), respiratory functioning (forced expiratory volume at phase 9), musculoskeletal (walking speed), and cognitive functioning (5 cognitive tests at phase 9)

Analysis

Analysis strategy: Principal component analysis of the 127 food-frequency questionnaire items was performed and two dietary patterns were derived: 'healthy foods patterns' (had high loadings for intake of vegetables, fruit, fish) and the 'Western-type diet' (high loadings for items such as fried food, processed and red meat, pies, etc.); for each dietary pattern: factor scores were divided into tertiles and participants were categorised into the appropriate tertile based on their score. Logistic regression was used to assess the association between dietary variables and each dichotomous aging outcome

Confounders: Age, sex, total energy intake, smoking, physical activity

Results, limitations, source of funding

- 4% of participants met ideal aging definition, 12.7% developed a nonfatal cardiovascular disease, 2.8% died from cardiovascular disease, 7.3% died from noncardiovascular causes over 16 year follow-up; 73.2% showed natural aging
- The odds for ideal aging were lower for participants in the top tertile of the Western-type diet (OR=0.58, [0.36, 0.93]) compared to the bottom tertile
- High adherence to the AEHI recommendations was associated with lower odds of CVD and non-CVD deaths (OR=0.60, [0.39, 0.92]; OR=0.75, [0.57, 0.98], respectively)

Limitations:

1. Possibly lack of statistical power
2. Generalizability issues as participants are mainly white, office-based civil servants
3. Somewhat imprecise method of assessing dietary intake using semi-quantitative food-frequency questionnaire
4. Residual confounding

Source of funding: None reported

Authors: Alonso A, Mosley TH Jr, Gottesman RF, Catellier D, Sharrett AR, Coresh J

Year: 2009

Citation: Journal of Neurology, Neurosurgery & Psychiatry 80(11): 1194-1201

Country of study: USA

Aim of study: To study the association between cardiovascular risk factors and incidence for dementia among Caucasians and African American people

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Population-based cohort of 15,792 participants ages 45-64 recruited in 1987-9 from Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; suburbs of Minneapolis, Minnesota in United States for Atherosclerosis Risk in Communities (ARIC) study. Participants were examined at baseline in 1987-9 and every three years until 1996-1998.

Study (eligible and selected) population
Analysis restricted to white individuals from Minnesota, Washington County and Forsyth County communities and African Americans from Jackson and Forsyth County (**n=11,151**) **Response rate:** 86% **Follow-up:** From 1990-92 to occurrence of hospitalisation with dementia, death, loss to follow-up, or 31 December 2004, whichever occurred earlier **Exclusion:** - **Attrition:** No details provided
Exposures at midlife
Lifestyles (e.g. smoking) assessed in 1990-92
Outcomes at 55 years or over
Incident dementia identified through participant or proxy report and chart abstraction of hospital discharge codes between 1990-92 and Dec. 31 2004 Dementia cases ascertained at annual follow-up of participants Cognitive function assessed via interviews using three neuropsychological tests measuring memory, sustained attention and psychomotor speed, flexibility of verbal thought processes
Analysis
Analysis strategy: Cox proportional hazard models to estimate hazard ratios of dementia by presence of cardiovascular risk factors at baseline **Confounders:** Sex, race, educational level, occupation, study centre, scores in cognitive assessment at baseline, presence of cardiovascular factors (hypercholesterolemia, BMI, hypertension, diabetes), APOE 4 -age assessed as confounder and as effect modifier
Results, limitations, source of funding
• 203 dementia cases identified during 142,625 person-years of follow-up • Current smokers were more likely to develop dementia compared to those who had never smoked [HR=1.7, (1.2, 2.5)]; no differences by race, sex, or APOE4 genotype categories (when baseline cognitive scores were not controlled for) • Stratification by age at examination: among those <60 years of age, current smokers were more likely to develop dementia than those who had never smoked [HR=2.2, (1.2, 4.1)] **Limitations:** 1. Hospital discharge diagnoses used to ascertain dementia cases likely underestimate disease burden; dementia may be undetected in subgroups with high prevalence of comorbidities (e.g. smokers) 2. Subgroups (e.g. smokers) have higher risk of hospitalisation, therefore dementia more likely to be detected in these groups **Source of funding:** National Heart, Lung and Blood Institute

Authors: Andel R, Crowe M, Pedersen NL, Fratiglioni L, Johansson B, Gatz M **Year:** 2008 **Citation:** Journals of Gerontology Series A-Biological Sciences & Medical Sciences 63(1): 62-66.

Country of study: Sweden **Aim of study:** Explored the association between physical exercise at midlife and subsequent risk of dementia **Study design:** Case-control analysis and co-twin control analysis **Quality score: (++, + or -):** +
 Source population
Number of people: 4506 **Demographics:** Not reported
 Study (eligible and selected) population
Number of people: 3224 **Characteristics** **Case control:** %Women 61; Age at cognitive screening, mean (SD) 79.5 (5.0); Age at baseline, mean (SD) 48.1 (5.0); Education, % more than basic 37; smoke,% yes 30; Drink alcohol, % yes 70; Fruits and vegetables in diet. % small or no part 21; BMI 11; Angina pectoris, % yes 25 **Twin study Controls:** Age at cognitive screening 82.2 (4.9); Age at baseline 50.8 (5.3); Education, 11 more than basic 30; Smoke, n yes 15; Drink yes 56; Fruits and vegetables in diet, small or no part 16; BMI, 15; Angina pectoris, 11 yes 22; Leisure time physical activity, 11 **Cases** Age at cognitive screening 82.1 (5.0); Age at baseline 50.9 (5.3); Education, 11 more than basic 23; Smoke, yes 23; Drink yes 56; Fruits and vegetables in diet, small or no part 15; BMI, 13; Angina pectoris, 11 yes 26; Leisure time physical activity, 11 **Location:** Sweden **Recruitment strategy**: Swedish Twin Registry **Length of follow-up:** Case-control: Hardly Any 31.3 (1.0); Light 31.5 (1.0); Regular 31.6 (0.9); Hard 31.4 (1.1) Twin Controls: 31.3 (1.4); case 31.2 (1.4) **Response rate and loss to follow-up:** 70% combined **Eligible population:** Swedish Twin Registry **Excluded populations:** 730 refused to participate, 173 could not be reached, 155 could not be interviewed due to physical problems and an informant was not available, and 82 died before they could be interviewed. An additional 232 persons were screened as suspect for cognitive impairment but were not worked up.
 Exposures at midlife
Relevant exposures: Physical exercise **Time:** 1967 or 1970 **Measurement of exposure:** Swedish Twin Registry
 Outcomes at 55 years or over
Outcomes: Dementia **Outcome measurement:** Screened for cognitive impairment followed by full clinical evaluation **Time:** Not reported

Analysis

Analysis strategy: Logistic regression and conditional logistic regression

Confounders: -

Case control: Age at cognitive screening, gender, education, smoking, alcohol consumption, portion of fruits and vegetables in diet, BMI and angina pectoris

Twin study: Education, portion of fruit/vegetables in diet, current smoking status, alcohol consumption, BMI and angina pectoris

Results, limitations, source of funding

Number: 264 cases with dementia (176 had Alzheimer's disease)**.** 90 twin pairs discordant for dementia

Effect estimates:

Case-Control

OR (95% CI) P

Dementia

Hardly Any 1.00 (ref.); Light 0.63 (0.43-0.91); p .014

Regular 0.34 (0. 16-0.72); p 0.05

Hard 0. 70 (0.40-1.24) p .215

p for Trend .178

AD

Hardly Any 1.00 (ref.); Light 0.64 (0.41-1.00) p .051

Regular 0.34 (0.14-0.86) p .022

Hard 0.65 (0.33-1.29) p .217

p for Trend .339

Twin study

Association Between Exercise at Midlife and Dementia

OR (95%CI) P

0.66 (0.24-1.83) .425

Significant trends: Exercise at midlife may reduce the odds of dementia in older adulthood

Limitations:

1. Self-report data; used prevalent cases of dementia; could not control for
2. Specific physical conditions; only able to identify a small number of twin pairs discordant for dementia

Source of funding: National Institute on Aging (NIA) grants ROl AG08724 and P30 AG17265, and by an Alzheimer's Association/Zenith Fellows Award

Authors: Anttila T, Helkala EL, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B… Kivipelto M

Year: 2004

Citation: BMJ 329(7465): 539

Country of study: Finland

Aim of study: Association between midlife alcohol consumption and subsequent mild cognitive impairment and dementia in old age

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Participants selected from eastern Finland during 1971-1987 as part of Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study. Study response rates between 82% and 90%

Study (eligible and selected) population

1018 out of 1464 people (70%) ages 65-79 years invited for re-examination in 1998 participated

632 women and 386 men with mean age of 48.3 years at midlife examination in 1972/1977, and 71.7 years at follow-up examination in 1998.

Follow-up: From 1972-77 to 1998

Exclusion: -

Attrition: Non-participants at the follow up visit in 1998 were, at the midlife assessment, older than the participants; had spent less time in education, and had dementia in old age more often than the participants. 40 cases of dementia did not participate

Exposures at midlife

Frequency of alcohol consumption assessed using self-administered questionnaire administered at midlife in 1972 and 1977, as well as in the follow-up examination in 1998

Frequency of alcohol consumption categorized as: never drank, drank infrequently (less than once a month), drank frequently (several times a month)

Outcomes at 55 years or over

Cognitive function assessed in 1998 using MMSE, with scores <=24 on MMSE selected for further examination

Mild cognitive impairment diagnosed according to Mayo Clinic Alzheimer Disease Research Center; diagnostic criteria; dementia diagnosis based on DSM-IV, Alzheimer's disease diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

Analysis

Analysis strategy: Logistic regression used to investigate association between midlife alcohol consumption and subsequent mild cognitive impairment and dementia. Effect modification by APOE4 assessed

Confounders: Age, sex, education, midlife BMI, total cholesterol concentration, smoking status, follow up time, midlife systolic and diastolic blood pressure, history of myocardial infarction and stroke at follow-up

Results, limitations, source of funding

- 61 (5.8%) participants had mild cognitive impairment, 48 (4.6%) had dementia of whom 37 (77%) had Alzheimer's disease
- The odds for mild cognitive impairment were higher for those who never drank and those who drank frequently compared to infrequent drinkers (OR=2.15 [1.01, 4.59] and OR=2.57 [1.19, 5.52], respectively)
- Among carriers of the APOE4, the risk of dementia was greater for frequent drinkers compared to non-drinkers (OR=7.07, [1.37, 36.60])

- E4 carriers who drank infrequently and e4 carriers who drank frequently were 2.3 and 3.6 times more likely to develop dementia, respectively, in comparison with participants who never drank and did not carry e4; similar results were observed when dementia and mild cognitive impairment were assessed together as one outcome
- Sex stratification: an increased risk of mild cognitive impairment was observed for frequent male drinkers compared to infrequent male drinkers [OR=5.03, p=0.02]

Limitations:

1. Recall bias with respect to self-reported alcohol consumption
2. Selective survival related to APOE4 (heavy drinkers may be more likely to develop vascular morbidity, and presence of APOE4 can increase mortality) – this can underestimate relationship between alcohol drinking and dementia

Source of funding: Aging Program of the Academy of Finland,EVO-grants of Kuopio University Hospital and Academy of Finland grants (Insamligsstiftelsen för Alzheimer- och Demensforskning), and the Gamla Tjänarinnor Foundation

Authors: Ascherio A, Zhang SM, Hernán MA, Kawachi I, Colditz GA, Speizer FE, Willett WC

Year: 2001

Citation: Annals of Neurology 50: 56–63

Country of study: USA

Aim of study: To examine the relationship of coffee and caffeine consumption to the risk of Parkinson's disease among health professionals and nurses

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

51,529 male health professionals (mostly white, of European ancestry), ages 40-75 years, were recruited in 1986 to participate in HPFS study. 121,700 female nurses ages 30-55 years, living in 11 states (mostly white, of European ancestry), recruited in 1976 to participate in NHS study. Follow-up every two years.

Study (eligible and selected) population

Average follow-up of 9.2 years for **47,351** men and 15.5 years for **88,565** women

Follow-up:

< 3% loss to follow-up for men and < 2% for women

Follow-up for deaths more than 98% complete

Follow-up: from 1986 (for men part of the HPFS) or 1980 (for women part of the NHS) to the occurrence of Parkinson's, death, or end of follow-up in June 1996

Exclusion:

i) Participants diagnosed with Parkinson's disease, stroke, or cancer before they answered baseline questionnaire

ii) Men and women with extreme daily caloric intakes or incomplete food-frequency questionnaires at baseline

Attrition: -

Exposures at midlife

Caffeine intake and dietary information assessed every 2-4 years using semi-quantitative food-frequency questionnaire (SFFQ); first administered in 1980 (NHS); assesses consumption of coffee, tea, chocolate, decaffeinated coffee, soft drinks with or without caffeine

Questionnaires assessed consumption (of 1 cup of coffee, 1 cup of tea, 1 glass of soft drink, 1 ounce of chocolate) during previous 12 months and allowed for 9 response categories ranging from never to 6 or more per day

Intakes of nutrients and caffeine calculated based on US Department of Agriculture assuming that caffeine content was 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or bottle of cola, 7 mg per serving of chocolate candy

Reproducibility and validity of SFFQ evaluated within the NHS and HPFS; has good validity and reproducibility (when self-reported coffee intake was compared with dietary records, correlation coefficient was 0.78-0.93)

For women, 1980 SFFQ and slightly more refined 1984 version was used to calculate caffeine consumption as well as cumulative average of caffeine consumption from all the available questionnaires prior to the beginning of each 2-year period

Outcomes at 55 years or over

Parkinson's disease cases

Measurement of outcomes:

Lifetime occurrence of Parkinson's disease included in 1988 (HPFS) and 1994 (NHS) questionnaires; Parkinson's disease diagnosis within last 2 years assessed in subsequent questionnaires

Medical records and/or neurologist/internist/GP confirmed new patient self-reported diagnoses of Parkinson's and certainty of diagnosis (definite, probable, possible)

Deaths were reported by next of kin, co-workers, postal authorities, or the National Death Index

When Parkinson's listed as cause of death on death certificate, same process of outcome ascertainment was followed as for non-fatal cases

Analysis

Analysis strategy: Pooled logistic regression with two-year intervals to assess the relationship between
caffeine intake from different sources and the risk of Parkinson's disease in men and women, separately

Confounders: Age, smoking, BMI, alcohol consumption, physical activity, niacin intake, use of HRT

Results, limitations, source of funding

- 157 cases of Parkinson's disease in men and 131 in women
- (in men and women, coffee consumption was strongly associated with smoking and weakly associated with alcohol use)
- Among men, after adjustment for age and smoking, the relative risk of Parkinson's disease was 0.42 (95% CI: 0.23–0.78; p for trend < 0.001) for participants consuming >6 cups/day compared to those consuming 0 cups/day
- Men: significant inverse association observed between: coffee consumption and risk of Parkinson's (p for trend= 0.004), caffeine from non-coffee sources and risk of Parkinson's (p for trend < 0.001), as well as, tea and Parkinson's (p for trend= 0.02)
- Women: the relationship between caffeine intake and risk of Parkinson's disease was U-shaped, with the lowest risk observed for those reporting one–three cups of coffee/day compared to those reporting zero cups/day

Limitations:

1. Possible non-differential misclassification of caffeine
2. Chance or interaction with other factors could be plausible explanations for associations observed

3. Participants were mostly white, of European ancestry, so limited generalizability

Source of funding: National Institutes of Health

Authors: Baba S, Iso H, Mannami T, Sasaki S, Okada K, Konishi M; Shoichiro Tsugane; JPHC Study Group

Year: 2006

Citation: European Journal of Cardiovascular Prevention & Rehabilitation 13(2): 207-213

Country of study: Japan

Aim of study: To determine the sex-specific relationships of smoking with the risk of CHD

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

27,063 men and 27,435 women, ages 40-59 years, and born between 1930-1949, and registered in 14 administrative districts supervised by public health centre areas on Jan 01, 1990

Study (eligible and selected) population

19,794 men and **21,513** women (registered, non-institutional residents)

Follow-up: 88% follow-up. 11 years follow-up from 1990 to 2001 (from collection of baseline questionnaire to first endpoint, death, or Jan. 1 2002)

Exclusion: Participants with history of MI, angina pectoris, stroke, cancer

Attrition: -

Exposures at midlife

Self-administered lifestyle questionnaire distributed in 1990 and completed between Jan. 1990 and May 1992

Smoking and drinking habits, diet and other lifestyles, including leisure time sports and sleeping hours

Smoking categorised as: never, ex, and current smoker (additional sub-categories for male 'current smokers': 1-14, 15-34, 35 per day or more)

Drinking categorised as: never, ex, current drinkers who drink more than once a month (frequency and kinds of alcoholic beverages, as well as average quantity per day)

Daily food intake: frequency of weekly intake asked for 27 food items and categorized as: rarely, 1-2 days per week, 3-4 days per week, almost every day; food items assessed included rice, miso soup, fruit, vegetables, fish

Outcomes at 55 years or over

Acute coronary events [MI, sudden cardiac death, other fatal coronary events] that occurred between 1990 and Jan 01, 2002

Medical records reviewed from hospitals with cardiology departments

MI confirmed according to criteria of the MONICA project (electrocardiograms, cardiac enzymes, autopsy – if this work-up was not performed, probably diagnosis was made)

Deaths occurring within 1 hour of symptom onset labelled as sudden cardiac deaths

Death certificate also reviewed for evidence of CHD and acute heart failure [ICD-10]

Other fatal coronary events were those in which medical records could not be found for cases

identified through death certificates, or coronary events identified through death certificates did not match study criteria for MI or sudden cardiac death Total MI includes both definite and probable cases
Analysis
Analysis strategy: Cox proportional hazards model to assess the sex-specific relationships of smoking with the risk of CHD **Confounders:** Age, alcohol intake, history of hypertension and diabetes, treated hyperlipidemia, food intake (fruit, vegetable, fish servings), education years, public health centre
Results, limitations, source of funding
• 461,761 person-years of follow-up: • Men: 260 CHD cases of which 174 were MI, 63 were sudden cardiac deaths, 23 were other fatal coronary events • Women: 66 CHD cases of which 43 were MI, 16 were sudden cardiac deaths, 7 were other fatal coronary events • Risk of (total) coronary heart disease and (total) myocardial infarction significantly higher in male current smokers compared to those who never smoked (RR=2.85, [1.98, 4.12] and RR=3.64, [2.27, 5.83], respectively) • Males: the risk of total coronary heart disease and total myocardial infarction increased with the number of cigarettes smoked per day (trend test p-values: <0.001 and <0.001, respectively) • Women: the risk of (total) coronary heart disease and (total) myocardial infarction greater for current smokers compared to never smokers (RR=3.07, [1.48, 6.40], RR=2.90, (1.18, 7.18), respectively); the risk of (total) myocardial infarction was also greater for past smokers compared to never smokers (RR=3.72, [1.10, 12.6]) • Population-attributable risk percent (95% CI) of CHD was 46% (34, 55) in men and 9% (0, 18) in women **Limitations:** None reported **Source of funding:** None reported

Authors: Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, van der Schouw YT **Year:** 2007 **Citation:** Journal of the American College of Cardiology 50(1): 14-21 **Country of study:** Netherlands **Aim of study:** Explore the association between dietary glycemic load and glycemic index with CVD; assess whether this association is modified by BMI **Study design:** Longitudinal **Quality score: (++, + or -):** ++
Source population
17,357 women (breast cancer screening participants part of the Prospect-European Prospective Investigation into Cancer and Nutrition [EPIC] cohort) ages 49-70 recruited between 1993-1997
Study (eligible and selected) population
10% random sample drawn from 15,714 women of original study, exclusion criteria applied to yield final cohort of **1,417** Dutch women

Time period: 1993-1997 to Jan. 1, 2005

Follow-up: follow-up from date of return of exposure assessment questionnaire until date of outcome of interest (CHD or CVA), participant date of death, or Jan. 1 2005

Exclusion:

i) Women who did not consent to linkage with vital status registries
ii) Women with missing questionnaires, who reported an energy intake of <500 kcal/day or >6000 kcal/day
iii) Women with history of CHD or cerebrovascular disease before baseline, or with established diabetes
iv) Study censoring: mortality due to non-cardiovascular causes (n=549), loss to follow-up due to emigration (n=60) and withdrawn alive (14,306)

Attrition: -

Exposures at midlife

Average exposure to glycemic index and glycemic load in the previous year (before completing questionnaire)

Food frequency questionnaire (validated – Spearman correlations between 0.56-0.78) used to assess average daily consumption of 178 foods; food glycemic index obtained

Glycemic load obtained by multiplication of glycemic index with carbohydrate content of food item and with frequency of consumption of food item – values over all food items summed

Unit of dietary glycemic load is 1g carbohydrate from glucose

Glycemic index (per gram of carbohydrate): glycemic load divided by total carbohydrate consumed

Outcomes at 55 years or over

Outcomes of interest: cardiovascular disease (coronary heart disease (CHD), cerebrovascular accidents (CVA), cardiovascular disease (CVD))

Hospital discharge diagnoses (ICD-9 codes) obtained from the Dutch Centre for Health Care Information register

Follow-up until Jan 01, 2005

Vital status information obtained from municipal administration registries; cause of death obtained from GPs

Analysis

Analysis strategy: Cox regression to estimate hazard ratios

Confounders: Age, hypertension, cholesterolemia, smoking, BMI, mean systolic blood pressure, total physical activity, menopausal status, HRT, oral contraceptive use, alcohol intake, total energy intake, energy-adjusted intake of vitamin E, protein, dietary fibre, folate, energy-adjusted intake of saturated fat, poly- and monounsaturated fat

Results, limitations, source of funding

- During 141,633 person-years of follow-up: 556 incident cases of fatal or nonfatal CHD and 243 incident cases of fata or nonfatal CVA
- The HR between the highest and lowest quartile of glycemic load was 1.47 (HR=1.47 [1.04, 2.09])
- The higher the quartile of energy-adjusted glycemic load, the greater the risk for cardiovascular disease (p-value for trend: 0.033)
- The HR between the highest and lowest quartile of glycemic index was 1.33 (HR=1.33 [1.07, 1.67])

- The higher the quartile of energy-adjusted glycemic index, the greater the risk for cardiovascular disease (p-value for trend: 0.02)
- Among women with high BMI (>25 kg/m2), there was an increased risk of CHD for both higher levels of glycemic load and glycemic index (p-values for trend: 0.04, 0.06, respectively)

Limitations:

1. Residual confounding by unknown risk factors
2. Misclassification of dietary exposure

Source of funding: None reported

Authors: Beulens JW, Rimm EB, Hu FB, Hendriks HF, Mukamal KJ

Year: 2008

Citation: Diabetes Care 31(10): 2050-55

Country of study: US

Aim of study: To determine whether the association between alcohol consumption and diabetes development is mediated by adiponectin concentrations and biomarkers of inflammation, endothelial dysfunction, and insulin resistance

Study design: Nested case-control study

Quality score: (++, + or -): +

Source population

121,700 female nurses aged 30-55 years initially took part in Nurses' Health Study in 1976

Study (eligible and selected) population

705 women free of diabetes in 1989-90 and with a confirmed diagnosis of type 2 diabetes by year 2000 constituted the cases

Cases matched to two controls on the basis of year of birth, date of blood draw, race, and fasting status at blood draw (one of the two controls was additionally matched to the case on the basis of BMI)

787 controls matched to **705** cases

Follow-up: 1990-2000

Exclusion:

i) Women with missing information for alcohol consumption and markers of inflammation and endothelial dysfunction
ii) Women providing blood in 1989-90 were free of diagnosed diabetes, coronary heart disease, stroke, or cancer at baseline

Attrition: Participants had a higher prevalence of obesity and family history of diabetes and a lower prevalence of current smoking than non-participants (those who did not provide blood)

Exposures at midlife

Self-reported alcohol intake

>1990 semi-quantitative food frequency questionnaire used to assess alcohol intake (among women who provided blood in 1989-90)

Standard portion defined as a glass, bottle, or can of beer; 4-ounce glass of wine; shot of liquor

Participant's average consumption over past year multiplied by alcohol content of portion size (12.8g for beer, 11g for wine, and 14g for liquor) and then summing across beverages

High validity of alcohol consumption (Spearman correlation coefficient: 0.90)

>Biennial self-administered questionnaire

Outcomes at 55 years or over

Type 2 diabetes

Diabetes self-reported and confirmed through validated supplementary questionnaire detailing symptoms, diagnostic laboratory test results, and treatment

Validity of self-reported diabetes confirmed through medical record review in 62 participants

Analysis

Analysis strategy: Logistic regression was used to determine if adiponectin concentrations and biomarkers of inflammation, endothelial dysfunction, and insulin resistance mediate the association between alcohol consumption and diabetes

Confounders: BMI, physical activity, smoking, family history of diabetes, postmenopausal HRT, energy intake, energy-adjusted intake of saturated fat, trans fatty acids, polyunsaturated fat, dietary fibre, glycemic load, coffee consumption

Results, limitations, source of funding

- By year 2000, 714 women had type 2 diabetes diagnosis
- The odds for type 2 diabetes were significantly lower for those who consumed alcohol with an OR of 0.67 (OR=0.67, [0.56-0.79]) per 12.5 g increment of alcohol intake (p<0.001)
- 25% of the association between alcohol intake and type 2 diabetes development was explained by adiponectin

Limitations:

1. Possible selection bias through use of slightly different subgroups for each group of biomarkers
2. Only included women who provided blood samples (these women had higher prevalence of obesity and family history of diabetes in comparison with women who did not provide blood) – may limit generalizability to women with lower diabetes risk
3. More robust markers of insulin sensitivity may be needed

Source of funding: National Institutes of Health grants, a travel grant from the Dutch Heart Association, and a research exchange award from European Research Advisory Board

Authors: Bielak AA, Anstey KJ, Christensen H, Windsor TD.

Year: 2012

Citation: Psychology and Aging 27(1):219-28

Country of study: Australia

Aim of study: Relationship between activity engagement and cognitive ability

Study design: Cohort-sequential design

Quality score: (++, + or -): +

Source population

Number of people: 7,485

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2,530 in the 40s; 2,551 in the 60s

Characteristics: Not reported

Location: Canberra or Queanbeyan, Australia

Recruitment strategy: Electoral rolls

Length of follow-up: 7.00 years (SD 2.43)

Response rate and loss to follow-up: Not reported

Eligible population: Only participants with available baseline data for all outcome variables were included. those aged 40–44 years on January 01, 2000; and those aged 60–64 years on January 01, 2001

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Activity participation

Time: 2000-2001

Measurement of exposure: RIASEC (Realistic, Investigative, Artistic, Social, Enterprising, and Conventional) Activity List

Outcomes at 55 years or over

Outcomes: Perceptual speed, Short-term memory, Working memory, Episodic memory and volcabulary

Outcome measurement: Symbol Digit Modalities Test, California Verbal Learning Test, digit span backward from the Wechsler Memory Scale, CVLT-Delayed and Spot-the-Word Test

Time: 2009-2010

Analysis

Analysis strategy: Custom equations

Confounders: sex, employment status, physical and mental health, and education

Results, limitations, source of funding

Number: Not reported

Effect estimates:

Activity-between X Age Group Estimate (SE)

60 vs. 40

Symbol Digit -0.06 (.02); CVLT-Immediate -0.07 (.03); Digit Backwards -0.002 (.03); CVLT-Delayed -0.02 (.03); Spot-the-word -0.03 (.03)

Change in model fit dfΔ=6

Symbol Digit 372; CVLT-Immediate 735; Digit Backwards 222; CVLT-Delayed 722; Spot-the-word 683

Significant trends: There was significant change across the eight years in each cognitive measure, and significant random variance within- and between-individuals remaining to be explained. Older adults showed a greater effect of activity participation than the middle-aged adults. The direction of the association was positive, with greater average activity participation linked to a higher cognitive score.

Limitations:

Author:

1. Did not assess the frequency of activity engagement
2. The number of activity questions contributing to the overall measure was relatively small; limited statistical power

Reviewer: Model 3 (activity between-person effects) was mentioned but data not presented

Source of funding: A. A. M. Bielak was supported by a postdoctoral research fellowship from the Canadian Institute of Health Research. K. J. Anstey and H. Christensen were supported by National Health and Medical Research Council (NHMRC) Fellowships (366756 and 525411, respectively). T. D. Windsor is the recipient of an Australian Research Council Future Fellowship (FT100100228). The PATH Through Life Study was funded by NHMRC Grants (229936 and 179839). We thank the study participants, PATH interviewers, Trish Jacomb, Karen Maxwell, Tony Jorm, Bryan Rodgers, Peter Butterworth, and Simon Easteal for their contribution to the research.

Authors: Blanco-Cedres L, Daviglus ML, Garside DB, Liu K, Pirzada A, Stamler J, Greenland P

Year: 2002

Citation: American Journal of Epidemiology 155(4): 354-360

Country of study: United States

Aim of study: To determine the association between smoking and cardiovascular disease (CVD), coronary heart disease (CHD), and all-cause mortality among men with various levels of serum total cholesterol

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

39,572 out of 70,000 men and women ages 18 years and older, employed by 84 Chicago-area companies agreed to participate in Chicago Heart Association Detection Project in Industry (CHA) study (55% response rate)

Study (eligible and selected) population

This study included **8,816** men aged 40-59 years at baseline

Sociodemographics: Study sample of men had mean age of 48.5 years, 5.3% were African Americans

Follow-up: 25 years follow-up with screening of men between 1967-1973

Exclusion:

1. Men and women 18-39 years and women 40-59 years at baseline
2. Of the men aged 40-59 years screened at baseline: excluded if they had missing data at baseline or follow-up (n=451), baseline evidence of prior myocardial infarction (n=62), previous diagnosis of diabetes mellitus (n=169)

Attrition: -

Exposures at midlife

Past and present smoking status ascertained by self-reported questionnaire

Outcomes at 55 years or over

CHD death, CVD death, all-cause mortalit

Deaths ascertained from Social Security Administration and National Death Index records

Analysis
Analysis strategy: Cox multivariate proportional hazards regression used to assess influence of baseline current smoking on cause-specific and all-cause mortality for men within four strata of serum cholesterol: <180, 180-199, 200-239, >=240 **Confounders:** Age, race, education, BMI, systolic blood pressure, presence of ECG abnormalities
Results, limitations, source of funding
• Of 8,816 men, 32% and 45.7% of men died of CHD and CVD, respectively • The relative risk for CHD death was greater for smokers compared to non-smokers and ranged from 1.50 (RR=1.50; [1.17, 1.88]) to 2.18 (RR=2.18, [1.54, 3.08]) across cholesterol levels • The relative risk for CVD death was greater for smokers than non-smokers and ranged from 1.58 (RR=1.58, [1.17, 2.14]) to 1.95 (RR=1.95, [1.48, 2.57]) across cholesterol level • The relative risk for all-cause mortality greater for smokers compared to non-smokers and ranged from 1.78 (RR=1.78, [1.54, 2.07]) to 2.19 (RR=2.19, [1.84, 2.61]) across cholesterol levels • Interactions between current smoking and cholesterol level were not significant for CHD, CVD, and all-cause mortality **Limitations:** Regression dilution bias (potentially underestimated results due to misclassification of cholesterol measurement) **Source of funding:** American Heart Association and its Chicago and Illinois affiliates; the Illinois Regional Medical Program; the National Heart, Lung, and Blood Institute; the Chicago Health Research Foundation; and private donors

Authors: Boudík F, Reissigová J, Hrach K, Tomecková M, Bultas J, Anger Z… Zvárová J **Year:** 2006 **Citation:** Atherosclerosis 184(1): 86-93 **Country of study:** Czech Republic **Aim of study:** To evaluate the relationship between health risk factors and atherosclerotic CVD death **Study design:** Longitudinal **Quality score: (++, + or -):** -
Source population
50% of 2370 middle-aged men living in Prague identified through electoral register
Study (eligible and selected) population
1390 out of 2370 men responded to and underwent screening examination in 1975-78 Mean age at study entry was 46.1 years Analysis restricted to **926** men **Follow-up:** 1979 to 1999-01 **Exclusion:** Diabetic patients at baseline **Attrition:** -
Exposures at midlife
Smoking was assessed through self-administered questionnaire in 1975-79

Smoking categories: >=15 cigarettes daily; non-smokers; ex-smokers for less than a year and who previously smoked >=15 cigarettes per day
 Outcomes at 55 years or over
Atherosclerotic cardiovascular disease (CVD) mortality ascertained in 1999-2001 Data on atherosclerotic CVD mortality and survival ascertained from outpatient departments, postal questionnaires, and registry offices (Institute of Health Information and Statistics of the Czech Republic)
 Analysis
Analysis strategy: Cox proportional hazards model used to assess influence of smoking on CVD mortality among 'risk group men'. Risk group men defined as those with one or more atherosclerosis risk factors and without apparent atherosclerotic CVD, diabetes mellitus, and other serious disease at baseline **Confounders:** Age, education, blood pressure, total cholesterol
 Results, limitations, source of funding
• The hazard rate of death from atherosclerotic CVD was 3 for participants reporting >=15 cigarettes daily compared to those reporting <15 cigarettes daily (HR=3, [2.0, 4.6]) **Limitations:** Lack of a true control group (ethical reasons) and risk factor profile of participants may have varied from that of general population **Source of funding:** Ministry of Education of the Czech Republic

Authors: Britton A, Shipley M, Singh-Manoux A, Marmot MG **Year:** 2008 **Citation:** Journal of the American Geriatrics Society 56(6): 1098-1105 **Country of study:** England **Aim of study:** The influence of early- and midlife predictors on successful aging **Study design:** Longitudinal **Quality score: (++, + or -):** +
 Source population
10,308 civil servants (6,895 men and 3,413 women) ages 35-55 in 20 London-based departments in England eligible for Phase 1 (1985-1988) of Whitehall II study. 73% response rate
 Study (eligible and selected) population
Analysis restricted to **5,823** participants (4,140 men and 1,683 women) ages 35-55, free of disease at Phase 1 and who had attended at least 5 phases of follow-up/data collection until Phase 7 (2002-2004), and with measures of functioning at Phase 7 **Follow-up:** From Phase 1 to Phase 7, 535 people died during follow-up Mortality was greater in those of lower social position **Exclusion:** i) Those with prevalent disease at Phase 1, attended fewer than 5 phases of follow-up, did not

	attend Phase 7, had missing data on functioning at Phase 7, had unknown metabolic syndrome during study period
ii)	4,485 people excluded from the analyses; they tended to be older (mean age at Phase 1 45.1 vs 43.9 years), were more often female (39% vs 29%), and were from the lowest socio-economic position groups (33% vs 15%) than those included

Exposures at midlife

Smoking: never-smoker, ex-smoker, current smoker

Alcohol: 0, 1-14, 15 units/week with 1unit=8g ethanol

Poor diet (yes/no): summary index of poor diet was defined if two or three of the following applied: most frequently used bread was white, consumption of whole milk, fruit or vegetables eaten less often than daily

Physical activity: frequency and number of hours per week spent on activities: grouped as vigorous or moderate (performed 1 or more hours per week of these); none or mild

Self-reported questionnaire used to ascertain exposures

Outcomes at 55 years or over

>Successful aging: free from major disease (coronary heart disease, stroke, cancer, diabetes mellitus, depression, metabolic syndrome) from Phase 1 up to Phase 7 and with good physical and mental functioning at Phase 7

Physical and mental functioning based on walking speed, lung function, Alice Heim 4-I cognitive test, physical component score of the 36-item Short Form General Health Survey

>Self-reported questionnaires, medication use, clinical examinations, evidence from GPs and hospitals used to ascertain outcome

Analysis

Analysis strategy: Logistic regression used to assess association between health behaviours (smoking, alcohol, diet, exercise) at Phase 1 and successful aging at Phase 7 for men and women, separately

Confounders: Age at Phase 1, number of phases attended, SES, early-life factors (father's social class, education, height), psychosocial factors, job demands, work support, network index

Results, limitations, source of funding

548/4,140 men and 246/1,683 women were aging successfully by Phase 7

>The odds of successful aging were higher in:

- Non-smokers compared to current smokers for men and women [OR= 2.7, (1.8, 4.1), OR=2.2 (1.3, 3.7), respectively];
- Men who did not have a poor diet compared to those who did [OR=1.4, (1.1,1.7)];
- Men and women with higher levels of physical activity [OR=1.9, (1.2, 3.1); OR=1.7 (1.1, 2.6), respectively];

>The odds of successful aging were lower for women who did not drink alcohol versus those who had 15 units/week [OR=0.5 (0.3, 0.9)]

>An increasing trend in the odds of successful aging occurred with:

- Less exposure to cigarette smoking for men (p<0.001) and women (p=0.006);
- Greater levels of physical activity for men (p<0.001) and women (p=0.03);
- Fewer units of alcohol consumed per week for women (p=0.01)

Limitations:

1. Potentially imprecise definition of successful aging
2. Limited generalizability as study consisted of relatively homogeneous group (London-based office workers)
3. Ethnicity not examined

Source of funding: British Medical Research Council; British Economic and Social Research Council; British Heart Foundation; UK Health and Safety Executive; UK Department of Health; National Heart Lung and Blood Institute, US National Institute of Health, National Institute on Aging, US National Institutes of Health, Agency for Health Care Policy Research; and the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health

Authors: Carlson MC, Helms MJ, Steffens DC, Burke JR, Potter GG, Plassman BL

Year: 2008

Citation: Alzheimer's & Dementia 4: 324–331

Country of study: US

Aim of study: To determine whether midlife cognitive and physical leisure activities are associated with delayed onset or reduced risk of dementia within older male twin pairs (World War II veterans)

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

15,942 white male twin pairs born 1917-1927 in 42 US states made up the NAS-NRC Twin registry of male World War II veterans. Registry created through linkage of birth certificates with files of Department of Veterans Affairs

Study (eligible and selected) population

Exposure assessment questionnaire administered to twins at around 45 years of age (84% response rate [n=7400 twin pairs])

Analysis restricted to **147 twin pairs** (at least one twin received a dementia diagnosis and the other twin remained non-demented for at least 3 years after the onset of dementia in the first twin)

Participants more educated than non-participants

Follow-up: 1967 to 1990-2005

Exclusion: -

Attrition: -

Exposures at midlife

Four physical exercise and leisure activities assessed using 1967 self-reported questionnaire that focused on: outdoor activities; sports; gardening and home improvement; physical exercise after age 35

For each participant, the number of activities was tallied to yield maximum activity score of four

Outcomes at 55 years or over

Dementia assessment and cognitive screening conducted from 1990 to 2005

50-point Telephone Interview for Cognitive Status-modified (TICS-m) used for cognitive screening

When participants could not complete phone interview, proxy was interviewed using Informant

Questionnaire on Cognitive Decline in the Elderly or another interview whereby a physician or psychologist reviewed participant's answers If suspected impairment on TICS-m or proxy instruments, Dementia Questionnaire (DQ) administered If possible dementia identified through DQ, participant underwent neurologic examination, neuropsychological testing, blood or buccal DNA collection, history of cognitive symptoms and medical history assessed
Analysis
Analysis strategy: Dependent proportional hazard Cox ratios used to model the elapsed time from date of leisure activity assessment to either dementia diagnosis or censoring age **Confounders:** Occupational history, age at date of activity assessment, education, natural matching (e.g., genes) **Effect modification:** APOE4 allele
Results, limitations, source of funding
• Dementia mean age of onset: 72.7 years • Physical activity did not predict dementia risk reduction • Risk for dementia by physical activity scores in discordant twin-pairs: OR=0.99 (0.73-1.33) • Risk for dementia among monozygotic twin pairs with and without APOE 4 allele [OR=0.82, (0.48-1.41) and OR=0.94 (0.48-1.87), respectively] **Limitations:** Possibly underpowered study and restricted measurement sensitivity **Source of Funding:** National Institute on Aging

Authors: Chang M, Jonsson PV, Snaedal J, Bjornsson S, Saczynski JS, Aspelund T… Launer LJ **Year:** 2010 **Citation:** Journals of Gerontology Series A-Biological Sciences & Medical Sciences 65(12): 1369-1374 **Country of study:** Iceland **Aim of study:** To evaluate the association between mid-life physical activity and late-life cognitive performance and dementia **Study design:** Longitudinal **Quality score: (++, + or -):** -
Source population
Men and women born in 1907-1935 and living in Reykjavik, Iceland part of Reykjavik Study that was initiated in 1967
Study (eligible and selected) population
In 2002, cohort members re-invited to participate **4,761** participants (2,006 women and 2,755 men) **Sociodemographics:** Mean age of 51 years of participants at midlife examination and 76 years at life-life **Follow-up:** On average, 26 years elapsed between mid-life and late-life examinations **Exclusion:** i) Participants with APOE e2/4 (n=32)

ii) People with missing data from cognitive performance tests (n=819)
iii) 184 people with prevalent dementia at baseline

Attrition: -

Exposures at midlife

>Midlife physical activity assessed through interview

Participants who had ever participated in sports or exercise during adults life then reported the number of hours per week of exercise during winter and summer time and were subsequently categorised as follows: none (0 hours/week); <=5 hours/week; >5 hours/week

Outcomes at 55 years or over

Cognitive function assessed using cognitive tests measuring speed of processing, memory, executive function

DSM-IV dementia diagnosed according to 3 step protocol; those with low scores on MMSE or digit symbol substitution test were administered second diagnostic cognitive test battery; last step involved neurological test and a proxy interview regarding medical history, social, cognitive and daily functioning changes of participant

Analysis

Analysis strategy: Logistic regression used to assess midlife physical activity on late-life dementia

Confounders: Demographic and health factors, including age at time of examination, blood pressure, BMI, serum cholesterol, smoking status, resting heart rate, depressive symptoms

Stratification by APOE: APOE allele genotyping on subsample of 2,113; participants categorized as carriers vs. non-carriers

Results, limitations, source of funding

- Those who exercised <=5 hours/week and >5 hours/week at midlife had significantly faster speed of processing (p<0.0001), better memory (p<0.0001), and higher executive function (p<0.0001) compared to those who never exercised at midlife
- The odds of dementia were lower among those who exercised <=5 hours/week compared to those who never exercised (OR=0.59, [0.40, 0.88])

<u>Stratification by APOE4:</u>

- APOE e4 non-carriers who reported midlife physical activity had very low risk for late-life dementia compared to those who reported no midlife physical activity and were APOE e4 carriers (OR=0.18, [0.07, 0.45])
- APOE e4 non-carriers who reported no midlife activity also had reduced risk for dementia (OR=0.59, [0.36, 0.98])

Limitations: Limited detail by which physical activity is characterised

Source of funding: National Institutes of Health contract N01-AG-12100, the National Institute on Aging Intramural Research Program, the Icelandic Heart Association, the Icelandic Parliament, and the Icelandic Center for Research

Authors: Chang M, Saczynski JS, Snaedal J, Bjornsson S, Einarsson B, Garcia M… Jonsson PV

Year: 2013

Citation: Journal of the American Geriatrics Society 61(2): 237-242

Country of study: Iceland

Aim of study: To evaluate the association between mid-life physical activity and late-life lower extremity function (LEF) in older adults **Study design:** Longitudinal **Quality score: (++, + or -):** -
Source population
Men and women born in 1907-1935 and living in Reykjavik, Iceland part of Reykjavik Study that was initiated in 1967
Study (eligible and selected) population
>In 2002, cohort members re-invited to participate **4,753** participants included in primary analysis of physical activity (PA) on LEF **4,359** participants with complete cognitive data selected for secondary analysis of PA on LEF, adjusting for cognitive function **Follow-up:** Average of 25 years **Sociodemographics:** 2,011 men and 2,742 women included in primary analysis **Exclusion:** >out of 5,764, people excluded from primary analysis because of: i) Missing data on LEF tests (n=797) ii) Had diagnosed dementia (n=214) Those excluded were older, more sick than participants **Attrition:** -
Exposures at midlife
>Midlife physical activity was assessed through interviews on the number of hours per week that people participated in sports or exercise in the summer and winter; participants were categorised as: Active: if they reported any physical activity hours in summer or winter Inactive: if they reported no physical activity
Outcomes at 55 years or over
Lower extremity function (LEF) was measured in late life using reliable gait speed test, walk test (TUG test for assessing balance problems in older people and ADL decline), and knee extension strength (KES)
Analysis
Analysis strategy: Primary analysis: linear regression used to assess influence of midlife PA on gait speed, TUG, and KES tests while adjusting for all confounders, except cognitive function. **Secondary analysis:** Same as above, with additional adjustment for cognitive function **Confounders:** Mid-life variables including education, blood pressure, height, weight, serum cholesterol, smoking, serum cholesterol. Late-life variables including diabetes mellitus, coronary events (history of myocardial infarction, coronary bypass surgery, heart bypass surgery, angioplasty, or others), stroke, depression, MMSE (only in primary analysis) or cognitive function (only in secondary analysis)
Results, limitations, source of funding

- Those who were active at midlife had significantly better LEF
- Primary analysis: the active group had 0.049-m/s faster gait speed (95% CI = 0.038, 0.059, P < .001), completed the TUG test 0.53 seconds faster (95% CI =0.71, 0.36, P < .001), and had 1.34-kg greater KES (95% CI = 0.83, 1.86, P < 0.001) than the inactive group
- Secondary analysis: the active group had 0.037-m/s faster gait speed (95% CI = 0.026, 0.048, P < .001), completed the TUG test 0.34 seconds faster (95% CI = 0.52, 0.16, P < .001), and had 0.87-kg greater KES (95% CI = 0.34, 1.42, P < .001) than the inactive group

Limitations: None reported by the study authors

Source of funding: Intramural Research Program of the National Institutes of Health, the National Institute on Aging, the Icelandic Heart Association, Landspitali University Hospital, and the Icelandic Parliament

Authors: Christensen U, Støvring N, Schultz-Larsen K, Schroll M, Avlund K

Year: 2006

Citation: Scandinavian Journal of Medicine & Science in Sports 16(4): 245-251

Country of study: Denmark

Aim of study: Determine the influence of physical inactivity from middle-age to early old-age on disability at age 75

Study design: Longitudinal

Quality score: (++, + or -): -

Source population

Cohort follow-up of 802 people selected for baseline study in 1964 from Copenhagen, Denmark (participation rate 84%)

Study (eligible and selected) population

387 people born in 1914 who participated in at least one of the three study phases in 1964, 1974, or 1984 and at the 25-year follow-up in 1989

Sociodemographics: Study had more women (54%) than men, 76% of participants had 7 years of school education and 84% were married or cohabiting

Follow-up: 25 years

Exclusion:

i) People who died, moved, or refused to participate (75% participation rate, n=666; and 74% participation rate, n=537 at 10-year and 20-year follow-up, respectively)

ii) At 20- and 25-year follow-up, non-participants were more likely to be men, have 7 years of basic school education, to be cohabiting and smoke in comparison with participants

Attrition: -

Exposures at midlife

>Self-reported physical activity in leisure time assessed in 1964, 1974, and 1984

Participants grouped as ‘mainly sedentary’ or ‘mainly active’ (e.g. light physical activity 1-4 h/week or moderate activity 1-3 h/week or vigorous activity more than 4h/week or in competitive sports several times/week)

Outcomes at 55 years or over

>Functional ability assessed by interviewer-administered Mob-T scale that measures tiredness after performing mobility activities with scores ranging from 0 to 6

Categorised participants into those with good function (score=6) and those with poorer function (score<6)

Cumulative physical activity measures formed for ages of 50+60, 60+70, and 50+60+70 – indicates average physical activity value during that time period

Construct validity, criterion-related validity and reliability of Mob-T scale described in different study

Analysis

Analysis strategy: Logistic regression used to assess influence of physical inactivity (accumulated and separately at each point in time) on disability

Confounders: Smoking, household composition at baseline

Stratification: By education

Results, limitations, source of funding

- Physical inactivity at age 60 to 70 was related to disability for the sub-group with more than 7 years of education (OR=8.62, [1.08, 68.54])

Limitations:

1. “Healthy participant effect”
2. If people who dropped out of study were more likely to be physically inactive, then effects of inactivity on functional ability may have been underestimated
3. Reporting bias and social desirability bias when participants self-reported sedentary lifestyle
4. Small sample size

Source of funding: None reported

Authors: Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C… DeCarli C

Year: 2011

Citation: Neurology 77(5): 461-468

Country of study: USA

Aim of study: To test the association of vascular risk factor exposure in midlife with progression of MRI markers of brain aging and measures of cognitive decline

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Number of people: 5,124

Demographics: Only report on includes at baseline:

Age, y, mean±SD 54±9

Women, n (%) 718 (53.1)

High school graduate, n (%) 1,319 (97.6)

Study (eligible and selected) population

Number of people: 1,352

Characteristics:

Age 61 ± 9
Women, n (%) 718 (53.1)
High school graduate, n (%) 1,319 (97.6)

Location: Framingham

Recruitment strategy: The present study includes participants from the offspring cohort of Framingham HS

Exposures at midlife

Relevant exposures: Smoking habits, educational achievement, BMI

Time: 1991–1995

Measurement of exposure: Body mass index (BMI) was defined as weight (kg) divided by the square of height (m). Standing waist circumference was measured at the level of the umbilicus; hip circumference at the level of the trochanter major. Waist-to-hip ratio was calculated as the ratio of waist to hip circumferences. Educational achievement was studied as a 4-class variable (no high school degree; high school degree, no college; some college; college degree).

Outcomes at 55 years or over

Outcomes: White matter hyperintensity volume, total brain volume, and temporal horn volume of the lateral ventricles, verbal memory, visuospatial memory, and executive function.

Outcome measurement: Brain MRI techniques, The delayed recall component of the Logical Memory subtest from the Wechsler Memory Scale provides a savings measure of retention for verbal memory. The delayed recall component of the Visual Reproductions test assesses visuospatial memory. The difference between the score on Trail-Making Tests B and A is a marker of executive function.

Time: Not reported

Analysis

Analysis strategy: Used multivariable linear regression to relate each vascular risk factor to continuous measures of change and multivariable logistic regression for dichotomous measures of change.

Secondary analysis: Tested whether the associations were similar when additionally adjusting for the baseline measure of the examined outcome variable. the association of hypertension and systolic blood pressure with WMHV progression was also adjusted for interim stroke. Also tested for interaction with APOE 4 carrier status.

Confounders: All analyses were adjusted for sex, age at the first NP/MRI assessment, time interval between the risk factor assessment and the first NP/MRI assessment, and education for cognitive outcomes. For the dichotomous measure of white matter hyperintensity volume change, we also adjusted for the time interval between the first and last NP/MRI evaluation

Source of funding: Framingham Heart Study's National Heart, Lung, and Blood Institute contract (N01-HC-25195) and by grants from the National Institute of Neurological Disorders and Stroke (R01 NS17950) and from the National Institute on Aging (R01 AG16495; AG08122; AG033193; AG031287). Dr. Debette was supported by a Fulbright grant and received an award from the Bettencourt-Schueller Foundation

Results, limitations, source of funding

Number: 1,352

Effect estimates:

Smoking

Estimate± SE p.
White matter hyperintensity volume -0.03±0.07 p.0.694
Total brain volume -0.15±0.07 p.0.025
Temporal horn volume -0.19±0.07 p.0.008
Logical Memory, delayed recall -0.08±0.08 p.0.316
Delayed recall component of the Visual Reproductions test -0.14±0.08 p.0.070
Trail-Making Test -0.04± 0.08 p.0.563

Significant trends: Vascular risk factors and structural brain aging.

Current smoking in midlife was associated with: greater annual increase in temporal horn volume and decrease in total brain volume and also predicted an increased risk of prominent change in temporal horn volume, Total Brain volume, and white matter hyperintensity volume.

Limitations:

1. Persons included are not representative of the general population
2. Vascular risk factors are highly correlated with each other, making it difficult to tease out the individual effects of each did not perform any correction for multiple testing as we considered our study as exploratory
3. Community sample of relatively young subjects, excluding persons with clinical dementia, thus leading to limited variability in cognitive performance longitudinal differences in brain structure may reflect an earlier effect of exposure to vascular risk than changes in cognition
4. Measures of change in brain structure are assessed using automated procedures. lack of a direct measure for longitudinal change in hippocampal volume
5. Measures of cognitive decline are subject to a learning effect

Authors: Dudas KA, Wilhelmsen L, Rosengren A

Year: 2007

Citation: European Journal of Cardiovascular Prevention & Rehabilitation 14(1): 122-127

Country of study: Sweden

Aim of study: Assess risk factors for future coronary bypass grafting as a first coronary event, and to compare them with risk factors for a first acute myocardial infarction

Study design: Prospective cohort study

Quality score: (++, + or -): ++

Source population

Number of people: 7434

Demographics: Not reported

Study (eligible and selected) population

Number of people: 7388

Characteristics:

No CHD. n=5578: Age, mean; SD (years) 51.4;2.3: BMI, mean; SD (kg/m2) 25.4;3.2: Family history, 1013 (18%): Diabetes, n 73 (1%): Current smoker, n 2653 (47%): Sedentary physical activity, n 1379 (25%): Permanent stress, n 1112 (20%) 375

All MI. n=1664: Age, mean; SD (years) 52.1;2.2: BMI, mean; SD (kg/m2) 26.0;3.4: Family history, 401 (24%): Diabetes, n 68 (4%): Current smoker, n 969 (58%): Sedentary physical activity, n 487 (29%): Permanent stress, n 375 (23%)

Cases CABG. without previous MI n=146: Age, mean; SD (years) 51.0;2.2: BMI, mean; SD (kg/m2) 25.8;3.2: Family history, n 48 (33%): Diabetes, n 6 (4%): Current smoker, n 60 (41%): Sedentary physical activity, n 28 (19%): Permanent stress, n 33 (23%)

Location: Goteborg

Recruitment strategy: All men in the city who were born between 1915 and 1925 (n=30 000), except those born in 1923, were randomised into three groups of 10 000 men each

Length of follow-up: 28 years

Response rate and loss to follow-up: Not reported

Eligible population: All men in the city who were born between 1915 and 1925

Excluded populations: Women excluded. Forty-six men undergoing CABG in connection with an operation for aortic stenosis were excluded

Exposures at midlife

Relevant exposures: Smoking habits, physical activity during leisure time, psychological stress

Time: 1970-1998

Measurement of exposure:

Smoking habits coded as never smoked, former smoker of more than 1 month's duration, smoking 1–14 g of tobacco per day, smoking 15–24 g and smoking 25 g or more per day. One cigarette was considered to contain 1 g of tobacco, a cigarillo 2 g and a cigar 5 g of tobacco.

Physical activity during leisure time was categorised into four levels with 1 representing sedentary activity, 2 moderate activity such as walking or light gardening during at least 4 h per week, and 3 regular, strenuous, or 4 very strenuous activities. Because there were few men in category 4, the two highest categories were combined.

Psychological stress was assessed by way of one single question in the postal questionnaire and rated from 1 to 6, with 5 and 6 defined as permanent stress during the last year, or the last 5 years, before the examination

Outcomes at 55 years or over

Outcomes: Coronary bypass

Outcome measurement: AMI was defined as a discharge, or death with International Classification of Diseases. To identify cases of aorto-coronary bypass operations classification codes 3066, 3067 and 3091 were used prior to 1997 and FNA and FNC during 1997 and 1998. Codes for coronary angioplasty were not registered for the purpose of the present study

Time: Not reported

Analysis

Analysis strategy: A multiple logistic regression analysis for the two diagnoses, AMI and CABG, was used in a generalized logit model. According to this we modelled the logits of three category's response variables (no risk, AMI and CABG) against the risk factors. In this model, age-adjusted odds ratios are obtained for the two separate outcomes, and then compared to see difference.

Confounders: Age, family history of AMI, BMI, cholesterol, systolic blood pressure, treatment for hypertension, diabetes, smoking, physical activity, stress

Source of funding: This study was supported by the Heart and Lung Foundation, the Swedish Research Council and FoU-radet in Goteborg and Sodra Bohuslan, Vastra Gotalandsregionen

Results, limitations, source of funding

Number: 128 men

Effect estimates:

All AMI

Hazard ratio (95% CI)
age adjusted
Never smoking 1.00
Former smoker 1.19 (1.02–1.38)
1–14 g/day 1.70 (1.50–1.94)
15–24 g/day 1.90 (1.64–2.21)
25 g/day or more 1.89 (1.45–2.46)

Physical activity
1 1.00
2 0.86 (0.76–0.96)
3 0.80 (0.68–0.95)

Stress
No 1.00
Yes 1.16 (1.04–1.31)

Odds ratio age-adjusted
95% CI
Age (years) 1.31 1.24–1.39
Smoking (1–5) 1.51 1.43–1.60
Physical activity (1–3) 0.83 0.76–0.90
Stress(yes/no) 1.16 0.99–1.35

CABG without prior AMI
Hazard ratio (95% CI)
age adjusted
Never smoking 1.00
Former smoker 1.29 (0.84–1.98)
1–14 g/day 0.96 (0.62–1.51)
15–24 g/day 1.11 (0.65–1.90)
25 g/day or more 2.19 (1.02–4.66)

Physical activity
1 1.00
2 1.23 (0.80–1.89)
3 1.66 (0.98–2.81)

Stress
No 1.00
Yes 1.28 (0.86–1.89)

Odds ratio age-adjusted
95% CI
Age (years) 0.85 0.72–1.00
Smoking (1–5) 0.78 0.66–0.92
Physical activity (1–3) 1.27 0.98–1.64
Stress (yes/no) 1.03 0.64–1.65

Significant trends: High BMI, low physical activity and psychological stress were significantly associated only with AMI. Even light to moderate smoking (1–14 g/day) was associated with increased risk of AMI, hazard ratio 1.70 (1.50–1.94); whereas only very heavy smokers were more likely to undergo CABG, hazard ratio for 25 g/day or more 2.19 (1.02–4.66). Moderate smoking was not associated with coronary bypass grafting.

Limitations:

1. Only men of a comparatively limited age span were studied.
2. Did not have angiographic data in any patient group.
3. Patients with mild angina who did not undergo CABG were not studied

Authors: Ekelund U, Brage S, Franks PW, Hennings S, Emms S, Wareham NJ

Year: 2005

Citation: Diabetes Care 28(5): 1195-120

Country of study: UK

Aim of study: Examine the prospective associations between physical activity energy expenditure, aerobic fitness, obesity, and the progression toward the metabolic syndrome

Study design: Population-based cohort

Quality score: (++, + or -): +

Source population

Number of people: Not reported

Demographics:
Men (n = 246)
Baseline
Age (years) 53.3 ± 10.5
Height (cm) 175.3 ± 6.8
Weight (kg) 80.6 ± 10.6
BMI (kg/m2) 26.2 ± 2.9

Women (n = 359)
Baseline
Age (years) 53.1 ±10.1
Height (cm) 162.3 ± 6.1
Weight (kg) 68.0 ± 12.6
BMI (kg/m2) 25.8 ± 4.4

Study (eligible and selected) population

Number of people:
Men (n = 246)
Women (n = 359)

Characteristics:
Men
Age (years) 58.9 ± 10.6
Height (cm) 175.0 ± 6.7
Weight (kg) 81.2 ± 12.2
BMI (kg/m2) 26.5 ± 3.5

Women
Age (years) 58.7 ± 10.2
Height (cm) 162.0 ± 6.2
Weight (kg) 69.5 ± 14.7
BMI (kg/m2) 26.4 ± 6.2

Location: Ely, UK

Recruitment strategy: Randomly selected

Length of follow-up: Median ± SD follow-up period of 5.6±0.30 years

Response rate and loss to follow-up: Not reported

Eligible population: Not reported

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Physical activity

Time: Not reported

Measurement of exposure: Height and weight were measured using a rigid stadiometer and calibrated scales in light clothing. Body circumference was measured in duplicate using a metal tape. Resistance was assessed using a standard bioimpedance technique

Physical activity energy expenditure measured using the flex heart rate method

Total body water and fat-free mass were calculated using the impedance index

Fat mass was calculated as body weight minus fat-free mass. Percentage of body fat was calculated as fat mass/body weight x 100

Blood pressure was measured in seated position using an Accutorr automatic sphygmomanometer. Systolic and diastolic blood pressures were measured in triplicate at minute intervals, and the mean of these measurements was used in analyses.

Outcomes at 55 years or over

Outcomes: Metabolic syndrome

Outcome measurement: Blood samples

Time: 2001–2003

Analysis

Analysis strategy: Generalized linear models

Confounders: Included all subcomponents of the metabolic syndrome and was adjusted for baseline zMS, sex, age, smoking, SES, and follow-up time

Results, limitations, source of funding

Number: 84 subjects (46 male)

Effect estimates:

Outcome (SD)
PAEE -coefficients (95% CI)
Insulin 0.002 (0.0037 to 0.00053)
BMI 0.00004 (0.00076 to 0.00084)
WHR 0.00058 (0.0006 to 0.0017)
2-h glucose 0.00008 (0.0016 to 0.0015)
DBP 0.00086 (0.0024 to 0.0007)
SBP 0.002 (0.0037 to 0.00064)
Triglycerides 0.000088 (0.0015 to 0.0015)
HDL 0.00074 (0.0005 to 0.002)
zMS 0.00085 (0.00177 to 0.000068)
zMS-Ob 0.0011 (0.0021 to 0.0006974)

Significant trends: Baseline PAEE significantly predicted fasting insulin at follow-up after adjustment for baseline age, sex, smoking, SES, fasting insulin, aerobic fitness, and duration of follow-up (standardized β 0.0012, P 0.01). This association was not affected by further adjustment for baseline BMI (standardized β 0.0013, P 0.005), baseline WHR (standardized β 0.0012, P 0.007), or baseline percentage body fat (standardized β 0.0012, P 0.006).

Limitations:

1. Not powered to explore the possibility of nonlinearity
2. Measure of aerobic fitness is less precise than a true maximal test

Source of funding: The Medical Research Council

Authors: Elwood P, Galante J, Pickering J, Palmer S, Bayer A, Ben-Shlomo Y… Gallacher J

Year: 2013

Citation: PLoS One 9;8(12): e81877

Country of study: South Wales (Caerphilly)

Aim of study: To assess influence of lifestyle on cognitive function

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Cohort of men ages 45-59 years in small South Wales UK town. After 1979 baseline survey, men were re-examined every five years

Study (eligible and selected) population

Study population: Analysis restricted to **2,235** men (89% of defined population) examined at baseline

Exclusion:

1. Men with evidence of disease at baseline (diabetes, a history of angina, chest pain, clinical or ECG evidence of infarction, stroke, high blood pressure
2. Men with evidence of cognitive impairment at baseline omitted

Attrition: -

Exposures at midlife

Self-reported smoking history, physical activity and alcohol consumption captured through food frequency questionnaire at baseline in 1979

Uptake of health behaviours assessed:

Health behaviour:

>Not smoking including ex-smokers;

>Diet: 3+ portions of fruit and/or vegetables a day and 30% less calories from fat;

>Physical activity: walking 2+ miles or cycling 10+ miles each day, or vigorous exercise;

>Alcohol: 3 or fewer units per day

Outcomes at 55 years or over

Incidence of diabetes, vascular disease, cancer, all-cause mortality, cognitive impairment and dementia ascertained through self-report, primary care and hospital records, CT scans and ECG, Office of National Statistics (for deaths and cancer registrations)

In 2004, cognitive impairment and dementia assessed in late-life in participants ages 70-85 years using CAMDEX, CAMCOG, Frontal Assessment Battery, the Clinical Dementia Rating, and the Informant Questionnaire on Cognitive Decline in the Elderly

Analysis

Analysis strategy: Logistic regression used to assess influence of lifestyle (number of healthy behaviours practiced) on cognitive function

Confounders: Age, social class

Results, limitations, source of funding
• The odds of diabetes were lower among those who regularly exercised (OR=0.63, [0.46, 0.85]) • The odds of vascular disease were lower among those who were classified as non-smoking (OR=0.70, [0.58, 0.84]); similar findings reported for cancer (OR=0.65, [0.54, 0.79]) • The odds of cognitive impairment were lower for those who regularly exercised (OR=0.62, [0.41, 0.92]); similar findings reported for dementia • The odds of death were lower among those who did not smoke (OR=0.42, [0.35, 0.51]) • Generally, the greater the number of healthy lifestyle behaviours the participants adopted, the lower the odds of diabetes, vascular disease, cognitive impairment, dementia, all-cause mortality **Limitations:** 1. Impact of healthy lifestyles underestimated due to small number of men adhering to all healthy behaviours (small cell sizes) 2. residual confounding **Source of funding:** None reported

Authors: Emberson JR, Shaper AG, Wannamethee SG, Morris RW, Whincup PH **Year:** 2005 **Citation:** American Journal of Epidemiology 161(9): 856-863 **Country of study:** UK **Aim of study:** Examine associations between alcohol intake and the 20-year risk of coronary heart disease, stroke, and all-cause mortality **Study design:** Cohort **Quality score: (++, + or -):** ++
Source population
Number of people: 7,735 men aged 40–59 years **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 6,544 **Characteristics:** Middle-aged British men **Location:** Throughout Britain **Recruitment strategy:** General practice **Length of follow-up:** Over 20 years from 1978/1980 to 1998/2000 **Response rate and loss to follow-up:** 77% **Eligible population:** One general practice in each of 24 British towns **Excluded populations:** Women and men with evidence of cardiovascular disease. 1,186 men with baseline evidence of CVD. five had incomplete baseline data
Exposures at midlife
Relevant exposures: Alcohol **Time:** Between 1998 and 2000. Time until censoring or first cardiovascular event, whichever is lowest **Measurement of exposure:** A five-point scale from zero (none) to four (heavy) was used to denote the alcohol intake level at the baseline assessment and at each of the follow-up assessments.

Categorised as:

1) Non-drinkers
2) Occasional drinkers (1–2 times/month or on special occasions)
3) Light drinkers (1–2 drinks/day or ‘‘weekend only’’ drinkers (1–6 drinks/day))
4) Moderate drinkers (3–6 drinks/day or weekend only drinkers (>6 drinks/day))
5) Heavy drinkers (>6 drinks every day)

From these average exposure levels, each individual was reclassified on the original scale (an average exposure of <0.5 was defined as ‘‘none’’ 0.5–1.49 was defined as ‘‘occasional” 1.5–2.49 was defined as ‘‘light’’ 2.5–3.49 was defined as ‘‘moderate’’ and 3.5 was defined as ‘‘heavy’’).

Outcomes at 55 years or over

Outcomes: Cardiovascular morbidity and all-cause mortality

Outcome measurement: Information on incident mortality was collected through the established ‘‘tagging’’ procedures provided by the National Health Service central registers.

Time: Between 1998 and 2000

Analysis

Analysis strategy: Cox proportional hazards regression. Hazard ratios were calculated as ‘‘floating absolute risks’’ and inverse variance-weighted quadratic curves were fitted through the values. The ‘‘relative informativeness’’ of baseline versus average alcohol intake was evaluated by examining the contributions made by each measure to the X^2 likelihood ratio statistic in the Cox regression model.

Confounders: Adjustment for cigarette smoking, physical activity, and body mass index. adjustment for intake variation

Limitations:

1. Misclassification of consumption
2. Misclassification of outcome

Source of funding: Not reported

Results, limitations, source of funding

Number: 6,544 men

Effect estimates:
<u>Major coronary heart disease</u>
Baseline exposure
Hazard ratio (95% CI)
None 1.00 (0.75, 1.34)
Occasional 1.00
Light 0.81 (0.68, 0.96)
Moderate 0.94 (0.78, 1.12)
Heavy 1.08 (0.86, 1.35)

Usual exposure
Hazard ratio 95% CI
None 0.91 (0.72, 1.15)
Occasional 1.00
Light 0.74 (0.63, 0.87)
Moderate 1.01 (0.84, 1.21)
Heavy 1.74 (1.31, 2.33)

<u>Stroke</u>
Baseline exposure
Hazard ratio 95% CI

None 1.58 (1.02, 2.44)
Occasional 1.00
Light 0.97 (0.72, 1.31)
Moderate 1.19 (0.88, 1.61)
Heavy 1.54 (1.06, 2.22)

Usual exposure
Hazard ratio 95% CI
None 1.08 (0.73, 1.60)
Occasional 1.00
Light 0.93 (0.71, 1.22)
Moderate 1.45 (1.08, 1.96)
Heavy 2.33 (1.46, 3.71)

<u>All-cause mortality</u>
Baseline exposure
Hazard ratio 95% CI
None 1.22 (0.98, 1.52)
Occasional 1.00
Light 0.88 (0.77, 1.01)
Moderate 1.12 (0.98, 1.29)
Heavy 1.44 (1.21, 1.72)

Usual exposure
Hazard ratio 95% CI
None 0.93 (0.77, 1.12)
Occasional 1.00
Light 0.82 (0.72, 0.93)
Moderate 1.32 (1.15, 1.52)
Heavy 2.27 (1.84, 2.81)

Significant trends: After adjustment for variation in alcohol intake risks among heavy drinkers were respectively, 32%, 86% and 70% higher than for occasional drinkers. After adjustment for intake, regular light alcohol consumption was associated with a statistically sig 26% reduced risk of CHD and 18% reduced risk of all-cause mortality, as well as a statistically insignificant 7% reduced risk of stroke. Moderate drinking and heavy drinking associated with substantially increased risks of stroke, all-cause mortality, and (to a lesser degree) major CHD

Limitations: No limitations reported by author

Authors: Englund U, Nordström P, Nilsson J, Hallmans G, Svensson O, Bergström U, Pettersson-Kymmer U

Year: 2013

Citation: Osteoporosis International 24(2): 533-540

Country of study: Sweden

Aim of study: Investigate whether a physically active lifestyle in middle-aged women was associated with a reduced risk of later sustaining a low-trauma wrist fracture

Study design: Population-based nested case–control study

Quality score: (++, + or -): +

Source population

Number of people: 35,000 subjects

Demographics: Mean age at baseline was 54.3±5.8 years, and mean age at fracture was 60.3±5.8 years

Study (eligible and selected) population

Number of people: 778

Characteristics:

Means (±SD)

Cases (n=376). Age (year) 54.3±5.9: Height (cm) 164.2±5.7: Weight (kg) 67.4±10.5: BMI 24.8±3.7: Follow-up time (year) 11.2±2.6: Distance to work (km) 12.5±15.2: Low active 18.1±16.1: Moderate active 6.9±11.4: High active 2.9±6.9: Current smokers 21.1: Never smokers 53.4: Alcohol users 79.3

Controls (n=402). Age (year) 54.3±5.8: Height (cm) 164.0±5.8: Weight (kg) 69.0±12.0: BMI 25.6±4.3: Follow-up time (year) 11.1±2.5: Distance to work (km) 11.9±17.3: Low active 21.5±20.2: Moderate active 6.5±12.6: High active 2.7±5.4: Current smokers 25.0: Never smokers 50.2: Alcohol users 76.5

Location: Sweden, county of Västerbotten

Recruitment strategy: All inhabitants 40, 50, or 60 years old are invited to a health survey and are also asked to donate a blood sample

Length of follow-up:

Cases: Follow-up time (year) 11.2±2.6

Controls: Follow-up time (year) 11.1±2.5

Response rate and loss to follow-up: Not reported

Eligible population: Inclusion in contains three population-based subcohorts. Fracture case was compared with at least one control drawn from the same cohort and matched for age and week of reporting data

Excluded populations: Subjects who had a wrist fracture before they were recruited into the VIP cohort were subsequently excluded. Another exclusion criterion was if the fracture had occurred before the age of 45 years or was the result of a major trauma

Exposures at midlife

Relevant exposures: Commuting activities, occupational physical activity, exercise, leisure time activities, walking and bicycling activities, smoking habits, alcohol habits

Time: 1985

Measurement of exposure: Self-assessment questionnaire includes questions relating to the subject's level of occupational activity, commuting activity (type of traveling to and from work), and different leisure time activities, if subject has performed any exercise wearing training clothes in the last 3 months and to training habits in youth

Commuting activities for each of the four seasons were defined in three categories: car-bus, bicycling, and walking.

Occupational physical activity divided into three categories: low, moderate, and high physically demanding work.

Exercise in training clothes two groups: performed or not performed.

Physical activity in youth was defined in three groups: physical training at school only (low activity), training and/or competing at an amateur level (moderate activity), and competing at an elite level (high activity).

Frequency of leisure time activities was based on seven different regular activities: walking and/or bicycling (besides the commuting activity), dancing, snow shovelling, gardening, hunting/fishing, and berry/mushroom picking.

The frequencies of walking and bicycling activities defined as low (<one to two times/month) moderate (three to four times/month), and high (two - three times/week or more). The remaining leisure time activities were categorized as not performed or performed (if performed at least every month during

the season).

Smoking habits were coded as “never smoker”, “former smoker” and “current smoker”.

Alcohol habits coded as “teetotaller” or “alcohol user”.

Outcomes at 55 years or over

Outcomes: Wrist fracture

Outcome measurement: Identified from a prospective injury-fracture database at the Umeå University Hospital

Time: 31 December 2008

Analysis

Analysis strategy: Conditional logistic regression analysis. Subgroup analyses performed in women with data on HRT, alcohol use, calcium and vitamin D intake.

Confounders: Adjustments for height, body mass index, smoking, and menopausal status, dietary habits and other physical activity variables

Subgroup analyses were also performed in women with available data on HRT and alcohol use and also on women with data on calcium and vitamin D intake

Results, limitations, source of funding

Number: 376

Effect estimates:
Risk factor Odds ratio (95% CI)
Height 1.00 (0.96–1.030
BMI 0.94 (0.89–0.99)
Smoking
Never smoker 1.00
Former smoker 1.10 (0.66–1.83)
Current smoker 0.84 (0.51–1.38)
Commuting activity
Low 1.00
Moderate 0.98 (0.60–1.59)
High 0.48 (0.27–0.88)
Occupational activity
Low 1.00
Moderate 0.80 (0.53–1.19)
High 0.96 (0.39–2.38)
Training activity 1.14 (0.75–1.74)
Bicycling
Low 1.00
Moderate 1.01 (0.54–1.92)
High 1.13 (0.70–1.82)
Dancing 0.42 (0.22–0.81)
Snow shovelling 0.50 (0.32–0.79)

Significant trends: Subjects with active commuting (especially walking) were at significantly lower risk of sustaining a wrist fracture (OR 0.48; 95 % CI 0.27–0.88) compared with those who commuted by car or bus, in middle-aged women

Reported limitations: No data on bone mineral density, neuromuscular functions or Vitamin D or increased muscle strength or balance. No estimation on the intensity or duration of the different activities or the loading characteristics. Differences in the level of outdoor activities and exposure to sunlight. All information about physical activity, health, and other lifestyle variables were selfestimated. Questionnaire was not validated. Assessments of the different physical variables were crude. Physical activity and other variables were only assessed at baseline

Limitations: Case-control

Source of funding: Swedish Research Council (K2006-72X-20155013), Swedish Sports Research Council (87/06), Swedish Society of Medicine, Medical Faculty of Umeå, and by project grants from the Erik and Anne-Marie Detlof Foundation and the J C Kempe Foundation

Authors: Englund U, Nordström P, Nilsson J, Bucht G, Björnstig U, Hallmans G… Pettersson U

Year: 2011

Citation: Osteoporosis International 22(2): 499-505

Country of study: Sweden

Aim of study: Investigate whether physical activity is associated with a decreased risk of later sustaining a hip fracture

Study design: Population-based case-control study

Quality score: (++, + or -): +

Source population

Number of people: 70,000

Demographics: Not reported

Study (eligible and selected) population

Number of people: 237

Characteristics:

Means (±SD)

Cases (n=81). Age (year) 57.2±5.0: Height (cm) 165.6±6.2: Weight (kg) 68.2±12.9: BMI 24.8±4.2: Percent (%) Smokers 33.8, Former smokers 6.8, Never smokers 59.5, Alcohol users 78.3

Controls(n=156). Age (year) 57.2±5.0: Height (cm) 162.1±6.9: Weight (kg) 68.8±11.9: BMI 26.2±4.8: Percent (%) Smokers 20.4, Former smokers 16.3, Never smokers 63.3, Alcohol users 72.7

Location: Sweden

Recruitment strategy: All inhabitants 40-60 years old were invited to a health survey and asked to donate a blood sample

Length of follow-up:
Case follow up time (year) 11.0±3.2
Control follow up time (year) 11.0±3.2

Response rate and loss to follow-up: Not reported

Eligible population: Involved in Västerbotten Intervention Programme

Excluded populations: Subjects who had a hip fracture or another fragility fracture before they were recruited into the VIP cohort. Women taking other medications known to affect bone metabolism were excluded from the study cohort

Exposures at midlife

Relevant exposures: Physical activity

Time: Not reported

Measurement of exposure: Self-assessment questionnaire includes questions relating to the subject's level of occupational activity, commuting activity (type of traveling to and from work), and different leisure time activities, if subject has performed any exercise wearing training clothes in the last 3 months and to training habits in youth

Commuting activities for each of the four seasons were defined in three categories (Car-bus, bicycling, and walking).

Occupational physical activity divided into three categories: low, moderate, and high physically demanding work.

Exercise in training clothes two groups: performed or not performed

Frequency of leisure time activities was based on seven different regular activities: walking and/or bicycling (besides the commuting activity), dancing, snow shoveling, gardening, hunting/fishing, and berry/mushroom picking

The frequencies of walking and bicycling activities defined as low (<one to two times/month) moderate (three to four times/month), and high (two - three times/week or more). The remaining leisure time activities were categorized as not performed or performed (if performed at least every month during the season)
Smoking habits were coded as “never smoker”, “former smoker” and “current smoker”

Alcohol habits coded as “teetotaller” or “alcohol user”

Outcomes at 55 years or over

Outcomes: Hip fracture

Outcome measurement: Fracture cases were identified from a prospective injury fracture database at the Umeå University Hospital

Time: Time from baseline to when the hip fracture occurred was 8.4±3.8 years and the mean age at fracture was 65.4±6.4 years

Analysis

Analysis strategy: Conditional logistic regression analysis. Multiple-adjusted associations were calculated with adjustments made for height, weight, smoking habits, and menopausal status. Subgroup analyses were also performed using HRT or alcohol habits as potential confounding variables.

Confounders: Adjustments for height, weight, smoking, and menopausal status

Results, limitations, source of funding

Number: 202

Effect estimates:
Independent predictors of hip fracture risk
Adjusted odds ratio (95% CI)
Height 1.26 (1.14–1.40)
Weight 0.94 (0.91–0.98)
Smoking
Never smoker 1
Former smoker 0.34 (0.08–1.50)
Smoker 2.37 (0.81–6.92)
Menopause 0.57 (0.03–11.4)
Walking
Never 1
1 time/week 0.14 (0.04–0.53)
≥2 times/week 0.33 (0.10–1.01)
Spare time activity
Low 1
Moderate 0.19 (0.08–0.46)

High 0.17 (0.05–0.64)

Significant trends: Walking and seasonal-dependent physical spare time activities were associated with a significant hip fracture risk reduction in middle-aged women. Significantly reduced hip fracture risk in women walking once a week only. Lower odds ratio for women with higher frequency of walking.

Limitations:

1. No data on bone mineral density, neuromuscular functions or Vitamin D. Information about lifestyle variables were self-reported.
2. Questionnaire was not validated.
3. Assessments of the different physical variables were crude.
4. Physical activity and other variables were only assessed at baseline.
5. Number of hip fracture cases in this cohort was also rather low.

Authors: Eskelinen MH, Ngandu T, Helkala EL, Tuomilehto J, Nissinen A, Soininen H, Kivipelto M.

Year: 2008

Citation: International Journal of Geriatric Psychiatry 23(7): 741-747

Country of study: Finland

Aim of study: Investigate the association of midlife dietary fat intake to cognitive performance, and to the occurrence of clinical mild cognitive impairment

Study design: Longitudinal population-based study

Quality score: (++, + or -): +

Source population

Number of people: 2000

Demographics: 835 women (62.3%) and 506 men (37.7%) had a mean age at midlife of 50.2 (6.0) years

Study (eligible and selected) population

Number of people: 1449

Characteristics: Mean age at midlife of 71.1 (4.0) years at the follow-up.

Location: Kuopio and Joensuu, Eastern Finland

Recruitment strategy: Random sample

Length of follow-up: 21 (SD 4.9) years

Response rate and loss to follow-up: 72%

Eligible population: Study came from four separate, independent population-based random samples studied within the North Karelia Project and the FINMONICA study in 1972, 1977, 1982 or 1987

Excluded populations: Individuals who had dementia (n=68) were excluded. Those individuals who had dementia (n=68) were excluded, and 40 individuals did not complete all evaluations

Exposures at midlife

Relevant exposures: Diet

Time: 1998

Measurement of exposure: Dietary habits investigated using a semi-quantitative food frequency questionnaire consisting of mostly qualitative or frequency-based questions. Consumption of milk, sour milk and spreads assessed quantitatively

Outcomes at 55 years or over

Outcomes: MCI, global cognitive and executive functions, episodic, semantic and prospective memory and
psychomotor speed

Outcome measurement: Mayo Clinic AD Research Center criteria; Mini Mental State Examination; Category Fluency Test; Purdue Peg Board task; letter digit substitution test; the Stroop test; memory task by Einstein

Time: 1998

Analysis

Analysis strategy: Logistic regression analyses were used to calculate Odds Ratios with 95% Confidence Intervals. Two models reported but third model undertaken controlling additionally for midlife leisure-time physical activity, alcohol consumption, or vascular disorders at late-life including myocardial infarction, stroke, and diabetes, the results remained unchanged or virtually the same

Confounders: Adjusted for midlife age, sex, education, follow-up time and other subtypes of fats, ApoE e4 carrier status, smoking, systolic blood pressure, cholesterol, and BMI

Results, limitations, source of funding

Number: 1,341

Effect estimates:

Association of midlife fat intake with clinical MCI in late-life
Total fat (from milk products and spreads)
Low (0–38.0 g) 1
High (>38.0 g) 1.69 (1.00–2.87)
saturated fatty acids (from milk products and spreads)
Low (0–21.6 g) 1
High (>21.6 g) 2.36 (1.17–4.74)
polyunsaturated fatty acids (from milk products and spreads)
Low (0–2.1 g) 1
High (>2.1 g) 0.94 (0.45–1.96)
PUFA-SFA ratio (milk products and spreads)
Low (0–0.05) 1
High (>0.05) 0.91 (0.53–1.56)
monounsaturated fatty acids (from milk products and spreads)
Low (0–11.3 g) 1
High (>11.3 g) 1.81 (0.87–3.80)
Association of midlife fat intake with Global cognitive function (MMSE)
Total fat from milk and spreads
Low (0–38.0 g) 26.2 (0.1)
High (>38.0 g) 25.9 (0.1)
p-value 0.05
SFA from milk and spreads
Low (0–21.6 g) 26.2 (0.1)
High (>21.6 g) 25.8 (0.1)
p-value 0.03
PUFA from milk and spreads
Low (0–2.1 g) 26.0 (0.1)
High (>2.1 g) 26.1 (0.1)
PUFA–SFA ratio (milk and spreads)
Low (0–0.05) 26.0 (0.1)
High (>0.05) 26.1 (0.1)

MUFA from milk and spreads
Low (0–11.3 g) 26.1 (0.1)
High (>11.3 g) 26.0 (0.1)
Association of midlife fat intake with Episodic memory
Total fat from milk and spreads
Low (0–38.0 g) 5.0 (0.04)
High (>38.0 g) 4.9 (0.1)
SFA from milk and spreads
Low (0–21.6 g) 5.0 (0.05)
High (>21.6 g) 4.9 (0.1)
PUFA from milk and spreads
Low (0–2.1 g) 5.0 (0.05)
High (>2.1 g) 4.9 (0.1)
PUFA–SFA ratio (milk and spreads)
Low (0–0.05) 5.0 (0.04)
High (>0.05) 4.9 (0.1)
MUFA from milk and spreads
Low (0–11.3 g) 5.0 (0.05)
High (>11.3 g) 4.9 (0.1)
Association of midlife fat intake with Semantic memory
Total fat from milk and spreads
Low (0–38.0 g) 20.3 (0.2)
High (>38.0 g) 20.0 (0.3)
SFA from milk and spreads
Low (0–21.6 g) 20.4 (0.2)
High (>21.6 g) 19.7 (0.4)
PUFA from milk and spreads
Low (0–2.1 g) 19.9 (0.2)
High (>2.1 g) 20.8 (0.3)
PUFA–SFA ratio (milk and spreads)
Low (0–0.05) 20.1 (0.2)
High (>0.05) 20.3 (0.3)
MUFA from milk and spreads
Low (0–11.3 g) 20.4 (0.2)
High (>11.3 g) 19.7 (0.4)
Association of midlife fat intake with Psychomotor speed
Total fat from milk and spreads
Low (0–38.0 g) 0.10 (0.03)
High (>38.0 g) -0.02 (0.04)
p-value 0.02
SFA from milk and spreads
Low (0–21.6 g) 0.08 (0.03)
High (>21.6 g) 0.02 (0.05)
PUFA from milk and spreads
Low (0–2.1 g) 0.04 (0.03)
High (>2.1 g) 0.1 (0.04)
PUFA–SFA ratio (milk and spreads)
Low (0–0.05) 0.04 (0.03)
High (>0.05) 0.1 (0.04)
MUFA from milk and spreads
Low (0–11.3 g) 0.09 (0.03)
High (>11.3 g) 0.01 (0.05)
Association of midlife fat intake with Executive function (Stroop)
Total fat from milk and spreads
Low (0–38.0 g) 39.8 (0.8)
High (>38.0 g) 41.0 (1.1)
SFA from milk and spreads

Low (0–21.6 g) 39.3 (0.9)
High (>21.6 g) 42.0 (1.5)
PUFA from milk and spreads
Low (0–2.1 g) 39.9 (0.9)
High (>2.1 g) 40.8 (1.3)
PUFA–SFA ratio (milk and spreads)
Low (0–0.05) 40.9 (0.8)
High (>0.05) 38.6 (1.1)
MUFA from milk and spreads
Low (0–11.3 g) 39.7 (0.9)
High (>11.3 g) 41.2 (1.5)
Association of midlife fat intake with Prospective memory
Total fat from milk and spreads
Low (0–38.0 g) 2.7 (0.03)
High (>38.0 g) 2.6 (0.04)
SFA from milk and spreads
Low (0–21.6 g) 2.7 (0.04)
High (>21.6 g) 2.6 (0.1)
p-value 0.05
PUFA from milk and spreads
Low (0–2.1 g) 2.7 (0.04)
High (>2.1 g) 2.7 (0.05)
PUFA–SFA ratio (milk and spreads)
Low (0–0.05) 2.7 (0.03)
High (>0.05) 2.7 (0.04)
MUFA from milk and spreads
Low (0–11.3 g) 2.7 (0.04)
High (>11.3 g) 2.7 (0.1)

Significant trends: Midlife dietary fat intake was related to cognitive performance, especially in domains of global cognitive function, semantic memory and psychomotor speed, and to the occurrence of MCI later in life

Limitations:

Author

1. Dietary data was available from limited sources
2. Results of stratified analyses may be inconclusive due to insufficient power

Reviewer

1. Authors undertake three models but show results from two. In conclusion refer to the three models.
2. Selective reporting bias. Revisit when we have time to go through thoroughly.

Source of funding: The study was supported by EVO-grants of Kuopio University Hospital (5772708, 5772720), Academy of Finland grants 103334, 120676 and 206951, EU grant QLK-2002-172, The Swedish Council for Working Life and Social Research, the Finnish Cultural Foundation, The Foundation of Juho Vainio, the Gamla Tjanarinnor Foundation, and Uulo Arhio foundation

Authors: Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M

Year: 2009

Citation: Journal of Alzheimer's Disease 16: 85-91

Country of study: Finland

Aim of study: To evaluate the association between mid-life coffee and tea drinking and the risk of late-life dementia

Study design: Longitudinal

Quality score: (++, + or -): +
Source population
A population-based random sample of 2000 people aged 65-79 years and living in Joensuu or Kuopio, Eastern Finland in 1997 were invited to participate in 1998. Response rate of 71% (1409), of which 875 (62%) were women and 534 (38%) were men.
Study (eligible and selected) population
See: 'Source population' **Sociodemographics:** At midlife examination, **875** women and **534** men had mean age of 50.4 years, while at late-life examination, mean age was 71.3 years **Follow-up:** Mean follow-up time of 21 years. Response rate of 71% **Exclusion:** - **Attrition:** -
Exposures at midlife
Coffee and tea consumption examined at midlife using validated semi-quantitative food-frequency questionnaire Coffee drinking categorised as: 0-2 cups/day (low), 3-5 cups/day (moderate), >5 cups/day (high) Tea consumption categorised as: none (0 cups/day), drinking tea (>=1 cups/day)
Outcomes at 55 years or over
Cognitive status assessing through screening, clinical and differential diagnosis Participants with score <=24 on MMSE addressed for further examination where dementia diagnosis may have been made
Analysis
Analysis strategy: Logistic regression was used to determine the influence of coffee or tea on the risk of developing dementia and AD **Confounders:** Midlife age, education, follow-up time and community of residence, midlife smoking, SBP, serum total cholesterol, BMI, physical activity, myocardial infarction, stroke, diabetes mellitus, depression; sex and APOE 4 assessed as effect modifiers
Results, limitations, source of funding
• 61 people had dementia, of which 48 had AD; • Moderate coffee drinkers had a 65-70% decreased risk of dementia and a 62-64% decreased risk of AD compared with low coffee consumers • Odds of developing dementia were lower for those consuming moderate amounts of coffee (3-5 cups) compared to low amounts (0-2 cups) [OR=0.30, (0.10, 0.93)] • APOE4 stratification: for APOE4 carriers, odds of developing dementia were lower among moderate coffee consumers compared to low coffee consumers [OR=0.32, (0.11, 0.92)] • Sex stratification: for males: lower odds for dementia were reported among moderate and high coffee consumers compared to low coffee consumers [OR=0.27, (0.08, 0.89); OR=0.36, (0.13, 0.97)] **Limitations:**

1. Residual confounding due to measurement error
2. Sample may have been too small to detect significant differences in interaction analyses and dose-response effects
3. Bias: self-reported data, residual confounding due to measurement error in the assessment of confounding factors

Source of funding: EVO-grant of Kuopio University Hospital, Academy of Finland grants, EU grant, the Swedish Council for Working Life and Social Research, the Finnish Cultural Foundation, the Foundation of Juho Vainio, the Gamla Tjanarinnor Foundation, the Helsingin Sanomain 100-vuotissaatio, and the Yrjo

Authors: Field AE, Malspeis S, Willett WC.

Year: 2009

Citation: Archives of Internal Medicine 169(9): 881-886

Country of study: USA

Aim of study: Assess the independent association of weight cycling with mortality

Study design: Prospective study

Quality score: (++, + or -): +

Source population

Number of people: 121 701

Demographics: Not reported

Study (eligible and selected) population

Number of people: 44,882

Characteristics

Non-cyclers: Age in 1992, mean (SD), y 57.7 (7.1); BMI in 1992, mean (SD) 25.0 (4.3); BMI categories in 1992 17.0-20.9 1.0, 21.0-24.9 53.4, 25.0-29.9 28.6, >30.0 11.4; Smoking status Never 45.4 , Past 38.7, Current 15.8; Alcohol intake g/day, mean (SD), 5.4 (9.8); Quintiles of MET hours of activity per week, % 1 (0.2-3.1 METs) 18.0, 2 (3.2-8.3 METs) 20.3, 3 (8.4-11.1 METs) 20.6, 4 (16.0-21.9 METs) 20.0, 5 (30.0-53.1 METs) 20.8

Mild Cyclers: Age in 1992, mean (SD), y 55.6 (6.7); BMI in 1992, mean (SD) 28.7 (4.8); BMI categories in 1992 17.0-20.9 0.1, 21.0-24.9 20.1, 25.0-29.42.1, >30.0 31.9; Smoking status Never 44.1, Past 45.1, Current 10.5; Alcohol intake g/day, mean (SD),4.3 (8.4); Quintiles of MET hours ofactivity per week, % 1 (0.2-3.1 METs) 18.4, 2 (3.2-8.3 METs) 20.5, 3 (8.4-11.1 METs) 19.8, 4 (16.0-21.9 METs) 21.6, 5 (30.0-53.1 METs) 19.3

Severe Cyclers: Age in 1992, mean (SD), y 55.2 (6.5); BMI in 1992, mean (SD) 32.6 (6.2); BMI categories in 1992 17.0-20.9 0.0, 21.0-24.9 7.8, 25.0-29.9 28.0, >30.0 58.7; Smoking status Never 41.6, Past 47.4; Current 10.7; Alcohol intake g/day, mean (SD), 3.1 (7.4); Quintiles of MET hours of activity per week, % 1 (0.2-3.1 METs) 23.6: 2 (3.2-8.3 METs) 21.7: 3 (8.4-11.1 METs) 18.3: 4 (16.0-21.9 METs) 18.2: 5 (30.0-53.1 METs) 18.0

Location: USA

Recruitment strategy: Postal questionnaire

Length of follow-up: Variable - from 1976 to 1992 or 2004

Exposures at midlife

Relevant exposures: Height and weight

Time: Height and weight were ascertained in 1976, and current weight was assessed on each follow-up questionnaire

Measurement of exposure: Body mass index was calculated from self-reported information on weight and height.

Net weight change, irrespective of intentionality, was assessed by calculating the difference in weight reported at two time points

“Within the last 20 years, how many times did you lose each of the following amounts of weight on purpose (excluding illness or pregnancy)?” and “Within the last four years, how many times did you lose each of the following amounts of weight on purpose (excluding illness or pregnancy)?” The responses were 0, 1 to 2, 3 to 4, 5 to 6, or 7 or more times for each of the magnitudes of weight loss (2.3-4.1 kg, 4.5-8.6 kg, 9.1-22.2 kg, and 22.7 kg)

Response rate and loss to follow-up: Women who did not answer the 1988 or 1992 questionnaire (n=23 914), were diagnosed as having cancer (other than non-melanoma skin cancer) or heart disease (n=9557), did not complete all of the intentional weight loss questions (n=34 560), reported no losses in the past 20 years but reported losses in the past four years (n=19), did not report their weight at age 18 years (n=5807)

Eligible population: Female registered nurses aged 30 to 55 years

Excluded populations: Women who had a body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, of less than 17 (n=286), reported bypass surgery (in 1992) (n=108), or died in the period of 1988 to 1994 (n=551) were excluded from the analysis

Outcomes at 55 years or over

Outcomes: Deaths

Outcome measurement: Deaths were reported by next of kin, the postal service, or ascertained by the National Death Index

Time: 1992 or 2004

Analysis

Analysis strategy: Multivariate Cox proportional hazards models, stratified by age in months and calendar time and that controlled for other potential confounders

Confounders: Age, body mass index at age 18 years, weight change from age 18 years to start of the cycling period (1976 for models assessing cycling during the past 20 years or 1988 for models assessing cycling during the past 4 years), smoking status with number of cigarettes currently smoked per day (never; past; current, 1-4; current, 5-24; current, 25-34; current, 35-45; current, number unknown), menopausal status, postmenopausal hormone therapy (premenopausal, never, past, or current), alcohol, activity level, and change in activity level, net weight change from the start of the cycling period (1976 for models assessing cycling during the past 20 years or 1988 for models assessing cycling during the past 4 years) until 1992 (ie, end of the cycling period). net weight change from the start of the cycling period (1976 for models assessing cycling during the past 20 years or 1988 for models assessing cycling during the past 4 years) until 2004 or the end of the follow-up period, instead of net weight change during the cycling period

Results, limitations, source of funding

Number:

Cycling Between 1972 and 1992
Non-cycler (n=32 836)
Mild Cycler (n=8452)
Severe Cycler (n=3594)
Cycling Between 1988 and 1992

Non-cycler (n=41 045)
Mild Cycler (n=3142)
Severe Cycler (n=695)

Effect estimates:

Cycling Between 1972 and 1992

Non-cycler
Deaths, No. 319
Person-years 315 836
HR (95% CI) 1 [Reference]
Mild Cycler
Deaths, No. 65
Person-years 81 874
HR (95% CI) 0.89 (0.67-1.18)
Severe Cycler
Deaths, No. 41
Person-years 34 663
HR (95% CI) 1.08 (0.75-1.56)

Cycling Between 1988 and 1992

Non-cycler
Deaths, No. 384
Person-years 395 312
HR (95% CI) 1 [Reference]
Mild Cycler
Deaths, No. 29
Person-years 12
HR (95% CI) 1.11 (0.75-1.64)
Severe Cycler
Deaths, No. 12
Person-years 6641
HR (95% CI) 1.65 (0.89-3.05)

Significant trends: Women who were severe cyclers from 1988 to 1992 were almost three times more likely than non-cyclers to die from cardiovascular events during the follow-up period

Limitations: Self-reported information

Source of funding: Not reported

Authors: Fogelholm M, Kujala U, Kaprio J, Sarna S

Year: 2000

Citation: Obesity Research 8(5): 367-373

Country of study: Finland

Aim of study: To assess influence of lifestyle on 10-year weight change

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Large cohort originally comprising former top male athletes (n=2675) and untrained referents. 2062 out of 2535 (81%) surviving subjects completed baseline questionnaire in 1985 and 1670 out of 2114 completed follow-up questionnaire in 1995.

Study (eligible and selected) population

Analysis restricted to **1143** Finnish participants who completed baseline and follow-up questionnaires and with complete data

Participants were ages 36-88 years at baseline

Follow-up: 10 years (1985-95)

Exclusion: Analysis restricted to subjects without malignant cancer or diabetes

Attrition: -

Exposures at midlife

Self-reported smoking, alcohol use

Dietary habits, leisure physical activity

Smoking categories: smoking, non-smoking, quit or started smoking

Alcohol consumption frequencies assessed; alcohol content of beer, wine, and spirits assumed to be 4, 9.5, and 32g/litre, respectively (subjects classified into intake quartiles ranging from low to high alcohol use)

Frequency of fruit and vegetable consumption assessed (healthy diet defined by presence of at least 2 of the following: fruit and vegetables intake at least 3 times/day; use of margarine; use of skimmed milk)

Frequency, duration, intensity of physical activity assessed, ranging from low to high

Outcomes at 55 years or over

Self-administered questionnaire captured 10-year weight change

Analysis

Analysis strategy: Step-wise linear regression was used to assess influence of lifestyle on 10-year weight change

Confounders: Age, chronic diseases, occupation, present occupational activity, living conditions, former athletic status

Results, limitations, source of funding

- Being a smoker (beta= -1.59, SE=0.48), and increased physical activity (beta=-1.27, SE=0.54) were significantly ($p<0.05$) associated with weight loss

Limitations:

1. Residual confounding
2. Self-reported body weight (may be underestimated) and physician-diagnosed diseases
3. Cohort was not a random, representative population sample

Source of funding: Academy of Finland

Authors: Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH… Debanne SM

Year: 2001

Citation: Proceedings of the National Academy of Sciences of the United States of America 98(6): 3440-3445

Country of study: USA

Aim of study: Examine if development of Alzheimer's disease later in life is reflective of environmental factors operating over the course of a lifetime

Study design: Case-control study **Quality score: (++, + or -):** +
Source population
Number of people: Not reported **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 551 **Characteristics:** **Case-group members (n=193)** Age [mean (SD)] 72.5 (8.0); Male 72.2 (7.3); Female 72.7 (8.5); Year of birth–median (range) 1919 (1898–1944); Male 1919 (1898–1940) Female 1918 (1901–1944); Gender–% (no.) Male 43.5% (84) Female 56.5% (109); Education–[mean (SD)] 13.0 (2.8); Income adequacy, lifetime average– [mean (SD)] 1.7 (0.4); MMSE–[mean (SD)] 17.8 (6.0); Number of activities ever performed 12.9 (4.1) **Control-group members (n=358)** Age [mean (SD)] 71.3 (6.0); Male 71.7 (5.2); Female 71.0 (6.4); Year of birth–median (range) 1923 (1899–1936); Male 1923 (1909–1934); Female 1924 (1899–1936); Gender–% (no.) Male 39.7% (142); Female 60.3% (216); Education [mean (SD)] 15.3 (2.8); Income adequacy, lifetime average [mean (SD)] 1.7 (0.4); MMSE–[mean (SD)] 28.8 (1.0); Number of activities ever performed 16.0 (3.4) **Location:** Cleveland, USA **Recruitment strategy:** Recruited from clinical settings and the community **Length of follow-up:** Not reported **Response rate and loss to follow-up:** Refusal rates for participation as control-group members were 65/346 (19%) for males and 106/537 (20%) for females **Eligible population:** Enrolled in the Research Registry of the University Alzheimer Center, University Hospitals of Cleveland. The control-group members (N=358) were the friends or neighbours of the case-group members or were members of the same organisations to which the case-group members belonged **Excluded populations:** Not reported
Exposures at midlife
Relevant exposures: Activities **Time:** 1991 **Measurement of exposure:** 26 different types of activities (not reported), asking three questions about each one: (i) Did subjects participate in the activity at least once per month? If yes, (ii) How many hours per month in their 20s and 30s; and (iii) How many hours per month in their 40s and 50s Data from the 26 activities were grouped into three general activity categories (passive, intellectual, and physical)
Outcomes at 55 years or over
Outcomes: Alzheimer's Disease **Outcome measurement:** Neuropsychological, laboratory, and neurological exams and all had X-ray

computed tomography or MRI scans of the brain.

Time: Not reported

Analysis

Analysis strategy: ANCOVA

Confounders: Year of birth, education, gender, and income adequacy

Results, limitations, source of funding

Number: 193

Effect estimates:

Comparisons between case- and control-group members on diversity scores (adjusted means)

Case: Passive diversity 0.84; Intellectual diversity 0.44; Physical diversity 0.42

Control: Passive diversity 0.91; Intellectual diversity 0.54; Physical diversity 0.53

ANCOVA: Passive diversity $F(1, 544) = 19.25$; Intellectual diversity $F(1, 544) = 33.33$; Physical diversity $F(1, 544) = 29.24$

Comparisons between case- and control-group members on ''intensity'' scores (adjusted means)

Case: Passive diversity 99.33; Intellectual diversity 68.15; Physical diversity 37.74

Control: Passive diversity 101.84; Intellectual diversity 79.21; Physical diversity 41.09

ANCOVA: Passive diversity $F(1, 544) = 0.16$; Intellectual diversity $F(1, 544) = 3.82$; Physical diversity $F(1, 544) = 0.96$

Significant trends: Diversity of activities and intensity of intellectual activities were reduced in patients with AD as compared with the control group

Limitations:

Author:

1. Not population-based.
2. Recruitment likely to produce overmatching.
3. Activity participation does not necessarily reflect quality of participation.
4. Did not include confounders such as apoE genotype

Reviewer: Case-control

Source of funding: This work was supported in part by grants from the National Institute on Aging (PO 263-MO-818915 and VO1 AG1713-01A1), the Alzheimer's Disease Research Center Program (P50 AG 08012), the Mandel Foundation, the Nickman family, the Institute for the Study of Aging (New York), and Philip Morris USA.

Authors: Gerber Y, Myers V, Goldbourt U

Year: 2012

Citation: American Journal of Epidemiology 175(10): 1006-1012

Country of study: Israel

Aim of study: Assessed survival and life expectancy according to changes in smoking intensity

Study design: Prospective cohort study

Quality score: (++, + or -): ++

Source population

Number of people: 10,059

Demographics: Not reported

Study (eligible and selected) population

Number of people: 4,633

Characteristics:

No.% Mean (SD)

Increased Smoking Intensity. Age, years 50.1 (6.5); Lowest SES category 126 35; Systolic blood pressure, mm Hg 134 (20); Diastolic blood pressure, mm Hg 85 (12); Cholesterol, mg/dL 207 (42); Body mass index 25.2 (3.4); Leisure-time physical activity; None 235 67%; Light 48 14%; Light daily 45 13%; Heavy 22 6%; Diabetes 23 6%; Known coronary heart disease 20 6%; Intermittent claudication 8 2%

Maintained Smoking Intensity. Age, years 50.6 (6.7); Lowest SES category 780 26; Systolic blood pressure, mm Hg 136 (21); Diastolic blood pressure, mm Hg 86 (12); Cholesterol, mg/dL 209 (39); Body mass index 25.6 (3.5); Leisure-time physical activity; None 1,876 63; Light 417 14; Light daily 487 16; Heavy 204 7; iabetes 178 6 ; Known coronary heart disease 249 8 ; Intermittent claudication 117 4

Reduced Smoking Intensity. Age, years 50.2 (6.4); Lowest SES category 255 33; Systolic blood pressure, mm Hg 136 (21); Diastolic blood pressure, mm Hg 85 (12); Cholesterol, mg/dL 210 (38); Body mass index 25.3 (3.4); Leisure-time physical activity; None 490 63; Light 120 15; Light daily 115 15; Heavy 57 7; Diabetes 52 7; Known coronary heart disease 68 9; Intermittent claudication 45 6

Quit. Age, years 51.9 (7.2); Lowest SES category 104 23; Systolic blood pressure, mm Hg 139 (22); Diastolic blood pressure, mm Hg 87 (12); Cholesterol, mg/dL 210 (40); Body mass index 26.4 (3.2); Leisure-time physical activity; None 287 62; Light 75 16; Light daily 74 16; Heavy 26 6; Diabetes 36 8; Known coronary heart disease 71 15; Intermittent claudication 26 6

P Value. Age, years <0.001; Lowest SES category <0.001; Systolic blood pressure, mm Hg 0.02; Diastolic blood pressure, mm Hg 0.004; Cholesterol, mg/dL 0.63; Body mass index <0.001; Leisure-time physical activity 0.59; Diabetes 0.50; Known coronary heart disease <0.001; Intermittent claudication 0.01

Exposures at midlife

Relevant exposures: Smoking behaviour, physical activity

Time: 1963

Measurement of exposure: Smoking behaviour was self-reported. Participants were asked to choose one of 5 smoking status groups: never smoker, past smoker, 1–10, 11–20, or more than 20 cigarettes per day.

Physical activity during leisure time was determined via personal interview, with subjects reporting their physical activity outside working hours.

Location: Tel Aviv, Haifa, and Jerusalem, Israel

Recruitment strategy: Stratified sampling

Length of follow-up: Median follow-up of 26 (quartiles 1–3: 16–35) years

Response rate and loss to follow-up: 87% of participants died

Eligible population: Israeli working men; civil servants and municipal employees

Excluded populations: Excluding 96 participants who stopped cigarette smoking and switched to cigar or pipe smoking. 87% of participants died

Outcomes at 55 years or over

Outcomes: Outcomes were timed to 1) all-cause death and 2) cause-specific death, dichotomised into CVD and non-CVD.

Outcome measurement: Information on death was derived from the Israeli Mortality Registry

Time: All-cause death (1965–2005); cause-specific death (1965–1997)

Analysis

Analysis strategy: Cox proportional hazards regression models

Confounders: Age, socioeconomic status, and smoking intensity in 1963, systolic blood pressure, blood cholesterol, body mass index, leisure-time physical activity, diabetes, known coronary heart disease, and intermittent claudication

Results, limitations, source of funding

Number

Increased (n=358; %=8)
Maintained (n=3,061; %=65)
Reduced (n=787; %=17)
Quit (n=472; %=10)

Effect estimates:

All-cause mortality
HR 95% CI
Increased 1.14 0.99, 1.32
Maintained 1 Referent
Reduced 0.85 0.77, 0.95
Quit 0.78 0.69, 0.89
Ptrend <0.001

CVD mortality
Increased 1.14 0.92, 1.41
Maintained 1 Referent
Reduced 0.77 0.66, 0.94
Quit 0.84 0.70, 1.05
Ptrend 0.01

Non-CVD mortality
Increased 1.05 0.88, 1.25
Maintained 1 Referent
Reduced 0.98 0.87, 1.10
Quit 0.90 0.77, 1.05
Ptrend 0.19

Significant trends: Survival benefit associated with smoking reduction was mostly evident among heavy smokers and for cardiovascular disease mortality

Limitations:

Author:

1. No information is available on smoking habits throughout follow-up.
2. Smoking was self-reported.
3. Couldn't control for dietary and physical activity patterns.
4. Male-only cohort

Reviewer: Difference in time for outcome

Source of funding: Supported by PL 480 counterpart funds, research agreement no. 375106. The Fund for Basic Research from the Israeli Academy of Sciences supported the mortality follow-up from 1970 to 1978.

Authors: Guallar-Castillón P, Rodríguez-Artalejo F, Tormo MJ, Sánchez MJ, Rodríguez L, Quirós JR… Moreno-Iribas C

Year: 2012

Citation: Nutrition Metabolism & Cardiovascular Diseases 22(3): 192-199

Country of study: Spain

Aim of study: Assess the association between major dietary patterns and the risk of coronary heart disease

Study design: Multi-centre prospective cohort study

Quality score: (++, + or -): +

Source population

Number of people: 519,978 (366,521 women and 153,457 men)

Demographics: Not reported

Study (eligible and selected) population

Number of people: 40,757 persons

Characteristics:

Westernised pattern

Quintile 1 (lowest). Age (years) 50.9; Body mass index (kg/m2) 28.6; Waist circumference (cm) 92.3; No formal education (%) 38.3; Current smokers (%) 18.2; Sedentary at work (%) 24.2; Physical activity at home (METs h/wk) 68.2; Physical activity in leisure time (METs h/wk) 31.1

Quintile 3. Age (years) 48.6; Body mass index (kg/m2) 28.2; Waist circumference (cm) 91.6; No formal education (%) 33.9; Current smokers (%) 22.7; Sedentary at work (%) 20.9 17.5; Physical activity at home (METs h/wk) 69.9; Physical activity in leisure time (METs h/wk) 28.3

Quintile 5 (highest). Age (years) 47.0; Body mass index (kg/m2) 28.1; Waist circumference (cm) 92.1; No formal education (%) 31.9; Current smokers (%) 28.5; Sedentary at work (%) 17.5; Physical activity at home (METs h/wk) 69.9; Physical activity in leisure time (METs h/wk) 25.9

Evolved Mediterranean pattern

Quintile 1 (lowest). Age (years) 48.0; Body mass index (kg/m2) 28.0; Waist circumference (cm) 91.0; No formal education (%) 33.6; Current smokers (%) 28.8; Sedentary at work (%) 19.4; Physical activity at home (METs h/wk) 69.2; Physical activity in leisure time (METs h/wk) 26.7

Quintile 3. Age (years) 48.7; Body mass index (kg/m2) 28.3; Waist circumference (cm) 91.8; No formal education (%) 34.7; Current smokers (%) 23.1; Sedentary at work (%) 22.0; Physical activity at home (METs h/wk) 69.4; Physical activity in leisure time (METs h/wk) 28.7

Quintile 5 (highest). Age (years) 49.6; Body mass index (kg/m2) 28.4; Waist circumference (cm) 92.6; No formal education (%) 34.3; Current smokers (%) 18.1; Sedentary at work (%) 21.0; Physical activity at home (METs h/wk) 68.0; Physical activity in leisure time (METs h/wk) 30.6

Location: Spain. Five regions: Asturias, Gipuzkoa, Navarra, Granada and Murcia

Recruitment strategy: Invited to participate either by mail or in person

Length of follow-up: Median follow-up of 11 years

Exposures at midlife

Relevant exposures: Dietary pattern, educational level, smoking, and physical activity

Time: Subject's age at recruitment and exit time as the age at the occurrence of a CHD event, death, or December 31, 2004

Measurement of exposure: Self-administrated questionnaires and interview

Response rate and loss to follow-up: Followed-up until December 31, 2004.

Eligible population: Participant eligibility within each cohort was based on geographic or administrative boundaries. Used only the data from the Spanish cohort of the EPIC study

Excluded populations: 193 for having CHD at baseline; 167 for an implausibly high or low dietary consumption, defined as 3 standard deviations from the mean of the cohort (<788 kcal/day or >5710 kcal/day); and 321 for lack of information on important variables such as date of CHD event (12), hypercholesterolemia (197), diabetes (71), hypertension (60) and smoking (22).

Outcomes at 55 years or over

Outcomes: Myocardial infarction and mortality

Outcome measurement: Hospital discharge registers. CHD events were classified on the basis of symptoms, signs, biomarkers, and electrocardiogram

Time: Between 1992 and 1996

Analysis

Analysis strategy: Cox regression models

Confounders: Age, sex, BMI, waist circumference, educational level, smoking, physical activity at work, physical activity at home, physical activity in leisure time, diabetes, hypertension, hypercholesterolemia, cancer, oral contraceptives, menopausal status, hormone replacement therapy, and total energy intake

Results, limitations, source of funding

Number: 606 definite CHD events (466 myocardial infarctions and 140 anginas requiring revascularisation).

Effect estimates:

<u>Definite CHD events</u>

Westernized Pattern
Quintile 1) 1 Ref. Quintile 2) 0.96 (0.75-1.24) Quintile 3) 0.81 (0.61-1.09) Quintile 4) 0.98 (0.72-1.34) Quintile 5) 0.86 (0.60-1.24)
P for trend 0.51

Evolved Mediterranean Pattern
Quintile 1) 1 Ref. Quintile 2) 0.77 (0.61-0.98) Quintile 3) 0.64 (0.50-0.83) Quintile 4) 0.56 (0.43-0.73) Quintile 5) 0.73 (0.57-0.94)
P for trend 0.0013

<u>Definite, possible and probable CHD events</u>

Westernized Pattern
Quintile 1) 1 Ref. Quintile 2) 1.02 (0.81-1.29) Quintile 3) 0.88 (0.67-1.15) Quintile 4) 1.04 (0.78-1.38) Quintile 5) 0.87 (0.62-1.22)
P for trend 0.55

Evolved Mediterranean Pattern
Quintile 1) 1 Ref. Quintile 2) 0.76 (0.61-0.95) Quintile 3) 0.64 (0.51-0.81) Quintile 4) 0.58 (0.46-0.74) Quintile 5) 0.72 (0.57-0.91)
P for trend <0.001

Significant trends: No association was found between the Westernized dietary pattern and CHD risk. A Mediterranean diet, as consumed in this study population, was associated with a lower risk of CHD.

Limitations:

1. Interpretation of the dietary patterns obtained by factor analysis is subjective.
2. Patterns derived depend on the number of foods included in the diet measurement instrument.
3. Percentage of the variance explained by the two major dietary patterns was only modest.
4. Diet was measured only at baseline.
5. Residual confounding may persist

Source of funding: Spanish Ministry of Health PI04-0257, PI06-0366, PI04-2342, PI04-1822, PI04-1821 and PI04-2188 from the “Instituto de Salud Carlos III”; RETIC (RD06/0020) of ISCIII Spanish Regional Governments of Andalusia, Asturias, Basque Country, Murcia and Navarra and the Catalan Institute of Oncology; EL-G has a “Ramo´n y Cajal” contract from the Ministry of Education.

Authors: Haapanen-Niemi N, Miilunpalo S, Pasanen M, Vuori I, Oja P, Malmberg J

Year: 2000

Citation: International Journal of Obesity Related Metabolic Disorders 24(11): 1465-74

Country of study: Finland

Aim of study: To investigate the independent associations and the possible interaction of BMI, leisure time physical activity and perceived physical fitness and functional capability with the risk of mortality.

Study design: Prospective 16-year follow-up study

Quality score: (++, + or -): +

Source population

Number of people: 6787

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1090 men and 1122 women

Characteristics

<u>Men</u>

Alive (n.882) %
Age (y)
35-44 48.1
45-54 37.0
55-63 15.0
Socioeconomic status
Upper-level employee 19.7
Lower-level employee 13.2
Manual worker 54.2
Farmer or other own-account worker 11.6
Other 0.8
Housewife -
Missing data 0.6
Employment status
Participant in work life 83.3
Not participant in work life 15.6
Housewife -
Missing data 1.0
Marital status
Married 82.2
Single 12.8

Widowed 1.1 Divorced, separated 3.6 Missing data 0.2 Perceived health Good or fairly good 44.0 Average 38.9 Poor or rather poor 16.9 Missing data 0.2 Smoking status Never smoked 27.9 Past smoker 37.2 Current smoker 32.5 Missing data 2.4 Alcohol consumption (g=day) 0 16.1 0.1-12 54.1 >12 29.4 Missing data 0.5 Deceased (n.208) % Age (y) 35-44 20.7 45-54 35.6 55-63 43.8 Socioeconomic status Upper-level employee 12.5 Lower-level employee 8.2 Manual worker 60.6 Farmer or other own-account worker 16.3 Other 01.9 Housewife - Missing data 0.5 Employment status Participant in work life 50.5 Not participant in work life 47.1 Housewife - Missing data 2.4 Marital status Married 80.8 Single 14.4 Widowed - Divorced, separated 4.8 Missing data - Perceived health Good or fairly good 24.0 Average 34.6 Poor or rather poor 41.3 Missing data - Smoking status Never smoked 13.5 Past smoker 33.2 Current smoker 47.1 Missing data 6.3 Alcohol consumption (g=day) 0 15.9 0.1-12 47.1 >12 35.1 Missing data 1.9

Women
Alive (n.1035) %
Age (y)
35-44 44.2
45-54 35.7
55-63 20.2
Socioeconomic status
Upper-level employee 9.3
Lower-level employee 34.9
Manual worker 30.7
Farmer or other own-account worker 15.7
Other 1.0
Housewife 8.3
Missing data 0.2
Employment status
Participant in work life 61.8
Not participant in work life 18.9
Housewife 18.6
Missing data 0.6
Marital status
Married 78.1
Single 8.1
Widowed 8.5
Divorced, separated 5.0
Missing data 0.3
Perceived health
Good or fairly good 43.5
Average 37.4
Poor or rather poor 19.0
Missing data 0.1
Smoking status
Never smoked 75.9
Past smoker 9.1
Current smoker 13.6
Missing data 1.4
Alcohol consumption (g=day)
0 54.9
0.1-12 41.5
>12 2.4
Missing data 1.2

Deceased (n.87) %
Age (y)
35-44 12.6
45-54 32.2
55-63 55.2
Socioeconomic status
Upper-level employee 5.7
Lower-level employee 27.6
Manual worker 34.5
Farmer or other own-account worker 11.5
Other 5.7
Housewife 13.8
Missing data 1.1
Employment status
Participant in work life 34.5
Not participant in work life 44.8

Housewife 18.4
Missing data 2.3
Marital status
Married 63.2
Single 13.8
Widowed 17.2
Divorced, separated 5.7
Missing data -
Perceived health
Good or fairly good 23.0
Average 37.9
Poor or rather poor 39.1
Missing data -
Smoking status
Never smoked 63.2
Past smoker 10.3
Current smoker 23.0
Missing data 3.4
Alcohol consumption (g=day)
0 69.0
0.1-12 24.1
>12 5.7
Missing data 1.1

Location: Medium-size industrial town and two rural municipalities in north-eastern Finland

Recruitment strategy: Census data

Length of follow-up: 16 years

Response rate and loss to follow-up:

77.5% (nˆ=5259)
1y 88%
5y 84%
10y 85%
16y 85%

Eligible population: Subjects aged 35y and older (men, n=ˆ1340; women, nˆ=1500), who were 51 - 79y of age at the end of the follow-up

Excluded populations: Those having an initial BMI of less than 20.0 and those suffering from a disease or symptoms that totally prevented participation in LTPA

Exposures at midlife

Relevant exposures: Living habits, health behaviour, health status, functional capacity and sociodemographic background

Time: 1980

Measurement of exposure: Self-administered questionnaire

LTPA was assessed with 23 questions concerning conditioning exercise, sports, physical recreation, different leisure time and household chores and active commuting to and from work.

Subjects were divided into high, moderate and low physical activity groups according to the index of total physical activity. For the men, the classes were designated as 0-1000, 1000.1-1900 and>1900 kcal per week, and for the women the respective categories were 0-800, 800.1-1500 and>1500 kcal per week.

Physical fitness was assessed by three measures indicating perceived fitness and functional status.

Outcomes at 55 years or over

Outcomes: Mortality

Outcome measurement: National census data

Time: September 1996

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, marital and employment status, perceived health status, smoking and alcohol consumption

Results, limitations, source of funding

Number: 208 men and 87 women

Effect estimates:

Relative risks for all-cause-, CVD and CHD mortality for the men in 1980-1996
All causes
RR 95% CI P
BMI
20.0-24.9 1.00
25.0-29.9 0.87 0.64 - 1.19 0.379
>30.0 1.06 0.67 - 1.69 0.796
LRa.1.1, df.2, P.0.577
Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.82 0.55 - 1.24 0.350
Low 1.20 0.82 - 1.76 0.349
LR.4.2, df.2, P.0.120
Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity weekly 1.26 0.89 - 1.77 0.193
LR.1.7, df.1, P.0.187
Perceived physical fitness compared with age-mates
Better 1.00
Similar 1.93 1.15 - 3.24 0.013
Worse 3.29 1.80 - 6.02 <0.001
LR.16.9, df.2, P<0.001
2 km walking ability
No difficulties 1.00
At least some difficulties 1.62 1.05 - 2.50 0.028
LR.4.7, df.1, P.0.030
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 1.47 0.97 - 2.23 0.070
LR.3.3, df.1, P.0.070
CVD
RR 95% CI P
BMI
20.0-24.9 1.00
25.0-29.9 0.87 0.56 - 1.35 0.541
>30.0 1.44 0.80 - 2.56 0.223
LR.2.6, df.2, P.0.274
Total LTPA energy expenditure index (kcal=week)
High 1.00

Moderate 0.94 0.52 - 1.71 0.846
Low 1.69 0.97 - 2.93 0.063
LR.6.5, df.2, P.0.039
Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity weekly 1.61 0.98 - 2.64 0.058
LR.3.8, df.1, P.0.050
Perceived physical fitness compared with age-mates
Better 1.00
Similar 2.39 1.09 - 5.22 0.029
Worse 34.37 1.80 - 10.62 0.001
LR.12.5, df.2, P.0.002
2 km walking ability
No difficulties 1.00
At least some difficulties 1.25 0.71 - 2.22 0.438
LR.0.6, df.1, P.0.441
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 1.85 1.04 - 3.30 0.036
LR.4.5, df.1, P.0.034
CHD
RR 95% CI P
BMI
20.0-24.9 1.00
25.0-29.9 0.94 0.57 - 1.56 0.813
>30.0 1.23 0.61 - 2.50 0.564
LR.0.5, df.2, P.0.767
Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.88 0.44 - 1.76 0.709
Low 1.70 0.90 - 3.21 0.105
LR.5.8, df.2, P.0.056
Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity 1.66 0.92 - 2.99 0.090
LR.3.1, df.1, P.0.079
Perceived physical fitness compared with age-mates
Better 1.00
Similar 2.82 1.06 - 7.46 0.037
Worse 4.64 1.56 - 13.84 0.006
LR.9.1, df.2, P.0.011
2 km walking ability
No difficulties 1.00
At least some difficulties 1.03 0.51 - 2.05 0.941
LR.0.005, df.1, P.0.941
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 1.61 0.82 - 3.16 0.167
LR.1.9, df.1, P.0.164

Relative risks for all-cause- and CVD mortality for the women in 1980-1996
All causes
RR 95% CI P
BMI
20.0-24.9 1.00
25.0-29.9 0.87 0.52 - 1.46 0.599
>30.0 1.35 0.76 - 2.41 0.310
LR.2.2, df.2, P.0.341

Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.59 0.30 - 1.18 0.136
Low 1.27 0.69 - 2.34 0.440
LR.6.8, df.2, P.0.033
Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity weekly 1.61 0.89 - 2.92 0.114
LR.2.7, df.1, P.0.101
Perceived physical fitness compared with age-mates
Better 1.00
Similar 0.82 0.41 - 1.65 0.582
Worse 1.71 0.72 - 4.05 0.221
LR.5.9, df.2, P.0.054
2 km walking ability
No difficulties 1.00
At least some difficulties 1.45 0.78 - 2.70 0.237
LR.1.4, df.1, P.0.243
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 2.39 1.25 - 4.60 0.009
LR.7.2, df.1, P.0.007
CVD
RR 95% CI P
BMI
20.0-24.9 1.00
25.0-29.9 0.85 0.42 - 1.74 0.664
>30.0 1.36 0.60 - 3.07 0.459
LR.1.3, df.2, P.0.527
Total LTPA energy expenditure index (kcal=week)
High 1.00
Moderate 0.43 0.16 - 1.16 0.093
Low 1.17 0.51 - 2.68 0.717
LR.6.2, df.2, P.0.046
Single-item self-assessment of LTPA
Vigorous activity at least once a week and some light activity 1.00
No or light intensity activity weekly 4.68 1.41 - 15.57 0.012
LR.9.4, df.1, P.0.002
Perceived physical fitness compared with age-mates
Better 1.00
Similar 0.82 0.32 - 2.16 0.693
Worse 1.89 0.57 - 6.27 0.299
LR.3.7, df.2, P.0.154
2 km walking ability
No difficulties 1.00
At least some difficulties 1.25 0.53 - 2.90 0.611
LR.0.3, df.1, P.0.614
Climbing several flights of stairs
No difficulties 1.00
At least some difficulties 3.38 1.22 - 9.41 0.020
LR.6.2, df.1, P.0.013

Significant trends: BMI was not associated with the risk of death among men or women

Limitations: Self-reported information about physical fitness and functional capability, LTPA and BMI

Source of funding: Juho Vainio Foundation, The Yrjo Jahnsson Foundation, the Finnish Ministry of Education and partially from the Emil Aaltonen Foundation

Authors: Halperin RO, Gaziano JM, Sesso HD

Year: 2008

Citation: American Journal of Hypertension 21(2): 148-52

Country of study: USA

Aim of study: Evaluate the relationship between smoking status and incident hypertension

Study design: Randomized, double blind, placebo-controlled trial

Quality score: (++, + or -): +

Source population

Number of people: 22,071

Demographics: 52.4 years (s.d. 8.9). 51.9% never smoked, 37.6% as past smokers, 6.6% as current smokers of <20 cigarettes/day, and 3.9% as current smokers of ≥20 cigarettes/day.

Study (eligible and selected) population

Number of people: 13,529

Characteristics: Not reported

Location: USA

Recruitment strategy: Not reported

Length of follow-up: Median follow-up was 14.5 years, with a maximum follow-up of 20.5 years.

Response rate and loss to follow-up: >99%

Eligible population: Male physicians

Excluded populations: Excluded participants who reported any past or current history of hypertension, or a SBP of ≥140 mm Hg, or a DBP of ≥90 mm Hg. Excluded all participants with missing information on either
baseline hypertension status or smoking status

Exposures at midlife

Relevant exposures: Age, body mass index, alcohol consumption, exercise

Time: Not reported

Measurement of exposure: Categorised as never smoker, past smoker, or current smoker, and those currently smoking were also asked to provide the number of cigarettes smoked per day

Alcohol consumption (rarely/never, monthly, weekly, daily)

Exercise to sweat ≥ once per week (yes, no)

Outcomes at 55 years or over

Outcomes: Hypertension

Outcome measurement: The diagnosis of hypertension was based on self-reported BP and/or the initiation of antihypertensive treatment.

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards models

Confounders: Adjusted for age, BMI, diabetes, any history of total cholesterol ≥240 mg/dl, alcohol use, exercise, parental history of myocardial infarction

Results, limitations, source of funding

Number: 4,904

Effect estimates:

Relative risks (RR) and 95% confidence intervals (CIs) of developing hypertension according to smoking status in 13,529 men
Never 1.00 (ref)
Past 1.08 (1.01, 1.15)
<20 cigarettes/day1.18 (1.01, 1.38)
≥20 cigarettes/day 1.12 (0.99, 1.27)
All current smokers 1.15 (1.03, 1.27)
P value 0.006

Significant trends: The multivariate models that considered changes in smoking status showed increased RR (95% CI) of developing hypertension for current and past smokers of 1.14 (1.00, 1.25) and 1.08 (1.01, 1.15) respectively, and an increased RR of developing hypertension for new smokers at 2 years and new quitters at 2 years of 1.21 (0.96, 1.52) and 1.35 (1.08, 1.68), respectively.

Limitations: Not reported

Source of funding: Supported by research grants CA 34944, CA 40360, and CA 97193 from the National Cancer Institute, and grants HL 26490 and HL 34595 from the National Heart Lung, and Blood Institute, National Institutes of Health, Bethesda, MD. Dr Halperin supported in part by a VA Special Ambulatory Fellowship award.

Authors: Hamer M, Lavoie KL, Bacon SL

Year: 2013

Citation: British Journal of Sports Medicine 48(3): 239-43

Country of study: England

Aim of study: Examine the association between physical activity and healthy ageing

Study design: Prospective study

Quality score: (++, + or -): ++

Source population

Number of people: 11,391

Demographics: Aged 63.7±8.9 years at baseline. Other details not reported

Study (eligible and selected) population

Number of people: 1,953

Characteristics:

Healthy ageing: Age (years) 67.0±4.2; Men 300 (45.1); Smoking Never 307 (46.2), Previous 301 (45.3), Current 57 (8.6); Alcohol intake Daily 217 (32.6), At least once per week (but not daily) 220 (33.1), Rarely 186 (28.0), ever 42 (6.3); Physical activity Inactive 55 (8.3), Moderate (at least once per week) 345 (51.9), Vigorous (at least once per week) 265 (39.8); Marital status Married 479 (72.0), Single, never married 25 (3.8), Separated/divorced 56 (8.4), Widowed 105 (15.8); Wealth quintile 1 (lowest) 45 (6.8), 2 103 (15.5), 3 135 (20.3), 4 172 (25.9), 5 (highest) 210 (31.6)

Unhealthy ageing: Age (years) 62.9±9.5; Men 1169 (41.9); Smoking Never 1010 (36.2), Previous) 1264 (45.3), Current 515 (18.5), Alcohol intake daily 804 (28.8), At least once per week (but not daily) 891 (31.9), Rarely 822 (29.5), Never 272 (9.8); physical activity Inactive 598 (21.4), Moderate (at least once per week) 1347 (48.3), Vigorous (at least once per week) 844 (30.3); Marital status Married 1890 (67.8), Single, never married 141 (5.1), Separated/divorced 341 (12.2), Widowed 417 (15.0); Wealth quintile 1 (lowest) 458 (16.4), 2 538 (19.3), 3 601 (21.5), 4 586 (21.0), 5 (highest) 606 (21.7)

Location: England

Recruitment strategy: Multistage-stratified probability sampling with postcode sectors selected at the first stage and household addresses selected at the second stage

Length of follow-up: Eight years of follow-up

Response rate and loss to follow-up: 70% at the household level and 67% at the individual level

Eligible population: Not reported

Excluded populations: Any participants with existing chronic disease at baseline and wave 2 were excluded. Between wave 1 and 5 2,158 died, 142 moved from UK, 109 institutionalised, 2809 non-response at wave 5. After wave 5 1586 had missing data and 1,133 had disease at baseline

Exposures at midlife

Relevant exposures: Baseline demographics, cigarette smoking, current frequency of alcohol intake, marital status, wealth, physical activity

Time: 2010-2011

Measurement of exposure: Self-reported physical activity, participants wore a GeneActiv device on their wrist for seven consecutive days

Outcomes at 55 years or over

Outcomes: Healthy aging

Outcome measurement: Defined as those participants who survived without developing major chronic disease, depressive symptoms, physical or cognitive impairment.

Disease status was measured using self-reported physician diagnosis of major chronic diseases

Cognitive function was assessed objectively using a battery of widely used neuropsychological tests

Depressive symptoms were assessed using the eight-item Centre of Epidemiological Studies Depression scale

Disability based on participants' responses to questions on perceived difficulties in basic and instrumental activities of daily living

Physical functioning was objectively assessed using walking speed measured over an eight-foot long course

Time: 2010-2011

Analysis

Analysis strategy: Multiple logistic regressions

Confounders: Adjustment for age, sex, smoking (never; previous; current), alcohol (daily; at least weekly; rarely; never), marital status (married; always single; separated; widowed), wealth quintile.

Results, limitations, source of funding

Number: 19.3% of the sample.

38.4% of the sample had developed a chronic illness, 17.6% reported depressive symptoms, 32% reported disability, 19.2% had cognitive impairment and 17.7% had inadequate gait speed

Effect estimates:

OR (95% CI) for the association of physical activity and different components of healthy ageing over eight years follow-up

Chronic disease
Inactive 1.00
Moderate physical activity 0.78 (0.64 to 0.95)
Vigorous physical activity 0.67 (0.54 to 0.84)
p-trend 0.001

Depressive symptoms (CES-D>3)
Inactive 1.00
Moderate physical activity 0.67 (0.53 to 0.85)
Vigorous physical activity 0.51 (0.39 to 0.67)
p-trend 0.001

Cognitive impairment
Inactive 1.00
Moderate physical activity 0.88 (0.69 to 1.13)
Vigorous physical activity 0.64 (0.48 to 0.85)
p-trend 0.005

ADL/IADL
Inactive 1.00
Moderate physical activity 0.57 (0.46 to 0.70)
Vigorous physical activity 0.41 (0.33 to 0.52)
p-trend <0.001

Impaired gait speed (<0.6 m/s)
Inactive 1.00
Moderate physical activity 0.54 (0.40 to 0.72)
Vigorous physical activity 0.41 (0.29 to 0.58)
p-trend <0.001

OR (95% CI) for the association of baseline physical activity and healthy ageing over 8 years follow-up (N=3454)
Inactive 1.00
Moderate physical activity 2.67 (1.95 to 3.64)
Vigorous physical activity 3.53 (2.54 to 4.89)
P trend <0.001

OR (95% CI) for the association of physical activity change over wave 1–3 and healthy ageing at follow-up (N=3051)

Remained inactive 12/273 1.00
Became inactive 37/363 2.36 (1.19 to 4.68)
Became active 34/275 3.37 (1.67 to 6.78)
Remained active 521/2140 7.68 (4.18 to 14.09)
p-trend <0.001

Odds ratio (95% confidence interval) for the association of baseline physical activity and healthy ageing over 8 years follow up in clinical sub-sample.

OR (95% CI)
Inactive 1.00
Moderate physical activity 2.13 (1.45 – 3.13)
Vigorous physical activity 2.85 (1.91 – 4.23)

Significant trends: Becoming active (multivariate adjusted,3.37, 1.67 to 6.78) or remaining active (7.68, 4.18 to 14.09) was associated with healthy ageing in comparison with remaining inactive over follow-up. Among the covariates, wealth and smoking predicted healthy ageing; compared with participants in the poorest quintile, those in the richest were more likely to be healthy agers (multivariate adjusted OR=2.81, 95% CI 1.93 to 4.10)

Limitations:

1. Assessment of physical activity change was crude.
2. Chronic disease was based on self-report of physician diagnosis

Source of funding: The funding is provided by the National Institute on Aging in theUSA (grants 2RO1AG7644-01A1 and 2RO1AG017644) and a consortium of UK government departments co-ordinated by the Office for National Statistics

Authors: Happonen P, Voutilainen S, Salonen JT

Year: 2004

Citation: Journal of Nutrition 134(9): 2381-6

Country of study: Finland

Aim of study: Study the effect of coffee consumption on the incidence of nonfatal acute myocardial infarction or coronary death

Study design: Population-based cohort study

Quality score: (++, + or -): +

Source population

Number of people: 2682

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1971

Characteristics: Median coffee consumption, mL 556; Age, y 52.5 ± 5.3; Current smoker, % 30; Packyears among smokers, y 28.4±18.3; Physical activity, kJ/d 581±707; Ischemia in exercise electrocardiogram, %18; Family history of CHD, % 46; Diabetes, % 5.2; Income, thousand Finnish Marks 130±74; Alcohol intake, g/wk 73±115; Total fat intake, % energy 39.7±5.9; Saturated fat intake, % energy 19.4±4.1; Daily total energy intake, MJ 10.8±2.7; Daily tea consumption, mL 110±194; Daily total water intake, L 2.35±0.60; BMI, kg/m2 26.7±3.5

Location: Finland

Recruitment strategy: Not reported

Length of follow-up: Mean follow-up of 14 years

Response rate and loss to follow-up: There were no losses to follow-up

Eligible population: Not reported

Excluded populations: 677 men with prevalent CHD at baseline

Exposures at midlife

Relevant exposures: Coffee and diet, smoking and alcohol

Time: Not reported

Measurement of exposure: Consumption of foods and beverages was assessed with an instructed and interview-checked 4-d food recording by household measures

Participant defined as a current smoker if he had ever smoked on a regular basis and had smoked within the past 30 days

Alcohol intake was measured with a recall of the frequency and usual amounts of alcoholic beverages consumed in the past 12 months

Mean daily coffee intake was divided into 4 categories: 0 (nondrinkers), 1 to 375 mL (light drinkers), 376 to 813 mL (moderate drinkers), and 814 mL and over (heavy drinkers).

Outcomes at 55 years or over

Outcomes: Acute coronary events

Outcome measurement: Obtained by computer linkage to the national hospital discharge registry; diagnostic information was collected from the hospitals and classified using identical diagnostic criteria

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards regression

Confounders: Age, smoking, exercise, ischemia, diabetes, income, serum insulin concentration, time, serum HDL and LDL cholesterol concentration, diastolic blood pressure, maximal oxygen uptake, and waist-hip ratio

Results, limitations, source of funding

Number: 269

Effect estimates:

Coffee intake category

None (n _ 77)
Number of events 1
Person-time, y 379
RR (95% CI) 0.66 (0.09–4.91)

Light (n _ 456)
Number of events 24
Person-time, y 2187
RR (95% CI) 1.93 (1.12–3.32)

Moderate (n _ 1087)
Number of events 29
Person-time, y 5316
RR (95% CI) 1.00

Heavy (n _ 351)
Number of events 21
Person-time, y 1672
RR (95% CI) 2.15 (1.20–3.83)

Significant trends: Heavy coffee consumption increases the short-term risk of acute myocardial infarction or coronary death, independent of the brewing method or currently recognized risk factors for CHD. The hazard rate of acute coronary events was 43% (95% CI, 5 to 94%) higher in heavy coffee drinkers compared with moderate drinkers.

Limitations: In Finland the consumption of decaffeinated coffee is minimal and our findings are confined to caffeine-containing coffee

Source of funding: Academy of Finland (201688 and 80185, S.V.), the Ministry of Education of Finland, the city of Kuopio, and the National Heart, Lung, and Blood Institute of the United States. Additional support was provided by the Juho Vainio Foundation, the Finnish Cultural Fund/North Savo Fund, the Yrjo Jahnsson Foundation, and the Finnish Foundation for Medical Science

Authors: Hara M, Sobue T, Sasaki S, Tsugane S

Year: 2002
Citation: Japanese Journal of Cancer Research 93(1): 6-14.

Country of study: Japan

Aim of study: Update the evidence on the association between smoking and mortality

Study design: Population-based prospective study

Quality score: (++, + or -): +

Source population

Number of people: 54,498 subjects (27,063 men and 27,435 women)

Demographics: Not reported

Study (eligible and selected) population

Number of people: 41,484 (19,950 men and 21,534 women)

Characteristics:

Men never smokers: Age (SD) 49.6 (5.6); Alcohol drinking, at least once per week (%) 59.1; Education, College or more (%) 15.2; Past history of Hypertension 15.1; Any drug for medication 20.9; Physical activity, 1+/week (%) 19.3; Body mass index (SD) 23.9 (2.9); Diet (daily, %) Fruit 30.0; Green vegetables 31.0; Yellow vegetables 16.6; White vegetables 34.0; Pickled vegetables 39.2; Soy products 37.1; Fresh fish 15.5; Red meat 26.2

Men past smokers: Age (SD) 50.2 (6.0); Alcohol drinking, at least once per week (%) 69.9; Education, College or more (%) 17.1; Past history of Hypertension 18.6; Any drug for medication 27.2; Physical activity, 1+/week (%) 21.3; Body mass index (SD) 23.9 (2.9); Diet (daily, %) Fruit 27.3; Green vegetables 30.3; Yellow vegetables 16.7; White vegetables 35.5; Pickled vegetables 41.7; Soy products 36.3; Fresh fish 14.7; Red meat 27.7

Men current smokers: Age (SD) 49.0 (6.0); Alcohol drinking, at least once per week (%) 71.7; Education, College or more (%) 13.4; Past history of Hypertension 13.1; Any drug for medication 19.8; Physical activity, 1+/week (%) 15.2; Body mass index (SD) 23.2 (2.9); Diet (daily, %) Fruit 20.8; Green vegetables 26.4; Yellow vegetables 12.3; White vegetables 32.6; Pickled vegetables 46.9; Soy products 34.5; Fresh fish 15.0; Red meat 28.9

Women never smokers: Age (SD) 49.6 (5.8); Alcohol drinking, at least once per week (%) 20.8; Education, College or more (%) 11.9; Past history of Hypertension 13.4; Any drug for medication 24.2; Physical activity, 1+/week (%) 14.5; Body mass index (SD) 23.6 (3.2); Diet (daily, %) Fruit 45.7; Green vegetables 36.7; Yellow vegetables 24.3; White vegetables 45.4; Pickled vegetables 53.1; Soy products 46.3; Fresh fish 19.8; Red meat 26.3

Women past smokers: Age (SD) 49.0 (6.3); Alcohol drinking, at least once per week (%) 41.3; Education, College or more (%) 19.5; Past history of Hypertension 19.3; Any drug for medication 33.8; physical activity, 1+/week (%) 18.2; Body mass index (SD) 24.0 (3.4); Diet (daily, %); fruit 37.1; Green vegetables 30.3; Yellow vegetables 19.3; White vegetables 35.9; Pickled vegetables 46.6; Soy products 35.6; Fresh fish 15.4; Red meat 31.6

Women current smokers: Age (SD) 48.6 (5.9); Alcohol drinking, at least once per week (%) 44.6; Education, College or more (%) 11.7; Past history of Hypertension 12.2; Any drug for medication 24.7; Physical activity, 1+/week (%) 13.1; Body mass index (SD) 23.2 (2.9); Diet (daily, %) Fruit 30.1; Green vegetables 31.6; Yellow vegetables 18.4; White vegetables 35.5; Pickled vegetables 46.3; Soy products 36.8; Fresh fish 14.9; red meat 30.7

Location: Five Public Health Center areas (Ninohe PHC in Iwate Prefecture, Yokote PHC in Akita Prefecture, Saku PHC in Nagano Prefecture, Ishikawa PHC in Okinawa Prefecture and Katsushika PHC in Tokyo Metropolitan area).

Recruitment strategy: Population registries

Length of follow-up: Until the date of death of the deceased, the last date when the survival status had been confirmed for censored cases, and the end of the study period (December 31, 1999)

Response rate and loss to follow-up: Men (76.5%) and women (82.1%)

Eligible population: Not reported

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Smoking and alcohol

Time: Not reported

Measurement of exposure: Smoking status was initially classified as current, past, or never smoker

Usual alcohol intake was first reported as frequency of consumption in six categories: <1 day/month, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week, and every day.

Outcomes at 55 years or over

Outcomes: Death

Outcome measurement: Death certificates

Time: Not reported

Analysis

Analysis strategy: Cox's proportional hazard model

Confounders: Adjusted for age and area, educational background, medication, past history of hypertension, sports in leisure time, dietary habits, alcohol habit and quintiled BMI

Significant trends: 22% of death from all causes, 25% of all cancer, and 17% of all circulatory system disease deaths, could be attributed to cigarette smoking in males, and 5%, 4%, and 11% in females, respectively.

Limitations: Smoking status was determined only once at baseline

Source of funding: Grants-in-Aid for Cancer Research and for the 2nd Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare of Japan. Megumi Hara was an Awardee of a Research Resident Fellowship from the Foundation for Promotion of Cancer Research in Japan.

Results, limitations, source of funding

Number: 1014 men and 500 women died

Effect estimates:

Risk Ratios According to Status of Cigarette Smoking for Selected Causes of Death

<u>Men</u>

Past
All causes 1.02 (0.82 – 1.28)
All Cancer 1.09 (0.77 – 1.54)
All circulatory system disease 0.99 (0.67 – 1.43)
Noncancer-noncirculatory system disease 0.97 (0.67 – 1.43)

Current
All causes1.55 (1.29 – 1.86)
All Cancer 1.61 (1.20 – 2.15)
All circulatory system disease 1.41 (0.97 – 2.03)
Noncancer-noncirculatory system disease 1.61 (1.17 – 2.19)

<u>Women</u>

Past

All causes 1.27 (0.65 – 2.48)
All Cancer 0.89 (0.28 – 2.81)
All circulatory system disease2.51 (0.90 – 6.99)
Noncancer-noncirculatory system disease 0.90 (0.22 – 3.68)

Current
All causes 1.89 (1.36 – 2.62)
All Cancer 1.83 (1.14 – 2.95)
All circulatory system disease 2.72 (1.45 – 5.07)
Noncancer-noncirculatory system disease 1.39 (0.71 – 2.73)

Effect from Cumulative Dose as Indicated by Pack-years among Current Smokers Compared with Never Smokers

RR (95%CI)

Men
Never smoker 1.00
Pack-year
– 19
All causes 1.44 (1.12 – 1.84)
All cancer 1.33 (0.88–2.00)
All circulatory system disease 1.02 (0.60–1.73)
Noncancer-noncirculatory system disease 1.89 (1.28–2.79)
20 – 29
All causes 1.56 (1.23 – 1.99)
All cancer 1.41 (0.94–2.10)
All circulatory system disease 1.44 (0.90–2.31)
Noncancer-noncirculatory system disease 1.82 (1.23–2.68)
30 +
All causes 1.57 (1.28 – 1.93)
All cancer 1.83 (1.34–2.51)
All circulatory system disease 1.41 (0.95–2.12)
Noncancer-noncirculatory system disease 1.37 (0.96–1.95)

Women
Never smoker 1.00
Pack-year
– 9
All causes 1.64 (0.98–2.72)
All cancer 1.03 (0.42–2.52)
All circulatory system disease 3.37 (1.52–7.47)
Noncancer-noncirculatory system disease 1.30 (0.47–3.57)
10 – 19
All causes 1.52 (0.80–2.88)
All cancer 0.64 (0.16–2.61)
All circulatory system disease 2.12 (0.65–6.95)
Noncancer-noncirculatory system disease 2.58 (1.10–6.02)
20 +
All causes 2.61 (1.52–4.47)
All cancer 4.51 (2.45–8.30)
All circulatory system disease 1.51 (0.35–6.57)
Noncancer-noncirculatory system disease 0

Effect from Dose for Number of Cigarettes and Age at Start of Smoking in Current Smokers

Number of cigarettes

Men

Number of cigarettes
1–19
All causes 1.00

All cancer 1.00
All circulatory system disease 1.00
Noncancer-noncirculatory system disease 1.00

20–29
All causes 0.95 (0.78–1.16)
All cancer 1.21 (0.89–1.64)
All circulatory system disease 0.93 (0.61–1.41)
Noncancer-noncirculatory system disease 0.73 (0.53–1.02)

30>
All causes 0.96 (0.76–1.21)
All cancer 1.00 (0.68–1.47)
All circulatory system disease 1.20 (0.76–1.88)
Noncancer-noncirculatory system disease 0.78 (0.53–1.14)

Women

Number of cigarettes
1–19
All causes 1.00
All cancer 1.00
All circulatory system disease 1.00
Noncancer-noncirculatory system disease 1.00

20–29
All causes 1.27 (0.63–2.57)
All cancer 1.77 (0.60–5.17)
All circulatory system disease 0.15 (0.01–1.56)
Noncancer-noncirculatory system disease 1.28 (0.23–7.12)

30>
All causes 2.20 (0.75–6.44)
All cancer 6.03 (1.36–26.64)
All circulatory system disease 1.25 (0.11–13.76)
Noncancer-noncirculatory system disease 0

Age at start of smoking

Men
–19
All causes 1.00
All cancer 1.00
All circulatory system disease 1.00
Noncancer-noncirculatory system disease 1.00
20–24
All causes 0.81 (0.67–0.98)
All cancer 0.86 (0.63–1.17)
All circulatory system disease 0.80 (0.54–1.16)
Noncancer-noncirculatory system disease 0.74 (0.54–1.03)
25+
All causes 0.69 (0.52–0.92)
All cancer 0.77 (0.49–1.19)
All circulatory system disease 0.51 (0.27–0.97)
Noncancer-noncirculatory system disease 0.71 (0.44–1.14)

Women
–24
All causes 1.00
All cancer 1.00
All circulatory system disease 1.00
Noncancer-noncirculatory system disease 1.00
25+

All causes 1.00 (0.50–2.02) All cancer 0.63 (0.20–1.92) All circulatory system disease 1.00 (0.21–4.66) Noncancer-noncirculatory system disease 1.62 (0.23–11.61)

Authors: Harmsen P, Lappas G, Rosengren A, Wilhelmsen L **Year:** 2006 **Citation:** Stroke 37(7): 1663-7 **Country of study:** Sweden **Aim of study:** To estimate the predictive value of risk factors for stroke measured in midlife **Study design:** Intervention trial **Quality score: (++, + or -):** +
Source population
Number of people: 7494 men **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 7457 **Characteristics:** Not reported **Location:** Göteborg, Sweden **Recruitment strategy:** Responders to a postal questionnaire **Length of follow-up:** 28 years **Response rate and loss to follow-up:** 75% of the sample **Eligible population:** Middle-aged men **Excluded populations:** Women
Exposures at midlife
Relevant exposures: Psychological stress, smoking, high body mass, physical activity **Time:** 1970 to 1973. **Measurement of exposure:** Psychological stress was assessed by using 1 question on self-perceived stress and rated from 1 through 6 Physical leisure time activity was coded as: (1) sedentary, (2) moderate, or (3) strenuous and regular. Socioeconomic class was coded according to the Swedish socioeconomic classification system: (1) unskilled and semiskilled workers, (2) skilled workers, (3) foremen in industrial production and assistant nonmanual employees, (4) intermediate nonmanual employees, and (5) employed and self-employed professionals, higher civil servants, and executives
Outcomes at 55 years or over
Outcomes: Stroke **Outcome measurement**: End points of first-ever stroke in participants free of previous stroke were registered from several sources. **Time:** 1998

Analysis
Analysis strategy: Multiple Cox regression analyses **Confounders:** Not reported. Paper says model adjusted for all other factors **Reported limitations:** Not reported **Source of funding:** Bank of Sweden Tercentenary Fund, the Swedish Research Council, and the Swedish Heart Lung Foundation
Results, limitations, source of funding
Number: 1019 **Effect estimates:** Hazard Ratio (95% CI) Systolic blood pressure quintile 5 vs quintile 2.04 (1.61–2.59) HypMed 1.56 (1.21–2.02) Previous transient ischemic attacks 1.74 (1.14–2.64) Atrial fibrillation 3.43 (1.60–7.32) Stroke in either parent 1.09 (0.93–1.28) History of diabetes 3.21 (2.19–4.72) Coronary events in parent 1.07 (0.90–1.27) Smoking 1.33 (1.15–1.53) History of chest pain 1.24 (1.01–1.52) Psychological stress 1.25 (1.03–1.51) BMI quintile 5 vs quintile 1.26 (1.00–1.60) Low physical activity 1.11 (0.90–1.36) S-Chol quintile 5 vs quintile 1.08 (0.86–1.35) Social class low, 5 vs 1.02 (0.79–1.31) Age 1.08 (1.04–1.11) **Significant trends:** Age, diabetes, and high blood pressure were independently associated with increased risk of stroke

Authors: He K, Hu FB, Colditz GA, Manson JE, Willett WC, Liu S **Year:** 2004 **Citation:** Journal of Obesity and Related Metabolic Disorders 28(12): 1569-74 **Country of study:** USA **Aim of study:** To determine the association between intake of fruit and vegetables and the risk of obesity and long-term weight gain among middle-aged women **Study design:** Longitudinal **Quality score: (++, + or -):** +
Source population
121,700 female registered nurses ages 30-55 years from 11 US states responded to a questionnaire in 1976
Study (eligible and selected) population
Study population: Analysis restricted to **74,063** women **Follow-up:** 12 years

Exclusion: Women with:

i) History of cardiovascular disease, cancer, diabetes
ii) Incomplete or implausible information

Attrition: -

Exposures at midlife

A semi-quantitative food frequency questionnaire (FFQ) was used to assess the intake of standard units of *fruit and vegetable* items in the previous year (responses ranging from 'never' to 'six or more times per day'); these were subsequently converted to average daily intake of food items for each participant

Changes in fruit and vegetable intake between 1984 (baseline) and 1994 were also computed

Certain vegetables were grouped as cruciferous vegetables; dark and yellow vegetables; green leafy vegetables; other vegetables

Validity of FFQ established with correlation coefficients ranging from 0.69-0.8

Vegetable/fruit consumption was divided into quintiles with the first quintile indicating the largest decrease in intake and the fifth quintile the largest increase in intake during follow-up

Median values of quintiles of changes in fruit and vegetable intake were used in linear trend tests

Outcomes at 55 years or over

Self-reported body weight captured through questionnaire every other year; when self-reported weight was compared with measured weight, correlation was 0.96

Obesity defined as BMI >=30 kg/m2 and major weight gain as weight gain of 25 kg or more during follow-up

Analysis

Analysis strategy: Logistic regression was used to assess the association between changes in fruit and vegetable intake (divided into quintiles) during follow-up. General linear models with least-square means were used to estimate the mean difference of changes in BMI during follow-up

Confounders: Age, year of follow-up, change in physical activity, change in cigarette smoking status, changes in alcohol consumption and caffeine intake, change in use of HRT, changes in energy-adjusted intake of saturated fat, polyunsaturated fat, monounsaturated fat, trans-unsaturated fatty acid, protein, and total energy and baseline BMI

Limitations:

1. If participants perceive themselves to be overweight, eating habits may change in accordance with dietary recommendations of past decades; this may result in an underestimation of association between intake of fruits and vegetables and weight gain
2. Issues of reliability due to self-reported weight information
3. Residual confounding

Source of funding: National Institutes of Health

Results, limitations, source of funding

- Of 65,294 non-obese participants at baseline, 6,530 became obese during follow-up
- 669 women reported major weight gain during follow-up
- Women with the largest increase in intake of fruits (median change=+1.86 servings/day) had the lowest risk for obesity compared to women with the largest decrease in intake of fruits (OR=0.76, [0.68, 0.84]; trend test p-value: 0.0007)
- Women with the largest increase in intake of vegetables (median change=+2.80 servings/day) had

the lowest risk for obesity compared to women with the largest decrease in intake of vegetables (OR=0.84, [0.75, 0.93]; trend test p-value= 0.0002)

- Women with the largest increase in intake of fruits and vegetables combined had the lowest risk for obesity and major weight gain compared to women with the largest decrease in intake of fruits and vegetables combined
(OR=0.76, [0.69, 0.86], trend test p-value<0.0001; and OR=0.72, [0.55, 0.93], trend test – value=0.01, respectively)
- There appeared to be a decreasing trend in risk for obesity with increasing intake of vegetables (trend test p-value: 0.0002); same observation noted for major weight gain in relation to fruits and vegetables combined (trend test p-value: 0.01)
- **Baseline BMI stratification:** Among overweight women, those reporting the greatest change in fruit and vegetable intake gained 0.76 kg less weight than women reporting the largest decrease in fruit and vegetable intake (among normal weight women at baseline, a change of 0.52 kg was observed)
- **Stratification by chronic disease presence:** Among women with incident chronic disease (e.g. cancer, CVD, diabetes), those reporting the largest increase in intake of fruits and vegetables gained 0.77 kg less weight than did women with the largest decrease in intake (among women without chronic diseases, a difference of 0.57 kg was observed)

Authors: Hodge A, Almeida OP, English DR, Giles GG, Flicker L

Year: 2013

Citation: International Psychogeriatrics 25(3): 456-466

Country of study: Australia

Aim of study: Investigate association between diet and psychological distress as a marker for depression

Study design: Cohort study

Quality score: (++, + or -): +

Source population

Number of people: 41,51

Demographics: Not reported

Study (eligible and selected) population

Number of people: 8,660

Characteristics:

K10 at follow-up

<u><20:</u> Age at baseline (years) 59.1 (5.4); Age at follow-up (years) 70.5 (5.7); Dietary energy (mJ) 9.4 (3.0); Female 61.8; At least some tertiary education 30.2; Top SEIFA quintile 32.9; Physically active 37.8; Current smoker 6.4

≥20: Age at baseline (years) 59.1 (5.6); Age at follow-up (years) 70.8 (6.0); Dietary energy (mJ) 9.5 (3.2); Female 72.1; At least some tertiary education 21.3; Top SEIFA quintile 28.4; Physically active 35.2; Current smoker 10.1

Location: Melbourne, Australia

Recruitment strategy: Electoral rolls, advertisements, and community announcements in local media

Length of follow-up: <20 Period of follow-up (years) 11.4 (1.3). ≥20 Period of follow-up (years) 11.6 (1.3)

Response rate and loss to follow-up: Italian-born <60%; Greek born <50%; Australian born 80%

Eligible population: Healthy men and women born in Australia and aged 50–69 years **Excluded populations:** Those who were taking medication for anxiety or depression, did have extreme dietary energy intakes (i.e. in the upper or lower 1% of the sex-specific distribution), and who did have health conditions, such as angina, diabetes, cancer, coronary artery disease, or stroke at baseline
Exposures at midlife
Relevant exposures: Diet (alcohol was included in the dietary indices) **Time:** 1990 and 1994 **Measurement of exposure:** 121-item food frequency questionnaire
Outcomes at 55 years or over
Outcomes: Psychological distress **Outcome measurement:** The K10 has 10 questions regarding symptoms experienced during the last 30 days; each item has 5 possible responses from "all the time" to "never," scored from 5 to 1, so the total score has a minimum of 10 and maximum of 50, with 50 implying severe psychological distress **Time:** 2003–2007
Analysis
Analysis strategy: Logistic regression **Confounders:** Physical activity, smoking status, alcohol use, education, history of arthritis, asthma, kidney stones or gallstones, dietary energy intake, and Socio-Economic Indexes for Areas
Results, limitations, source of funding
Number: Not reported **Effect estimates:** **Associations OR (95%CI) between quintiles of the modified Mediterranean-style pattern and ADP at baseline and psychological distress according to K10 score at follow-up** Modified Mediterranean-style pattern 0.98 (0.92–1.04) 1 1.00 2 0.96 (0.78–1.20) 3 0.92 (0.73–1.16) 4 0.90 (0.70–1.16) 5 0.92 (0.69–1.24) Austrailan Dietry Pattern 0.94 (0.87–1.01) 1 1.00 2 0.64 (0.43–0.95) 3 0.60 (0.41–0.88) 4 0.51 (0.34–0.75) 5 0.61 (0.40–0.91) **Significant trends:** Observed an inverse association between the Mediterranean-style diet at baseline and psychological distress at follow-up. A Mediterranean-style diet was associated with less psychological distress, possibly through provision of a healthy nutrient profile.

Limitations:

Author:

1. Did not assess psychological distress at baseline.
2. Participants who completed the K10 at follow-up were generally healthier than those who did not.
3. Diet relying on self-report.
4. Dietary change over time.
5. K10 does not necessarily yield specific psychiatric diagnoses

Reviewer: Low response rates from non-Australia born

Source of funding: A. Hodge was funded by the National Health and Medical Research Council (NHMRC) (grant 520316). This work was funded by VicHealth, the Cancer Council Victoria, and the National Health and Medical Research Council (grant 209057).

Authors: Holmberg AH, Johnell O, Nilsson PM, Nilsson J, Berglund G, Akesson K

Year: 2006

Citation: Osteoporosis International 17(7): 1065-77

Country of study: Sweden

Aim of study: To investigate the risk factors for fractures among men and women in middle age

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

72% of invited population recruited for Malmo Preventive Project

22,444 men ages 27-61 years and 10,902 women ages 28-58 years recruited during 1974-84 and 1977-92, respectively

Mean response rate to core questions of baseline questionnaire was 98% for women and 72% for men, and approximately 100% for questions added during recruitment period

Study (eligible and selected) population

Regression analysis restricted to **11** women and **10** men. Women and men had 11-year and 16-year follow-up, respectively.

Sociodemographics: Baseline mean age of 44 years for men and 48 years for women

Follow-up: Men and women followed up for average of 19 and 15 years, respectively (men: 1974-1984 until 1999; women: 1977-1992 until 1999)

Exclusion:

i) Missing data for 6,368 men
ii) High-energy fractures and fractures caused by cancer or other bone diseases

Attrition: -

Exposures at midlife

Self-reported smoking behaviour

Outcomes at 55 years or over

Incident low-energy fractures and mortality data was obtained through data linkage with hospital medical and radiological files using personal identification numbers

Fractures were categorised as those of the forearm, vertebral, proximal humerus, or ankle Outcomes restricted to fractures that were classified as *low-energy* or those resulting from falling from standing height or less (high-energy fractures or those caused by high-energy trauma were included in the non-fracture population) Individuals were still classified under low-energy fracture even if they had previous or subsequent high-energy fractures The first fracture of each fracture type was assessed
Analysis
Analysis strategy: Cox proportional hazard regression was used to assess risk factors for fragility fracture in middle age **Confounders: A**ge, height, weight, >10 kg weight gain since age 30, skinfold, forced vital capacity, SBP, DBP, resting pulse, diabetes, triglycerides, cholesterol, y-glutamyl transferase, serum phosphate, serum creatinine, serum uric acid, blood haemoglobin, sedimentation rate, sick leave at present, chest pressure, poor self-rated health, poor appetite, premature awakening, hospitalization for mental disorder, physical activity, HRT, history of previous fracture
Results, limitations, source of funding
• 1,257 out of 1,292 women and 1,262 out of 1,505 men were affected by incident low-energy fractures • Among women and men, the total number of low-energy fracture were: 622 and 330 for forearm, 155 and 123 for proximal humerus, 160 and 168 were vertebral, 233 and 259 ankle, and 141 and 174 hip • Smoking was more common among men with vertebral, proximal humerus, and hip fractures • Among women, smokers had a higher risk for vertebral fractures (RR=1.96, [1.47, 2.64]) than non-smokers • Among men, smokers had a greater risk for low energy fractures (RR=1.25, [1.11, 1.39]), vertebral fractures (RR=1.85, [1.41, 2.42]), proximal humerus fractures (RR=1.58, [1.08, 2.33]), and hip fractures (RR=2.14, [1.51, 3.01]) than non-smokers **Limitations:** 1. Healthy volunteer effect: participants may have fewer fractures than non-participants 2. Incomplete data sets **3.** Residual confounding **Source of funding:** The Swedish Research Council Project, The Kock Foundation, The Herman Järnhardt Foundation, Malmö University Hospital Funds, and regional research grants supported this study

Authors: Holme I, Tonstad S, Sogaard AJ, Larsen PG, Haheim LL **Year:** 2007 **Citation:** BMC Public Health 12(7): 154 **Country of study:** Norway **Aim of study:** To assess association between smoking or physical activity and metabolic syndrome **Study design:** Longitudinal **Quality score: (++, + or -):** +
Source population
16,209 men ages 40-49 years, born in 1923-32 and living in Oslo were invited and attended screening

examination (represented 63% of this age group)
Study (eligible and selected) population
Men living in Oslo in 2000-01 were surveyed and men originally invited to participate in study in 1972-73 and also living in Oslo or Akershus were invited for re-examination Of 10,328 eligible participants, 6410 (62%) men attended the baseline and follow-up Analysis restricted to **6382** men without baseline diabetes and with blood pressure measurements at baseline and follow-up **Follow-up:** 28 years **Exclusion:** Men who: i) Were dead or had emigrated (n=1655) ii) Lived outside Oslo and Akershus (n=1278) iii) Had unknown addresses (n=2944) **Attrition: P**articipants who answered question on LTPA smoked less and had a greater level of education. Plus participants who attended in 2000 had lower body weight, height, systolic and diastolic blood pressure, total cholesterol, triglycerides and glucose values, and smoked less at baseline than non-participants
Exposures at midlife
Self-reported physical activity at work and leisure, and smoking habits measured in 1972-73 Leisure-time physical activity (LTPA) categorized as light (e.g., reading, watching TV); moderate (e.g., walking, bicycling – totally at least 4 hours/week); moderately vigorous (e.g., exercise, sports, heavy gardening – totalling at least 4 hours/week); vigorous (e.g., hard training several times/week) Reliability and validity of LTPA question has been established
Outcomes at 55 years or over
At baseline, physical measurements, blood pressure, and a blood sample were taken. Metabolic syndrome was defined as presence of at least three out of the following five criteria: a. Triglycerides >=1.7 mmol/l adjusted for the last meal b. Glucose >= 6.1 mmol/l adjusted for the last meal c. BMI >=30 kg/m2, d. Blood pressure >= 135/85 mmHg, and e. HDL cholesterol <1.03 mmol/l Smoking was categorised into 'never', 'previous', and 'current' smoker groups Diabetes definition included self-reported diabetes, antidiabetic medication, insulin use or non-fasting glucose >=11.1 mmol/l
Analysis
Analysis strategy: Logistic regression was used to assess association between smoking or physical activity and metabolic syndrome or diabetes **Confounders:** Age, education
Results, limitations, source of funding
• The odds of metabolic syndrome were higher for current smokers compared to those who never smoked (OR=1.29, [1.11, 1.51]) • The odds of metabolic syndrome were lower for those who reported vigorous, moderately

vigorous, or moderate levels of LTPA in comparison with those who reported sedentary/light levels (OR=0.46, [0.28, 0.74]; OR=0.65, [0.54, 0.80]; OR=0.83, [0.71, 0.98])
- The odds of diabetes were lower for those who reported vigorous, moderately vigorous, or moderate levels of LTPA in comparison with those who reported sedentary/light levels (OR=0.28, [0.11, 0.71]; OR=0.68, [0.52, 0.91]; OR=0.75, [0.60, 0.94])

Limitations:

1. If diseases started before year 2000, then biological, anthropometric indices and lifestyle factors may have been affected
2. Imperfect measurement/definition of metabolic syndrome leading to possible underestimation of its prevalence
3. Participants with metabolic syndrome at baseline were not excluded
4. Residual confounding, such as, dietary habits and alcohol consumption

Source of Funding: Norwegian Council for Cardiovascular Diseases of the Norwegian National Association for Public Health

Authors: Holtermann A, Mortensen OS, Burr H, Søgaard K, Gyntelberg F, Suadicani P

Year: 2009

Citation: Scandinavian Journal of Work, Environment and Health 35(6): 466-74

Country of study: Denmark

Aim of study: To determine the association between physical activity and risk of ischemic heart disease and all-cause mortality

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

5249 Copenhagen male employees ages 40-59 years were invited and agreed to participate (87% response rate) and undergo an interview, a clinical examination, and complete a questionnaire in 1970-71

Study (eligible and selected) population

Analysis restricted to **4952** men

Follow-up: From 1970-71 to 2001

Exclusion: Men with:

i) History of myocardial infarction (n=74), angina pectoris (n=165), intermittent claudication (n=105) at baseline
ii) Missing answers (n=9)
iii) Men who had emigrated during follow-up (n=14)

Attrition: -

Exposures at midlife

<u>Physical activity at work:</u> Was assessed using questionnaire and participants were classified as: a) ‘low’: mainly sedentary/not walking around much at workplace, b) ‘moderate’: walking around quite a bit but not having to carry heavy items, c) ‘high’: walking around most of the time or undertaking heavy/strenuous physical work

Strenuous work was assessed with answer options of ‘seldom or never’, ‘occasionally’, and ‘often’

A dichotomous variable was created to assess presence of physically demanding work

Another variable combined information on physical activity and strenuous work to assess physical work demands, with possible scores ranging from 2-6 (higher scores representing higher demands)

Physical activity during leisure time: Self-reported physical activity level during leisure time categorized as 'low' (mainly sedentary), 'moderate' (light activities for at least 4 hours/week), 'high' (active for at least 3 hours/week or taking part in high intensity activities several times/week)

Outcomes at 55 years or over

IHD mortality diagnoses between 1970-71 and 2001 obtained from national registers

Analysis

Analysis strategy: Cox proportional hazard regression used to assess influence of physical activity on ischemic heart disease (IHD) and all-cause mortality

Confounders: Age, BMI, SBP, DBP, treatment of diabetes or hypertension, alcohol use, smoking, social class

Results, limitations, source of funding

- 591 died from IHD during study period

Among men with moderate physical work demands:

- The risk of IHD mortality was significantly lower for those with a high level of physical activity during leisure time (HR=0.37, [0.19, 0.70]) compared to those with a low level of physical activity during leisure
- The risk for all-cause mortality was significantly lower for those with a moderate and high level of physical activity during leisure time (HR=0.82, [0.71, 0.94]; and HR=0.64, [0.50, 0.81], respectively) compared to those with a low level of physical activity during leisure
- The risk for all-cause mortality was significantly lower for those with moderate and high (combined) physical activity during leisure time (HR=0.80, [0.70, 0.92]) compared to those with low levels of physical activity reported during leisure time

Limitations:

1. Self-reported information resulting in possible misclassification
2. Misclassification of exposure due to lack of continuous exposure data and repeated measures of exposure during follow-up
3. Unknown if results also apply to women, people of different races, ages, with varying levels of physical fitness, or from rural areas (generalizability issues)

Source of funding: None reported

Authors: Holtzman RE, Rebok GW, Saczynski JS, Kouzis AC, Wilcox Doyle K, Eaton WW

Year: 2004

Citation: The Journals of Gerontology Series B Psychological Sciences and Social Sciences 59(6):278-84

Country of study: USA

Aim of study: To determine the influence of social networks on cognitive change

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

4,238 participants were recruited for wave 1 in 1981 using probability sampling methods. Of 4,238 people, 3,481 were interviewed at wave 1 and 1,920 (73% of survivors) were re-interviewed in 1993-96 at wave 3
Study (eligible and selected) population
Analysis restricted to **354** out of 881 participants with age >= 50 years and MMSE >=28 at wave 1 **Exclusion:** i) 107 with missing longitudinal data ii) 88 had missing MMSE data at wave 3 iii) 5.4% of 354 people with missing cross-sectional data at wave 3 iv) People with MMSE <28 **Attrition:** 420 lost to follow-up. Non-assessed participants were older, had fewer years of formal education, were less likely to be female, and had lower baseline MMSE scores compared to assessed participants
Exposures at midlife
Social network included network size, frequency of contact, and emotional support Network size at waves 1 and 3: The number of relatives, family members, friends and neighbours with whom the respondent kept in touch with via phone or visits, with corresponding scores assigned that were subsequently summed (range of possible scores of 0-10) Frequency of contact at wave 3: Frequency of contact by phone or getting together with relatives or family and friends or neighbours with the range of possible scores of 0-10 Emotional support at wave 3: Support from partners, relatives, and friends was assessed; scores were subsequently assigned and summed with a possible range of 0-27
Outcomes at 55 years or over
Cognitive change between wave 3 and wave 1 was assessed using MMSE
Analysis
Analysis strategy: Simultaneous linear or logistic regression was used to determine whether interactions in larger networks at wave 1 are associated with MMSE change between wave 1 and wave 3 **Confounders:** Cerebrovascular disease or risk, age, education, depression, race, gender, physical disability, alcohol use disorder
Results, limitations, source of funding
• Mean MMSE at wave 3 was 26.5 • A linear effect was observed for baseline network size (p=0.006, effect size=0.06); also, less increase - more decrease in network size is associated with decreased wave 3 MMSE (p=0.03, effect size=-0.06) • Top tertiles of interpersonal activity and emotional support (paired as categorical variables) were significantly related to MMSE scores (activity betas=0.13 and 0.12, p <=0.04; support betas 0.16 and 0.17, p<=0.01) • More frequent contact in larger networks and higher levels of emotional support positively influence cognitive change **Limitations:**

1. Cannot assess whether decline in MMSE is due to regression to the mean
2. If follow-up period is too short, directionality confound may exist (particularly given the long prodromal period before clinical symptoms in Alzheimer's begin to manifest)
3. Generalizability may be restricted as assessed participants were healthier, better educated, younger, and with larger networks than non-assessed individuals

Source of funding: National Institutes of Mental Health

Authors: Hu G, Qiao Q, Silventoinen K, Eriksson JG, Jousilahti P, Lindström J… Tuomilehto J

Year: 2003

Citation: Diabetologia 46(3): 322-9

Country of study: Finland

Aim of study: Examine the relationship of occupational, commuting and leisure-time physical activity with the incidence of Type 2 diabetes

Study design: Prospective cohort

Quality score: (++, + or -): +

Source population

Number of people: 21,630

Demographics: Not reported

Study (eligible and selected) population

Number of people: 6898 men and 7392 women

Characteristics:

Men

Physical activity
Light
Participants n 2688
Age at baseline 50.9±8.8
BMI 27.0±3.9
Education 10.2±4.5
Obesity 20.3
Smoking 31.8

Moderate
Participants n 1563
Age at baseline 46.5±7.9
BMI 26.9±3.7
Education 10.1±3.7
Obesity 18.1
Smoking 23.6

Active
Participants n 2647
Age at baseline 47.5±8.0
BMI 26.9±3.6
Education 7.8±2.2
Obesity 17.8
Smoking 33.6

p value for trend
Age at baseline <0.001

BMI >0.2
Education <0.001
Obesity 0.056
Smoking <0.001

Women
Physical activity
Light
Participants n 3255
Age at baseline 51.0±9.2
BMI 26.5±5.1
Education 9.8±3.9
Obesity 21.6
Smoking 13.6

Moderate
Participants n 2357
Age at baseline 47.2±8.0
BMI 26.1±4.2
Education 10.1±3.8
Obesity 16.0
Smoking 12.9

Active
Participants n 1780
Age at baseline 47.9±7.9
BMI 27.0±4.7
Education 8.4±2.6
Obesity 24.2
Smoking12.9

p value for trend
Age at baseline <0.001
BMI <0.001
Education <0.001
Obesity <0.001
Smoking >0.2

Location: North Karelia and Kuopio, and the Turku-Loimaa region in south-western Finland

Recruitment strategy: Not reported

Length of follow-up: Mean follow-up of 12 years

Response rate and loss to follow-up: The participation rate varied by year from 74% to 88%

Eligible population: General population 25 to 64 years of age

Excluded populations: Subjects diagnosed with coronary heart disease or stroke (n=590), subjects with known diabetes (n=435) at baseline, and subjects with incomplete data on all required factors or on physical activity (n=1355)

Exposures at midlife

Relevant exposures: Physical activity and smoking habits

Time: Through the end of 1998 or until death

Measurement of exposure: Occupational physical activity according to the following three categories: (i) ‘light’ was physically very easy, sitting office work, e.g. secretary; (ii) ‘moderate’ was work including standing and walking, e.g. store assistant; (iii) ‘active’ was work including walking and lifting, or heavy manual labour. subjects asked whether they walked, rode a bicycle, or used motorized transportation to and from work as well as the daily duration of this activity

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: From the National Hospital Discharge Register and the National Social Insurance Institution's Register

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, study year, education, systolic blood pressure, smoking, the other two types of physical activity, BMI, and sex

Results, limitations, source of funding

Number: 373

Effect estimates:

Occupational physical activity
No. of new cases Person- years Adjusted hazards ratios (95% confidence intervals)

Men
Light 97 29216 1.00
Moderate 32 18874 0.67 (0.44–1.01)
Active 71 32955 0.73 (0.52–1.02)
p value for trend 0.075

Women
Light 102 38034 1.00
Moderate 31 29310 0.72 (0.46–1.12)
Active 40 22740 0.78 (0.52–1.18)
p value for trend 0.267

Men and women combined
Light 199 67250 1.00
Moderate 63 48184 0.70 (0.52–0.96)
Active 111 55695 0.74 (0.57–0.95)
p value for trend 0.020

Commuting physical activity
Adjusted hazards ratios (95% confidence intervals)

Men
0 min 1.00
1–29 min 1.00 (0.71–1.42)
≥30 min 0.75 (0.46–1.23)
p value for trend 0.501

Women
0 min 1.00
1–29 min 0.94 (0.63–1.42)
≥30 min 0.57 (0.34–0.96)
p value for trend 0.105

Men and women combined
0 min 1.00
1–29 min 0.96 (0.74–1.25)
≥30 min 0.64 (0.45–0.92)
p value for trend 0.048

Leisure-time physical activity
Adjusted hazards ratios (95% confidence intervals)

Men
Low 1.00
Moderate 0.78 (0.57–1.06)
High 0.84 (0.52–1.37)
p value for trend 0.282

Women
Low 1.00
Moderate 0.81 (0.58–1.15)
High 0.85 (0.43–1.66)
p value for trend 0.49

Men and women combined
Low 1.00
Moderate 0.81 (0.64–1.02)
High 0.84 (0.57–1.25)
p value for trend 0.186

Significant trends: The multivariate-adjusted hazards ratios of diabetes with none, 1 to 29, and more than 30 min of walking or cycling to and from work were 1.00, 0.96, and 0.64 (p=0.048 for trend). The multivariate-adjusted hazards ratios of diabetes for low, moderate, high levels of leisure-time physical activity were 1.00, 0.67, and 0.61 (p=0.001 for trend); after additional adjustment for BMI, the hazards ratio was no longer significant

Limitations:

1. Self-report of physical activity.
2. Did not carry out a glucose tolerance test in the baseline and follow-up

Source of funding: Finnish Academy (grants 38387, 46558, 52342, 53585, 76502, 77618)

Authors: Hu G, Bidel S, Jousilahti P, Antikainen R, Tuomilehto J

Year: 2007

Citation: Movement Disorders 22(15): 2242-2248

Country of study: Finland

Aim of study: Examine the association of coffee and tea consumption with the risk of incident Parkinson’s disease

Study design: Independent cross-sectional population surveys

Quality score: (++, + or -): +

Source population

Number of people: 29,890

Demographics: Not reported

Study (eligible and selected) population

Number of people: 29,335

Characteristics:

Coffee consumption

Men
0
Participants (n) 891

Age (yr) 44.8 (13.0)
Body mass index (kg/m2) 26.2 (3.9)
Education (yr) 10.9 (4.4)
Low leisure time physical activity (%) 26.4
Tea drinker (%) 66.0
Current smoker (%) 18.3
Alcohol drinker (%) 56.5

1–4
Participants (n) 5,583
Age (yr) 47.6 (12.8)
Body mass index (kg/m2) 26.6 (3.8)
Education (yr) 10.6 (4.1)
Low leisure time physical activity (%) 23.2
Tea drinker (%) 50.3
Current smoker (%) 26.9
Alcohol drinker (%) 67.5

5
Participants (n) 7,819
Age (yr) 45.4 (11.4)
Body mass index (kg/m2) 26.8 (3.9)
Education (yr) 9.7 (3.7)
Low leisure time physical activity (%) 29.5
Tea drinker (%) 19.7
Current smoker (%) 46.3
Alcohol drinker (%) 61.2

P-trend
Age (yr) <:0.001
Body mass index (kg/m2) <:0.001
Education (yr) <:0.001
Low leisure time physical activity (%) <:0.001
Tea drinker (%) <:0.001
Current smoker (%) <:0.001
Alcohol drinker (%) <:0.001

Women
0
Participants (n) 1,022
Age (yr) 40.4 (12.8)
Body mass index (kg/m2) 25.6 (4.8)
Education (yr) 11.1 (4.1)
Low leisure time physical activity (%) 30.7
Tea drinker (%) 70.8
Current smoker (%) 11.2
Alcohol drinker (%) 37.3

1–4
Participants (n) 7,439
Age (yr) 46.4 (12.4)
Body mass index (kg/m2) 25.8 (4.9)
Education (yr) 11.0 (4.0)
Low leisure time physical activity (%) 29.0
Tea drinker (%) 50.3
Current smoker (%) 14.7
Alcohol drinker (%) 44.7

5
Participants (n) 6,581
Age (yr) 45.4 (10.8)

Body mass index (kg/m2) 26.3 (4.9)
Education (yr) 10.1 (3.6)
Low leisure time physical activity (%) 34.6
Tea drinker (%) 22.5
Current smoker (%) 27.3
Alcohol drinker (%) 39.4

P trend
Age (yr) <:0.001
Body mass index (kg/m2) <:0.001
Education (yr) <:0.001
Low leisure time physical activity (%) <:0.001
Tea drinker (%) <:0.001
Current smoker (%) <:0.001
Alcohol drinker (%) <:0.001

Exposures at midlife

Relevant exposures: Physical activity, smoking habits, and alcohol, coffee and tea consumption, leisure-time physical activity

Time: 1982, 1987, 1992, and 1997

Measurement of exposure: Self-administered questionnaire.

Leisure-time physical activity was classified into three categories: low, moderate, or high

Participants were classified as never, ex-, and current smokers. Current smokers then categorised according to the amount of cigarettes smoked daily

Participants were asked, "How many cups of coffee or tea do you drink per day?" Coffee consumption categorised: none, 1 to 4 cups, and 5 cups per day. Tea consumption was categorised: none, 1 to 2 cups, and 3 cups per day

Alcohol consumption was categorised: none, 1 to 100, >100 g per week.

Location: North Karelia and Kuopio, and the Turku-Loimaa region in south-western Finland

Recruitment strategy: Not reported

Length of follow-up: Mean follow-up of 12.9 years

Response rate and loss to follow-up: Participation rate varied by year from 74% to 88%

Eligible population: 25 to 74 years

Excluded populations: 91 subjects due to prevalent PD at the baseline and 464 subjects due to incomplete data. Exclusion of subjects with stroke or those who used neuroleptic drugs

Outcomes at 55 years or over

Outcomes: Parkinson's disease

Outcome measurement: National Social Insurance Institution's Register on special reimbursement for drug costs

Time: 1964 through December 31, 2002

Analysis

Analysis strategy: Cox proportional hazards models

Confounders: Age, body mass index, systolic blood pressure, total cholesterol, education, leisure-time physical activity, smoking, alcohol and tea consumption, and history of diabetes

Results, limitations, source of funding
Number: 102 men and 98 women **Effect estimates:** HR (CI 95%) **Volume of coffee consumption** <u>Men</u> 0 1.00 1–4 0.55 (0.26–1.15) 5 0.41 (0.19–0.88) P-trend 0.063 <u>Women</u> 0 1.00 1–4 0.50 (0.22–1.12) 5 0.39 (0.17–0.89) P trend 0.073 <u>Men and Women</u> 0 1.00 1-4 0.53 (0.31–0.92) 5 0.40 (0.23–0.71) P trend 0.005 **Volume of tea consumption** <u>Men</u> 0 1.00 1–4 1.06 (0.67–1.69) 5 0.55 (0.24–1.25) P-trend 0.31 <u>Women</u> 0 1.00 1–4 0.97 (0.62–1.52) 5 0.21 (0.05–0.90) P trend 0.11 <u>Men and Women</u> 0 1.00 1-4 1.02 (0.74–1.41) 5 0.41 (0.20–0.83) P trend 0.038 **Significant trends:** Coffee drinking is associated with a lower risk of PD. More tea drinking is associated with a lower risk of PD **Limitations:** 1. Self-report for data on coffee drinking 2. No data on possible changes of coffee drinking during the follow-up. 3. Lack of information about other caffeine sources in participants' diet **Source of funding**: The Finnish Parkinson Foundation and Special Research Funds of the Social Welfare and Health Board, City of Oulu

Authors: Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P **Year:** 2005 **Citation:** International Journal of Obesity 29: 894-902 **Country of study:** Finland

Aim of study: Examine the association of physical activity and body mass index, and their combined effect, with the risk of total, cardiovascular disease and cancer mortality

Study design: Prospective follow-up study

Quality score: (++, + or -): +

Source population

Number of people: 52,058

Demographics: Not reported

Study (eligible and selected) population

Number of people: 47,212

Characteristics:

Physical activity (men)

Low
Number of participants 2132
Age (y) 45.6
BMI (kg/m2) 26.9
Total cholesterol (mmol/l) 6.3
Education level (y) 9.5
Current smoking (%) 52.3
BMI (%)
<18.5 0.9
18.5–24.9 35.5
25–29.9 40.6
>30.0 23.0

Moderate
Number of participants 9659
Age (y) 44.3
BMI (kg/m2) 26.3
Total cholesterol (mmol/l) 6.2
Education level (y) 9.5
Current smoking (%) 43.4
BMI (%)
<18.5 0.3
18.5–24.9 39.2
25–29.9 45.9
>30.0 14.6

High
Number of participants 10 737
Age (y) 41.3
BMI (kg/m2) 25.9
Total cholesterol (mmol/l) 6.2
Education level (y) 9.2
Current smoking (%) 41.2
BMI (%)
<18.5 0.2
18.5–24.9 42.7
25–29.9 46.1
>30.0 11.0

Physical activity (women)

Low	
Number of participants	3613
Age (y)	45.7
BMI (kg/m2)	27.1
Total cholesterol (mmol/l)	6.2
Education level (y)	9.3
Current smoking (%)	21.5
BMI (%)	
<18.5	2.0
18.5–24.9	39.1
25–29.9	31.8
>30.0	27.1
Moderate	
Number of participants	11 782
Age (y)	44.2
BMI (kg/m2)	25.9
Total cholesterol (mmol/l)	6.1
Education level (y)	9.5
Current smoking (%)	17.9
BMI (%)	
<18.5	1.2
18.5–24.9	47.4
25–29.9	33.7
>30.0	17.7
High	
Number of participants	9289
Age (y)	42.4
BMI (kg/m2)	25.3
Total cholesterol (mmol/l)	6.0
Education level (y)	10.0
Current smoking (%)	16.1
BMI (%)	
<18.5	1.1
18.5–24.9	52.2
25–29.9	33.5
>30.0	13.2

Exposures at midlife

Relevant exposures: Physical activity and smoking

Time: 1972, 1977, 1982, 1987, 1992 and 1997

Measurement of exposure: Self-administered questionnaire. Questions on physical activity included both occupational and leisure time physical activity

Occupational physical activity three categories: ‘light’; ‘moderate’; and ‘active’

Participants were classified as never, ex-, and current smokers. Current smokers then categorised according to the amount of cigarettes smoked daily

Location: Kuopio and North Karelia provinces, Turku-Loimaa, Oulu

Recruitment strategy: Random selection

Length of follow-up: Mean follow-up of 17.7 y

Response rate and loss to follow-up: Participation rate varied by year from 74 to 88%

Eligible population: Born between 1913 and 1947

Excluded populations: Subjects previously diagnosed with coronary heart disease (n=1252), stroke (n=423), heart failure (n=1732) and cancer (n=138) at baseline, and subjects with incomplete data on any required factors (n=1301)

Outcomes at 55 years or over

Outcomes: Cardiovascular disease and cancer mortality

Outcome measurement: Computerised register linkage.Mortality data was obtained from Statistics Finland.

Time: Until the end of 2001

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, study year, education, smoking, systolic blood pressure, total cholesterol, diabetes and physical activity or BMI

Results, limitations, source of funding

Number: 7394 deaths

Effect estimates:

Hazard ratios for total, cardiovascular and cancer mortality according to different levels of physical activity among Finnish men and women

Men
Total mortality
Low 1.00
Moderate 0.74 (0.68–0.81)
High 0.63 (0.58–0.70)
P-value for trend <0.001
Cardiovascular mortality
Low 1.00
Moderate 0.82 (0.72–0.93)
High 0.71 (0.62–0.82)
P-value for trend <0.001
Cancer mortality
Low 1.00
Moderate 0.83 (0.69–1.00)
High 0.79 (0.65–0.96)
P-value for trend 0.05

Women
Total mortality
Low 1.00
Moderate 0.64 (0.58–0.70)
High 0.58 (0.52–0.64)
P-value for trend <0.001
Cardiovascular mortality
Low 1.00
Moderate 0.62 (0.54–0.71)
High 0.55 (0.47–0.65)
P-value for trend <0.001
Cancer mortality
Low 1.00
Moderate 0.85 (0.71–1.01)
High 0.73 (0.60–0.88)
P-value for trend 0.005

Hazard ratios for total mortality according to different levels of BMI and smoking status among Finnish men and women

Never smoker
BMI
<18.5 1.39 (0.34–5.62)
18.5–24.9 1.00
25–29.9 1.03 (0.88–1.20)
>30.0 1.78 (1.47–2.15)
P-value for trend <0.001

Ex-smoker
BMI
<18.5 1.87 (0.59–5.92)
18.5–24.9 1.00
25–29.9 1.03 (0.88–1.21)
>30.0 1.48 (1.23–1.78)
P-value for trend <0.001

Current smoker
BMI
<18.5 3.17 (1.99–5.06)
18.5–24.9 1.00
25–29.9 0.98 (0.90–1.06)
>30.0 1.14 (1.01–1.28)
P-value for trend <0.001

Significant trends: Total mortality was increased both among lean and obese subjects. Statistically significant increased total mortality was observed among the obese men in all smoking categories. Regular physical activity and normal weight are both important indicators for a decreased risk of mortality from all causes, CVD and cancer.

Limitations:

1. Self-report of physical activity.
2. Changes to physical activity behaviours among the cohort members over time causes misclassification.
3. Standardised alcohol drinking data was not available across the survey.

Source of funding: Finnish Academy (grant numbers 46 558, 53 585, 204 274 and 205 657).

Authors: Hu G, Tuomilehto J, Silventoinen K, Barengo N, Jousilahti P

Year: 2004

Citation: European Heart Journal 25(24): 2212-9

Country of study: Finland

Aim of study: Assess joint associations of physical activity and different indicators of obesity with the risk of cardiovascular disease

Study design: Prospective follow-up study

Quality score: (++, + or -): +

Source population

Number of people: 20,547

Demographics: Not reported

Study (eligible and selected) population

Number of people: 18,892

Characteristics:

Baseline characteristics according to physical activity levels among the Finnish population by sex

<u>Physical activity (men)</u>

Low
Age (year) 47.9
Body mass index 27.3
Total cholesterol (mmol/l) 5.8
Education (year) 11.3
Current smoking (%) 44.6
Obesity (%) 26.7

Moderate
Age (year) 48.0
Body mass index 26.6
Total cholesterol (mmol/l) 5.7
Education (year) 11.3
Current smoking (%) 33.5
Obesity (%) 17.9

High
Age (year) 42.9
Body mass index 26.6
Total cholesterol (mmol/l) 5.7
Education (year) 10.3
Current smoking (%) 34.3
Obesity (%) 14.1

p-Value
Age (year) <0.001
Body mass index <0.001
Total cholesterol (mmol/l) 0.002
Education (year) <0.001
Current smoking (%) <0.001
Obesity (%) <0.001

<u>Physical activity (women)</u>

Low
Age (year) 46.7
Body mass index 27.0
Total cholesterol (mmol/l) 5.6
Education (year) 11.3
Current smoking (%) 25.4
Obesity (%) 28.5

Moderate
Age (year) 46.4
Body mass index 25.9
Total cholesterol (mmol/l) 5.6
Education (year) 11.3
Current smoking (%) 20.3
Obesity (%) 18.8

High
Age (year) 43.3
Body mass index 25.7
Total cholesterol (mmol/l) 5.6

Education (year) 11.2 Current smoking (%) 19.6 Obesity (%) 13.8 **p-Value** Age (year) <0.001 Body mass index <0.001 Total cholesterol (mmol/l) 0.4 Education (year) 0.04 Current smoking (%) <0.001 Obesity (%) <0.001
Exposures at midlife
Relevant exposures: Physical activity and smoking **Time:** 1972, 1977, 1982, 1987, 1992 and 1997 **Measurement of exposure:** Self-administered questionnaire. Questions on physical activity included both occupational and leisure time physical activity Occupational physical activity, three categories: 'light'; 'moderate'; and 'active' Participants were classified as never, ex-, and current smokers. Current smokers then categorised according to the amount of cigarettes smoked daily **Location:** Kuopio and North Karelia provinces, Turku-Loimaa, Oulu **Recruitment strategy:** Random sample, stratified by area, gender and 10-year age group **Length of follow-up:** Median follow-up time was 9.8 years **Response rate and loss to follow-up:** Participation rate varied by year from 74 to 88% **Eligible population:** Born between 1913 and 1947s **Excluded populations:** Previously diagnosed with coronary heart disease (CHD) (n = 672), stroke (n = 390) and heart failure (n = 408), incomplete data on any required factors (n=185)
Outcomes at 55 years or over
Outcomes: Cardiovascular disease and cancer mortality **Outcome measurement**: Finnish hospital discharge register for non-fatal outcomes (hospitalised myocardial infarction and stroke) and the mortality register by the Statistics Finland for fatal outcomes (cardiovascular death) **Time:** Until the end of 2001
Analysis
Analysis strategy: Cox proportional hazards model **Confounders:** Age, study year, education, smoking, systolic blood pressure, total and HDL cholesterol, diabetes at baseline, and body mass index
Results, limitations, source of funding
Number: 818 **Effect estimates:** Hazard ratios for risk of cardiovascular disease according to different levels of physical activity by sex <u>Men</u> Physical activity Low 1.00

Moderate 0.72 (0.57–0.91)
High 0.68 (0.52–0.88)
P trend 0.007

<u>Women</u>
Physical activity
Low 1.00
Moderate 0.73 (0.55–0.97)
High 0.64 (0.45–0.89)
P trend 0.02

Significant trends: Both regular physical activity and normal weight can reduce the risk of CVD

Limitations:

1. Self-report of physical activity.
2. Residual confounding.
3. Data on several risk factors, such as triglycerides and apolipoprotein B, are not available.

Source of funding: Finnish Academy (Grants 46558, 53585, 204274, and 205657).

Authors: Hughes TF, Andel R, Small BJ, Borenstein AR, Mortimer JA, Wolk A… Gatz M

Year: 2010

Citation: American Journal of Geriatric Psychiatry 18(5): 413-20

Country of study: Sweden

Aim of study: Examine the association between fruit and vegetable consumption in midlife and risk for all types of dementia and AD

Study design: Three population-based cohorts of like-sexed twin pairs

Quality score: (++, + or -): +

Source population

Number of people: 5,692

Demographics: Not reported

Study (eligible and selected) population

Number of people: 3052

Characteristics:

<u>No CHD event</u>
(n=2122)
Age (years) 55·7 (3·2)
Body-mass index (kg/m2) 26·2 (3·4)
Current smokers (number [%]) 573 (27%)

<u>CHD event</u>
(n=136)
Age (years) 56·34 (3·4)
Body-mass index (kg/m2) 27·0 (3·4)
Current smokers (number [%]) 52 (38%)

Location: UK

Recruitment strategy: Not reported. Parts registered with nine general medical practices

Length of follow-up: 11 years

Response rate and loss to follow-up: RR (77%)

Eligible population: Middle-aged men

Excluded populations: Women

Exposures at midlife

Relevant exposures: Smoking

Time: Not reported

Measurement of exposure: Smoking habit divided into groups: smokers (any man who had smoked at least one cigarette daily on average for a year or more), ex-smokers (those who had smoked less than one cigarette a day), and never-smokers

Outcomes at 55 years or over

Outcomes: Coronary heart disease

Outcome measurement: ECG

Time: Not reported

Analysis

Analysis strategy: Cox's proportional hazards model

Confounders: Practice and conventional risk factors by including age, BMI, cholesterol, triglyceride, fibrinogen, and systolic blood pressure

Results, limitations, source of funding

Number: 96 men had an acute myocardial infarction, 26 needed coronary artery surgery, and 14 had silent myocardial infarctions

Effect estimates:

Adjusted hazard ratio (95% CI)
Never-smokers 1.00

Ex-smokers
E3/E3 1.49 (0.93–2.37)
E2+ 0.47 (0.11–1•94)
E4+ 0.74 (0.35–1.55)

Smokers
E3/E3 1.47 (0.87–2.51)
E2+ 0.85 (0.30–2.43)
E4+ 2.79 (1.59–4.91

Significant trends: Smoking increases the risk of coronary heart disease in men of all genotypes but particularly in men carrying the E4 allele

Limitations: CIs for the risk estimates are large

Source of funding: British Medical Research Council, the US National Institute of Health (NHLBI 33014), and DuPont Pharma, Wilmington, USA. SEH, PJT, MB, and DMW are supported by the British Heart Foundation, and INMD is a Lister Institute fellow

Authors: Humphries SE, Talmud PJ, Hawe E, Bolla M, Day IN, Miller GJ

Year: 2001

Citation: Lancet 358: 115-19

Country of study: UK

Aim of study: Investigated whether the effect of smoking on coronary heart disease risk is affected by APOE genotype

Study design:

Quality score: (++, + or -): +

Source population

Number of people: 3984

Demographics: Not reported

Study (eligible and selected) population

Number of people: 3052

Characteristics

No CHD event
(n=2122)
Age (years) 55·7 (3·2)
Body-mass index (kg/m2) 26·2 (3·4)
Current smokers (number [%]) 573 (27%)

CHD event
(n=136)
Age (years) 56·34 (3·4)
Body-mass index (kg/m2) 27·0 (3·4)
Current smokers (number [%]) 52 (38%)

Location: UK

Recruitment strategy: Not reported. Patientss registered with nine general medical practices

Length of follow-up: 11 years

Response rate and loss to follow-up: RR (77%)

Eligible population: Middle-aged men

Excluded populations: Women

Exposures at midlife

Relevant exposures: Smoking

Time: Not reported

Measurement of exposure: Smoking habit divided into groups: smokers (any man who had smoked at least one cigarette daily on average for a year or more), ex-smokers (those who had smoked less than one cigarette a day), and never-smokers

Outcomes at 55 years or over

Outcomes: Coronary heart disease

Outcome measurement: ECG

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Practice and conventional risk factors by including age, BMI, cholesterol, triglyceride, fibrinogen, and systolic blood pressure

Results, limitations, source of funding

Number: 96 men had an acute myocardial infarction, 26 needed coronary artery surgery, and 14 had silent myocardial infarctions

Effect estimates:

Adjusted hazard ratio (95% CI)
Never-smokers 1.00

Ex-smokers
E3/E3 1.49 (0.93–2.37)
E2+ 0.47 (0.11–1•94)
E4+ 0.74 (0.35–1.55)

Smokers
E3/E3 1.47 (0.87–2.51)
E2+ 0.85 (0.30–2.43)
E4+ 2.79 (1.59–4.91)

Significant trends: Smoking increases the risk of coronary heart disease in men of all genotypes but particularly in men carrying the E4 allele

Limitations:

Reviewer: CIs for the risk estimates are large

Source of funding: British Medical Research Council, the US National Institute of Health (NHLBI 33014), and DuPont Pharma, Wilmington, USA. SEH, PJT, MB, and DMW are supported by the British Heart Foundation, and INMD is a Lister Institute fellow

Authors: Inoue M, Hanaoka T, Sasazuki S, Sobue T, Tsugane S; JPHC Study Group

Year: 2004

Citation: Preventive Medicine 38(5): 516-22

Country of study: Japan

Aim of study: Obtain a relevant epidemiological index of the impact of tobacco smoking on the subsequent risk of cancer in Japan

Study design: Population-based prospective study

Quality score: (++, + or -): +

Source population

Number of people: 116,896

Demographics: Not reported

Study (eligible and selected) population

Number of people: 92,792 subjects (44,521 men and 48,271 women)

Characteristics:

Men
Number of subjects 44,521
Proportion (%)
Age (years) ± SD 52.9 ± 7.9
Alcohol drinking status (%)
none 23.1

occasional 9.4
<150 g/week 22.2
150–299 g/week 19.9
300–449 g/week 13.2
z450 g/week 12.2
Body mass index (%)
<18.9 4.1
19.0 – 20.9 14.5
21.0 – 22.9 25.7
23.0 – 24.9 27.9
25.0 – 26.9 16.6
27.0 – 29.9 9.0
>30.0 2.2
Green vegetable intake (%)
less 75.8
everyday 24.2

Women
Number of subjects 48,271
Proportion (%)
Age (years) ±F SD 53.3 ± 8.0
Alcohol drinking status (%)
none 79.4
monthly 9.8
<100 g/week 7.3
>100 g/week 3.5
<18.9 5.3
Body mass index (%)
19.0 – 20.9 15.2
21.0 – 22.9 26.0
23.0 – 24.9 24.6
25.0 – 26.9 15.5
27.0 – 29.9 10.1
>30.0 3.3
Green vegetable intake (%)
Less 68.7
Everyday 31.3

Location: Ninohe City and Karumai Town in the Ninohe PHC area of Iwate Prefecture, Yokote City and Omonogawa town in the Yokote PHC area of Akita, eight districts of Minami-Saku County in the Saku PHC area of Nagano, Gushikawa City and Onna Village in the Ishikawa PHC area of Okinawa

Recruitment strategy: Self-administered questionnaire was distributed to all registered non-institutional residents in 1990.

Length of follow-up: 10 years, up to 31st December, 2001

Response rate and loss to follow-up: Response rate of 82% to the baseline questionnaire. Proportion of losses to follow-up (0.05%)

Eligible population: General population

Excluded populations: Two metropolitan areas. 210 subjects were found to be ineligible for the study and excluded because of non-Japanese nationality (n = 51), late reports of out-migration before the start of the follow-up (n = 156) and age ineligibility due to wrong birth date (n = 3).

Exposures at midlife

Relevant exposures: Alcohol

Time: 2001

Measurement of exposure: Alcohol consumption was represented in the questionnaire by the frequency of consumption during the past month and categorised into six classes: 1 day/month, 1 to 3 days/month, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, and every day

Outcomes at 55 years or over

Outcomes: Cancer

Outcome measurement: Occurrence of cancer was identified by active patients' notification from local major hospitals in the study area and data linkage with population-based cancer registries with permission. Death certificate information was used as a supplementary information source

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age at baseline, study area, weekly ethanol intake, body mass index and green vegetable intake

Results, limitations, source of funding

Number: 4,922 newly diagnosed cancer cases (2,969 men and 1,953 women) and 2,132 cases of cancer deaths (1,411 men and 721 women)

Effect estimates:

Hazard ratios of cancer incidence and death according to smoking status in men

<u>Total cancer incidence (n = 2,969)</u>
Number of cases Hazard ratio 95% CI
Smoking status
Never 488 1.00 (reference)
Former 777 1.37 (1.22 – 1.54)
Current 1704 1.64 (1.48 – 1.82)
Daily cigarette consumption
<19 483 1.48 (1.29 – 1.68)
20 – 29 796 1.71 (1.52 – 1.93)
>30 425 1.72 (1.51 – 1.98)
trend P < 0.05
Pack-years
<19 190 1.26 (1.06 – 1.49)
20 – 29 307 1.54 (1.33 – 1.79)
30 – 39 474 1.76 (1.54 – 2.08)
>40 732 1.76 (1.56 – 1.98)
trend P < 0.001
Age started smoking
>25 283 1.50 (1.28 – 1.74)
20 – 24 1001 1.62 (1.45 – 1.82)
<19 420 1.81 (1.58 – 2.08)
trend P < 0.05

<u>Total cancer death (n = 1,411)</u>
Number of cases Hazard ratio 95% CI
Smoking status
Never 223 1.00 (reference)
Former 351 1.35 (1.13 – 1.53)
Current 837 1.78 (1.53 – 2.09)
Daily cigarette consumption

<19 244 1.64 (1.35 – 1.98)
20 – 29 391 1.86 (1.56 – 2.21)
>30 202 1.84 (1.51 – 2.25)
trend n.s
Pack-years
<19 96 1.49 (1.16 – 1.91)
20 – 29 153 1.75 (1.41 – 2.17)
30 – 39 220 1.86 (1.53 – 2.26)
>40 367 1.86 (1.56 – 2.22)
trend n.s
Age started smoking
>25 142 1.65 (1.32 – 2.06)
20 – 24 473 1.71 (1.45 – 2.03)
<19 222 2.11 (1.73 – 2.57)
trend P < 0.05

Hazard ratios and of cancer incidence and death according to smoking status in women

Total cancer incidence (n = 1,953)
Number of cases Hazard ratio 95% CI
Smoking status
Never 1779 1.00 (reference)
Former 37 1.47 (1.05 – 2.05)
Current 137 1.46 (1.21 – 1.75)
Daily cigarette consumption
<19 90 1.45 (1.16 – 1.81)
20 – 29 32 1.42 (0.99 – 2.03)
>30 15 1.63 (0.98 – 2.72)
trend n.s.
Pack-years
<19 80 1.34 (1.06 – 1.69)
20 – 29 30 1.78 (1.20 – 2.63)
30 – 39 10 1.32 (0.71 – 2.47)
>40 17 1.83 (1.13 – 2.96)
Trend n.s.
Age started smoking
>25 92 1.39 (1.12 – 1.73)
20 – 24 40 1.73 (1.24 – 2.41)
<19 5 1.10 (0.45 – 2.66)
Trend n.s.

Total cancer death (n = 721)
Number of cases Hazard ratio 95% CI
Smoking status
Never 656 1.00 (reference)
Former 10 1.03 (0.53 – 1.99)
Current 55 1.58 (1.18 – 2.12)
Daily cigarette consumption
<19 32 1.36 (0.93 – 2.00)
20 – 29 16 1.99 (1.20 – 3.31)
>30 7 1.96 (0.93 – 4.15)
Trend n.s.
Pack-years
<19 23 1.08 (0.69 – 1.67)
20 – 29 20 3.37 (2.09 – 5.44)
30 – 39 7 2.18 (1.03 – 4.62)
>40 5 1.26 (0.52 – 3.06)
Trend n.s.
Age started smoking

>25 35 1.41 (0.99 – 2.00)
20 – 24 18 2.22 (1.34 – 3.70)
<19 2 1.36 (0.34 – 5.51)
Trend n.s.

Significant trends: From the baseline questionnaire, 52.2% of men were current smokers and they presented a significantly increased HR of subsequent cancer occurrence compared with never-smokers [HR 1.64, 95% confidence interval (95% CI) 1.48–1.82]. Only 5.6% of women were current smokers and their HR also represented a significant increase (HR 1.46, 95% CI 1.21–1.75).

Limitations:

1. Could not fully evaluate the effect of passive smoking due to the lack of detailed information.
2. The proportion of female current smokers was 12–20% in two metropolitan areas.
3. This is very high compared with the 4–10% proportion included in the analysis

Source of funding: Grant-in-Aid for Cancer Research and for the Second Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare, Japan.

Authors: Iso H, Baba S, Mannami T, Sasaki S, Okada K, Konishi M, Tsugane S; JPHC Study Group

Year: 2004

Citation: Stroke 35(5): 1124-9

Country of study: Japan

Aim of study: Examine impact of light-to-moderate alcohol consumption on risk of stroke

Study design: Prospective study

Quality score: (++, + or -): +

Source population

Number of people: 27,063 men and 27,435 women

Demographics: Not reported

Study (eligible and selected) population

Number of people: 19 54

Characteristics:

Nondrinker
N at risk 4063
Age, year 50.0
Smoking history, %
Never 30
Past 22
Current 48
Mean body mass index, kg/m2 23.5
History of hypertension, % 11
History of diabetes, % 6
College or higher education, % 13
Sport at leisure time 2:1 d/wk, % 15
Diet, n of frequencies
Fruit, d/wk 3.2
Green vegetables, d/wk 3.5
Yellow vegetables, d/wk 2.8
Other vegetables, d/wk 3.7
Fresh fish, d/wk 2.5
Dried fish, d/wk 1.7

Occasional Drinker

N at risk 2133
Age, year 48.9
Smoking history, %
Never 33
Past 20
Current 46
Mean body mass index, kg/m2 24.0
History of hypertension, % 11
History of diabetes, % 5
College or higher education, % 17
Sport at leisure time 2:1 d/wk, % 19
Diet, n of frequencies
Fruit, d/wk 3.1
Green vegetables, d/wk 3.6
Yellow vegetables, d/wk 2.8
Other vegetables, d/wk 3.5
Fresh fish, d/wk 2.4
Dried fish, d/wk 1.4

Location: Ninohe City and Karumai Town in the Ninohe PHC area of Iwate Prefecture, Yokote City and Omonogawa town in the Yokote PHC area of Akita, 8 districts of Minami-Saku County in the Saku PHC area of Nagano, Gushikawa City and Onna Village in the Ishikawa PHC area of Okinawa

Recruitment strategy: Self-administered questionnaire was distributed to all registered non-institutional residents in 1990

Length of follow-up: 10-year follow-up questionnaire (88% followed-up)

Response rate and loss to follow-up: 20,665 men (76%) initially. 11.0 years of follow-up from 1990 to the end of 2001. 10-year follow-up questionnaire (88% followed-up)

Eligible population: Men aged 40-59

Excluded populations: Data for women are not presented because of the small number of moderate-to-heavy drinkers in this group. Excluded men who reported stroke, myocardial infarction, angina pectoris, or cancer at baseline

Exposures at midlife

Relevant exposures: Alcohol consumption, diet

Time: 1990

Measurement of exposure: Alcohol consumption was represented in the questionnaire by the frequency of consumption during the past month and categorized into 6 classes: 1 day/month, 1 to 3 days/month, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, and every day

Frequency of weekly intake of 27 food items was reported under 4 categories: rarely, 1 to 2 days/week, 3 to 4 days/week, and almost every day

Outcomes at 55 years or over

Outcomes: Stroke

Outcome measurement: Registered a total of 25 hospitals facilitated by computer tomographic scan and/or magnetic resonance images in the 4 PHC areas. Medical records were reviewed by registered hospital workers or PHC physicians, blinded to the lifestyle data. Systematic search for death certificates was also undertaken.

Time: Stroke events were registered if they occurred after the date of return of the baseline questionnaire and before January 01, 2002.

Analysis

Analysis strategy: Cox proportional hazards models

Confounders: Age, smoking status, body mass index, history of diabetes, education level, sports at leisure time, and dietary intake categories of fruits, total vegetables, and fish. History of hypertension as well as the confounding variables to examine the residual or independent effect of alcohol consumption on risk of stroke

Results, limitations, source of funding

Number: 694

Effect estimates:

Non-drinker

Person-years 44 379
Total stroke
N of cases 133
RR (95% CI)
Further adjusted for hypertension 1.09 (0.80–1.48)
Definite total stroke N of cases 106
Further adjusted for hypertension 0.95 (0.68–1.33)
Hemorrhagic stroke
N of cases 48
Further adjusted for hypertension 1.48 (0.84–2.62)
Intraparenchymal hemorrhage
N of cases 38
Further adjusted for hypertension 1.35 (0.73–2.51)
Subarachnoid hemorrhage
N of cases 10
Further adjusted for hypertension 2.40 (0.52–11.0)
Ischemic stroke
N of cases 58
Further adjusted for hypertension 0.72 (0.47–1.08)
Lacunar infarction
N of cases 27
Further adjusted for hypertension 0.64 (0.36–1.16)
Large-artery occlusive infarction
N of cases 11
Further adjusted for hypertension 0.73 (0.28–1.89)
Embolic infarction
N of cases 10
Further adjusted for hypertension 0.58 (0.23–1.47)

Occasional drinker
Person-years 23,532
Total stroke
N of cases 59
Further adjusted for hypertension 1.0
Definite total stroke
N of cases 53
Further adjusted for hypertension 1.0
Hemorrhagic stroke
N of cases 16
Further adjusted for hypertension 1.0
Intraparenchymal hemorrhage
N of cases 14

Further adjusted for hypertension 1.0
Subarachnoid hemorrhage
N of cases 2
Further adjusted for hypertension 1.0
Ischemic stroke
N of cases 37
Further adjusted for hypertension 1.0
Lacunar infarction
N of cases 19
Further adjusted for hypertension 1.0
Large-artery occlusive infarction
N of cases 7
Further adjusted for hypertension 1.0
Embolic infarction
N of cases 8
Further adjusted for hypertension 1.0

Significant trends: There was a lower risk of ischemic stroke, more specifically lacunar infarction, a higher risk of hemorrhagic stroke, and no excess risk of total stroke among drinkers of 1 to 149 g ethanol per week compared with occasional drinkers; the respective multivariate RR (95% CI) was 0.59 (0.37 to 0.93), 0.43 (0.22 to 0.87), 1.73 (0.98 to 3.07), and 0.98 (0.71 to 1.36).

Limitations:

1. Residual uncontrolled confounding of the association between alcohol consumption and risk of stroke.
2. Data on hypertension and diabetes were self-reported.
3. Generalizability of findings to women

Source of funding: Cancer Research and for the Second Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor, and Welfare of Japan

Authors: Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE… Ascherio A

Year: 2009

Citation: American Journal of Clinical Nutrition 89(5): 1425-32

Country of study: Various

Aim of study: Associations between energy intake and risk of coronary heart disease

Study design: Follow-up study in which data from 11 American and European cohort studies were pooled

Quality score: (++, + or -): +

Source population

Number of people: Not reported

Demographics: Not reported

Study (eligible and selected) population

Number of people: 344,696

Baseline cohort n by study: AHS F 13,430; M 9212; ARIC F 6481 M 5240; ATBC M 21,141; FMC F 2481 M 2712; GPS F 1666 M 1658; HPFS M 41,754; IIHD M 8272; IWHS F 30,180; NHSa F 81,415; NHSb F 61,706; VIP F 10,555, M 9521; WHS F 37,272

Characteristics:

Median age at baseline by study: AHS F 57 (39–76) M 55 (39–74); ARIC F 53 (47–62) M 54 (47–

63); ATBC M 57 (51–65); FMC F 49 (38–65); M 47 (37–63); GPS F 50 (40–60) M 50 (40–60); HPFS M 53 (42–67); IIHD M 48 (41–59); IWHS F 61 (56–67); NHSa F 47 (38–57); NHSb F 52 (43–62); VIP F 50 (40–60) M 50 (40–60); WHS F 52 (46–64)

Location: America and Europe

Recruitment strategy: Various

Length of follow-up: Various

Response rate and loss to follow-up: Various

Eligible population: Various

Excluded populations: Age <35 y; history of cardiovascular disease, diabetes, or cancer (other than non-melanoma skin cancer); and extreme energy intake (ie, > or <3 SDs from the study-specific log-transformed mean energy intake of the population)

Exposures at midlife

Relevant exposures: Dietary intake

Time: Calendar year of inception**:** AHS 1977; ARIC 1987; ATBC 1985; FMC 1966; GPS 1974; HPFS 1986; IIHD 1963; IWHS 1986; NHSa 1980; NHSb 1986; VIP 1992; WHS 1993

Measurement of exposure: Food frequency questionnaire or a dietary history interview

Outcomes at 55 years or over

Outcomes: Fatal coronary heart disease (including sudden death) and nonfatal myocardial infarction

Outcome measurement: Various

Time: Various

Analysis

Analysis strategy: Cox proportional hazards regression

Confounders: Intakes of MUFAs, PUFAs, trans fatty acids, carbohydrates, and protein expressed as percentages of total energy intake and total energy intake, smoking, body mass index, physical activity, highest attained educational level, alcohol intake, history of hypertension, and energy-adjusted quintiles of fiber intake and cholesterol intake

Results, limitations, source of funding

Number: 5249 coronary events and 2155 coronary deaths occurred

Effect estimates:

Coronary events HR (95% CI) P-trend

MUFAs for SFAs 1.19 (1.00, 1.42) 0.32

PUFAs for SFAs 0.87 (0.77, 0.97) 0.70

CHs for SFAs 1.07 (1.01, 1.14) 0.51

Coronary deaths HR (95% CI) P-trend

MUFAs for SFAs 1.01 (0.73, 1.41) 0.18

PUFAs for SFAs 0.74 (0.61, 0.89) 0.40

CHs for SFAs0.96 (0.82, 1.13) 0.05

Significant trends: Replacing Saturated fatty acid with polyunsaturated fatty acids rather than monounsaturated fatty acids or carbohydrates prevents CHD over a wide range of intakes

Limitations:

Author: None reported

Reviewer:

1. Diet relying on self-report.
2. Dietary change over time

Source of funding: Supported by the National Heart, Lung, and Blood Institute, National Institutes of Health (grant R01 HL58904) and the Danish Heart Foundation (grants 02-1-9F-7-22961 and 02-2-9-8-22010). The establishment of the Research Unit for Dietary Studies was financed by the Female Researchers in Joint Action program from the Danish Medical Research Council.

Authors: Janzon E, Hedblad B, Berglund G, Engström G

Year: 2004

Citation: Journal of Internal Medicine 256(2): 111-8

Country of study: Sweden

Aim of study: Explored how the risk of myocardial infarction in current and former smokers is modified by other cardiovascular risk factors

Study design: Cohort study

Quality score: (++, + or -): +

Source population

Number of people: 10 902

Demographics: Not reported

Study (eligible and selected) population

Number of people: 10,619

Characteristics:

Never-smokers (n = 4848)
Age (year) 50.5 ± 6.6 (28.3–57.6)
BMI (kg m)2) 25 ± 4
Occupation, low (%) 77.5
Civil status, married (%) 77.4

Ex-smokers (n = 2035)
Age (year) 49.8 ± 7.3 (28.2–57.2)
BMI (kg m)2) 24 ± 4
Occupation, low (%) 72.1
Civil status, married (%) 73.2

Current smokers (n = 3738)
Age (year) 48.3 ± 8.2 (28.2–56.9)
BMI (kg m)2) 23 ± 4
Occupation, low (%) 81.4
Civil status, married (%) 64.6

Location: Malmo, Sweden

Recruitment strategy: Not reported

Length of follow-up: Mean follow-up was 14.0 ± 4.5 years (range 0.5–21.9 years)

Response rate and loss to follow-up: Overall attendance rate was 71

Eligible population: Women 28–58 years old

Excluded populations: Exclude women with a history of MI or stroke (n=176)

Exposures at midlife
Relevant exposures: Smoking **Time:** Not reported **Measurement of exposure:** Self-administered questionnaire. Women asked 'Are you a smoker?' or 'Are you a daily smoker?' Women who reported that they had stopped smoking were considered to be ex-smokers. Women who did not report any history of smoking were never-smokers Tobacco consumption amongst daily smokers was classified as low consumption (<10 cigarettes day), medium consumption (>10, <20 cigarettes day) and high consumption (>20 cigarettes day).
Outcomes at 55 years or over
Outcomes: Myocardial infarction **Outcome measurement:** Cases of nonfatal MI were retrieved from the Malmo Myocardial Infarction register and from the Swedish Myocardial Infarction register **Time:** All subjects were followed from the baseline examination until death, cardiac event, emigration out of Sweden, or to 31 December 1998
Analysis
Analysis strategy: Cox proportional hazards model **Confounders**: Systolic blood pressure, age, BMI, cholesterol, diabetes, occupation, marital status and HRT
Results, limitations, source of funding
Number: 228 **Effect estimates:** RR (CI 95%) <u>Never-smoker</u> Normotension 1.0 Hypertension 2.4 (1.4–4.3) Normal cholesterol 1.0 High cholesterol 1.8(1.02–3.2) No diabetes 1.0 Diabetes 8.8 (4.4–17.4) <u>Ex-smoker</u> Normotension 1.8 (0.99–3.2) Hypertension 2.7 (1.1–6.0) Normal cholesterol 1.6 (0.9–2.9) High cholesterol 2.4 (1.2–5.0) No diabetes 1.7 (1.01–2.8) Diabetes 7.8 (2.4–25.6) <u>Current smoker</u> Normotension 5.3 (3.3–8.1) Hypertension 12.2 (7.5–19.8) Normal cholesterol 5.6 (3.6–8.6) High cholesterol 8.2 (5.2–12.9) No diabetes 6.0 (4.1–8.6) Diabetes 19.0 (10.2–35.4) **Significant trends:** Smoking is a major risk factor for MI, however the risk varies widely between

women with similar tobacco consumption. There was a statistically significant interaction between smoking and hypertension for the risk of cardiac events

Limitations:
Author:

1. Crude categorisation of occupation.
2. No question about occasional smoking.
3. Misclassification of occasional smokers as never-smokers.
4. No information on age of initiation of smoking.
5. No information on smoking cessation during follow-up

Reviewer: Self-reported exposure

Source of funding: Swedish Council for Work Life and Social Research

Authors: Johnsen NF, Christensen J, Thomsen BL, Olsen A, Loft S, Overvad K, Tjønneland A

Year: 2006

Citation: European Journal of Epidemiology 21(12): 877-84

Country of study: Denmark

Aim of study: Investigate the effects of occupational activity and leisure time activity on incident colon cancer risk

Study design: Prospective cohort

Quality score: (++, + or -): -

Source population

Number of people:160,725

Demographics: Not reported

Study (eligible and selected) population

Number of people: 57,053

Characteristics:

Women
Age (years) 56 (50–64)
BMI 25 (20–34)
Education (years)
< 7 8751 (31)
8–10 14,296 (50)
>10 5309
Smoking
Never 12,460 (44)
Former 6716 (24)
Present 9180 (32)
Alcohol (g/day) 27,764 (97)
Total number of Leisure time physical activity 28,356 (100)
Occupational physical activity
Sitting 9248 (33)
Standing 4964 (18)
Manual 6219 (22)
Not working 7925 (28)

Men
Age (years) 56 (50–64)

BMI 26 (21–33) < 7 9000 (34) 8–10 10,894 (42) >10 6228 (24) Smoking Never 6764 (26) Former 9104 (35) Present 10,254 (39) Alcohol (g/day) 25,787 (98) Total number of Leisure time physical activity 26,064 (100) Occupational physical activity Sitting 10,369 (40) Standing 4417 (17) Manual) 7282 (28) Not working 4054 (16) **Location:** Copenhagen and Aarhus, Denmark **Recruitment strategy:** Not reported **Length of follow-up:** Mean follow-up of 7.6 years **Response rate and loss to follow-up:** Less than 0.8% of the participants were completely lost to follow-u **Eligible population:** Danish middle-aged population **Excluded populations:** -
Exposures at midlife
Relevant exposures: Smoking, daily intake of dietary fibre, red meat, alcohol and dietary fat **Time:** 1993-1997 **Measurement of exposure:** Self-report questionnaire
Outcomes at 55 years or over
Outcomes: Colon cancer **Outcome measurement:** Danish Cancer Registry **Time:** Date of diagnosis of any cancer (except for non-melanoma skin cancer), date of death or emigration, or December 31, 2003, whichever came first
Analysis
Analysis strategy: Cox proportional hazards model **Confounders:** Model 1) participation in each of the six activities, occupational physical activity (four categories), BMI, education, NSAID, present use of HRT, smoking and intake of total energy, fat, dietary fibre, red meat and alcohol. Model 2) occupational activity, BMI, education, NSAID, present use of HRT, smoking and intake of total energy, fat, dietary fibre, red meat and alcohol
Results, limitations, source of funding
Number: 140 women and 157 men were diagnosed with colon cancer **Effect estimates:** **Incidence rate ratios for colon cancer per additional hour/week of six types of leisure time physical activity**

IRR (95% CI)

Women
MET-score (per 10 units) 1.00 (0.96–1.04
Sports (per one hour) 1.03 (0.93–1.14)
Cycling (per one hour) 1.00 (0.94–1.06)
Walking (per one hour) 0.99 (0.95–1.03)
Gardening (per one hour) 0.95 (0.87–1.03)
Housework (per one hour) 1.01 (0.98–1.03)
Do-it-yourself (per one hour) 1.00 (0.91–1.11)

Men (cases = 157)
MET-score (per 10 units) 0.97 (0.93–1.01)
Sports (per one hour) 1.00 (0.91–1.10)
Cycling (per one hour) 1.00 (0.94–1.07)
Walking (per one hour) 1.01 (0.98–1.04)
Gardening (per one hour) 0.98 (0.92–1.04)
Housework (per one hour) 0.95 (0.89–1.02)
Do-it-yourself (per one hour) 0.97 (0.92–1.02)

Incidence rate ratios for colon cancer for active compared to non-active for six types of leisure time physical activity

IRR (95% CI)

Women
Total number of activities (per extra activity) 0.89 (0.77–1.03)
Sports 0.85 (0.60–1.20)
Cycling 0.89 (0.62–1.28)
Walking 0.94 (0.48–1.86
Gardening 0.96 (0.67–1.39)
Housework *d*
Do-it-yourself 0.86 (0.60–1.23)

Men
Total number of activities (per extra activity) 0.90 (0.79–1.03)
Sports 0.90 (0.64–1.25)
Cycling 0.92 (0.66–1.28)
Walking 1.19 (0.65–2.16)
Gardening 1.12 (0.74–1.69)
Housework 0.78 (0.51–1.19)
Do-it-yourself 0.69 (0.45–1.06)

Significant trends: No associations were found between risk of colon cancer and occupational activity, MET-hours per week of total leisure time activity, residuals from a regression of each activity on the total MET-hours or the time spent on any of the six types of leisure time activities

Limitations:

1. Not all the aspects of activity (type, frequency, duration and intensity) were measured.
2. Self-administered questionnaires.
3. Study is based on persons of a relatively high age.
4. Adding random variation by applying an assumed intensity to the included activities

Source of funding: Danish Medical Research Council and the Danish Cancer Society.

Authors: Kåreholt I, Lennartsson C, Gatz M, Parker MG

Year: 2011

Citation: International Journal of Geriatric Psychiatry 26(1): 65–74

Country of study: Sweden

Aim of study: Examine the relationship between leisure time activity and cognition over two decades.

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Number of people: 7483

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1,643

Characteristics:

Age
Range 46–75 years
mean 57.4

Age at FU
Range 69–98
Mean 80.2

Sex % Women 58.7
Men 41.3
Mobility problems %
0 70.8
1 13.8
2 8.8
3 6.6
Employment status %
Employed 70.1
Unemployed 29.9
Years of education
Range 0–29
Mean 8.4
Adult socioeconomic status
% Blue-collar (unskilled) 33.4
Blue-collar (skilled) 21.1
Lower white-collar 19.5
Intermediate and upper white-collar 26.0

Childhood socioeconomic status
% Blue-collar (unskilled) 24.7
Blue-collar (skilled) 35.1
Lower white-collar 28.4
Intermediate and upper white-collar 11.0
Missing and unclassifiable 0.9
Smoking %
No 74.6
Yes, 1–10 cigarettes 12.8
Yes >10 cigarettes 12.5
Alcohol drinking %
No 24.4
Moderate 44.9
>Moderate 30.7
Total 1643

Location: Sweden

Recruitment strategy: Randomised recruitment

Length of follow-up: From 1968 to 1992 was 24 years, from 1981 to 2002 was 21 years, and from 1981 to 2004 was 23 years (average 22.8 years)

Response rate and loss to follow-up: 'Has a low nonresponse rate'. Number not provided

Eligible population: Not reported

Excluded populations: 1871 persons aged 56–75 were interviewed in 1968. Of these, 534 were still alive in 1992 and cognitive data could be collected for 430 individuals. From the 1981 baseline survey, cognitive data could be collected for 416 individuals in 2002 and for 797 individuals in 2004.

Exposures at midlife

Relevant exposures: Smoking and alcohol, political, mental, and socio-cultural activities

Time: Baseline

Measurement of exposure: Smoking: Non-smoker; smoking 10 cigarettes (corresponding to 20 pipes or 5 cigars); >10 cigarettes.

Alcohol drinking: Non-drinker; moderate drinker; drinking more than moderately. Moderate drinking is less than two times per month and normally not more than 1–2 glasses

Political activities: Ever having appealed a decision made by a public authority, delivered a speech at a meeting, written an article or a letter to the editor, or participated in a demonstration during the past year

Organizational activities: Being an active trade union member (at least attending meetings), member of a political party, sports, temperance, religious, or other organization.

Mental activities: Reading books, playing an instrument/
singing, and doing hobby activities.

Socio-cultural activities: Going to the movies, the theatre, and attending study circles.

Social activities: Four questions concerning visiting and/or being visited by friends and/or relatives.

Physical activities: Doing sports, gardening, and dancing

Outcomes at 55 years or over

Outcomes: Cognition

Outcome measurement: MMSE

Time: 1992, 2002, or 2004

Analysis

Analysis strategy: Ordered logistic regressions

Confounders: Age, age-square, sex, follow-up-time, mobility problems, symptoms of mental distress, employment status, education, adult and childhood socioeconomic status, income, smoking, and drinking

Results, limitations, source of funding

Number: Not reported

Effect estimates:

β p-Value
Political 0.17 0.004
Mental 0.11 0.047
Socio-cultural0.04 0.415

Social 0.01 0.904
Organizational -0.03 0.628
Physical, all 0.21 0.05 0.375
Men -0.06 0.477
Women 0.14 0.055

Significant trends: Significant association between later cognition and earlier political, mental, and socio-cultural activities. Physical activities had a significant association with cognition only among women.

Limitations:
Author**:**

1. Low level for moderate drinking.
2. Absence of a baseline measure of cognition

Reviewer**:**

1. Unclear reporting of study design and process.
2. Do not report how many people developed cognitive issues

Source of funding: Swedish Research Council (2007-1947) obtained by Marti G. Parker and by the Zenith award from the Alzheimer's Association (ZEN-02-3895) to Margaret Gatz

Authors: Kato M, Noda M, Inoue M, Kadowaki T, Tsugane S; JPHC Study Group

Year: 2009

Citation: Endocrinology Journal 56(3): 459-68

Country of study: Japan

Aim of study: Assess association between psychological factors and the onset of diabetes

Study design: Community-based, prospective cohort study

Quality score: (++, + or -): +

Source population

Number of people: 95,373

Demographics: Not reported

Study (eligible and selected) population

Number of people: 55,826

Characteristics: J and K cells

Location: Ninohe, Yokote, Saku, Chubu, and Katsushika. Mito, Nagaoka, Chuohigashi, Kamigoto, Miyako and Suita

Recruitment strategy: Not reported

Length of follow-up: 10 years

Response rate and loss to follow-up: 75%, 32,369 men and 39,344 women

Eligible population: Middle-aged Japanese adults 40-69 years

Excluded populations: Individuals who had; cardiovascular disease, chronic liver disease, kidney disease or any type of cancer (n=4,515), also excluded any subjects with diabetes at baseline (n=3,092). Individuals who had missing baseline data for any of the exposure parameters (n=9,256). Individuals with a body mass index of less than 14 or more than 40 (n=741).

Exposures at midlife

Relevant exposures: Behaviours, diet

Time: 1990-1993

Measurement of exposure: Self-administered questionnaire, food frequency questionnaire

Mental stress was assessed based on three levels of response (low, medium and high) to the question, 'How much stress do you feel in your daily life?'

Type A behavioural patterns: competitive drive, speed and impatience, aggressiveness and irritability

Outcomes at 55 years or over

Outcomes: Diagnosed diabetes

Outcome measurement: 94% of the self-report cases of diagnosed diabetes were confirmed by medical records

Time: 5- or 10-years after wave 1

Analysis

Analysis strategy: Logistic regression

Confounders: Age, body mass index, smoking status, alcohol intake, family history of diabetes, physical activity, history of hypertension, and coffee consumption

Results, limitations, source of funding

Number: 1,601 incident cases (6.4%) of diabetes among men and 1,093 cases (3.5%) among women

Effect estimates:

Odds ratios for the 1 0-year incidences of diabetes mellitus according to perceived mental stress

Men
Low Perceived Mental Stress (reference)
Medium Perceived Mental Stress 1.19 (1.01-1.40)
High Perceived Mental Stress 1.36 (1.13-1.63)
p for trend 0.001

Women
Low Perceived Mental Stress (reference)
Medium Perceived Mental Stress 1.12 (0.94-1.34)
High Perceived Mental Stress 1.22 (0.98-1.51)
p for trend 0.080

Odds ratios for the 1 0-year incidences of diabetes mellitus according to levels of Type A behaviour pattern index

Men
4 (reference)
3 1.06 (0.91-1.22)
2 1.00 (0.84-1.20)
1 1.09 (0.94-1.27)
P for trend 0.381

Women
4 (reference)
3 0.93 (0.79-1.09)
2 1.03 (0.85-1.26)
1 1.22 (1.01-1.47)
P for trend 0.031

Odds ratios (95%CI) for the 10-year incidences of diabetes mellitus according to levels of constituent items of Type A behaviour pattern index

Men
Low (reference)
Impatience (reference)
Irritability (reference)
Aggressiveness (reference)
Competitiveness (reference)

Medium
Impatience 1.01 (0.85-1.18)
Irritability 1.08 (0.92-1.28)
Aggressiveness 1.05 (0.89-1.25)
Competitiveness 0.87 (0.73-1.03)

High
Impatience 1.02 (0.86-1.22)
Irritability 1.14 (0.95-1.37)
Aggressiveness 1.12 (0.92-1.36)
Competitiveness 0.90 (0.74-1.09)

Women
Low
Impatience (reference)
Irritability (reference)
Aggressiveness (reference)
Competitiveness (reference)

Medium
Impatience 1.05 (0.88-1.26)
Irritability 0.99 (0.80-1.23)
Aggressiveness 0.96 (0.80-1.15)
Competitiveness 0.99 (0.83-1.19)

High
Impatience 1.23 (1.00-1.51)
Irritability 1.16 (0.91-1.48)
Aggressiveness 1.08 (0.87-1.36)
Competitiveness 1.01 (0.80-1.29)

Odds ratios (95% CI) for the 1 0-year incidences of diabetes mellitus according to coffee consumption

Men
almost never (reference) 1
1-2 days per week 0.93 (0.80-1.08)
3-4 days per week 0.84 (0.71-1.01)
1-2 cups/day 0.84 (0.73-0.97)
3-4 cups/day 0.83 (0.68-1.02)
>5 cup/day 0.82 (0.60-1.112
p for trend 0.006

Women
almost never (reference) 1
1-2 days per week 0.90 (0.76-1.06)
3-4 days per week 0.95 (0.77-1.17)
1-2 cups/day 0.81 (0.69-0.96)
3-4 cups/day 0.62 (0.45-0.84)
>5 cup/day 0.40 (0.20-0.78)
p for trend <0.00

Significant trends: The risk of diabetes increased with an increasing stress level, especially among men. This association remained almost unchanged after adjustments for known risk factors of diabetes, type A and hours of sleep.

Limitations:

1. Assessment of diabetes mellitus was based on the results of a self-reported questionnaire.
2. Perceived mental stress was assessed based on a single simple question

Source of funding: Cancer Research H16-S2 and for the Third Term Comprehensive Ten-Year Strategy for Cancer Control H16-010, and Health Sciences Research grants (Medical Frontier Strategy Research H13-008, Clinical Research for Evidence-based Medicine H14-008, H15-006, Comprehensive Research on Cardiovascular Diseases H16-019, H17-019, H18-028, H19-019) from the Ministry of Health, Labour and Welfare of Japan.

Authors: Kesse-Guyot E, Andreeva VA, Jeandel C, Ferry M, Hercberg S, Galan P

Year: 2012

Citation: Journal of Nutrition 142(5): 909-15

Country of study: France

Aim of study: Evaluated association between empirically derived dietary patterns in midlife and cognitive performance

Study design: Randomized, double-blind, placebo-controlled, primary prevention trial

Quality score: (++, + or -): -

Source population

Number of people: 12,741

Demographics: Not reported

Study (eligible and selected) population

Number of people: 3054

Characteristics: Cells J & K

Location: France

Recruitment strategy: Not reported. At end of trial phase, the participants were invited for an additional 2-y follow-up for the SU.VI.MAX 2 observational study

Length of follow-up: 13.4 ± 0.7 y.

Response rate and loss to follow-up: Not reported

Eligible population: Not reported

Excluded populations: Younger than 45 y at baseline (n = 1267), those with missing neuropsychological test scores (n = 1136), those with fewer than 3 dietary records during the first 2 y of follow-up (n = 1085), or those with missing data on any of the covariates (n = 308). Dietary records that reported <100 or >6000 kcal/d were excluded; men reporting <800 kcal/d and women reporting <500 kcal/d in 60% or more of their dietary records were also excluded.

Exposures at midlife

Relevant exposures: Diet

Time: 1995–1996

Measurement of exposure: 24-h dietary records. Food and nutrient intakes were based on the reported mean intakes across all 24-h records

Outcomes at 55 years or over
Outcomes: Cognitive performance **Outcome measurement:** Neuropsychological tests **Time:** 2007–2009
Analysis
Analysis strategy: ANCOVA **Confounders:** Age, gender, intervention group, education, alcohol and energy intake, number of dietary records, physical activity, BMI, tobacco use, self-reported memory troubles, diabetes, hypertension, follow-up time, history of cardiovascular disease, and depressive symptoms and, for women, menopausal status and hormone therapy use.
Results, limitations, source of funding
Number: 3054 **Effect estimates:** Healthy pattern <u>Global cognitive function</u> Q1 48.9 ± 0.7 Q2 49.4 ± 0.7 Q3 50.8 ± 0.7 Q4 50.1 ± 0.7 P2 0.001 <u>Verbal memory</u> Q1 49.1 ± 0.7 Q2 49.5 ± 0.7 Q3 50.6 ± 0.7 Q4 50.3 ± 0.7 P2 0.01 <u>Executive functioning</u> Q1 49.3 ± 0.7 Q2 49.6 ± 0.7 Q3 50.6 ± 0.7 Q4 49.8 ± 0.7 P2 0.13 Traditional pattern <u>Global cognitive function</u> Q1 50.1 ± 0.7 Q2 49.5 ± 0.7 Q3 49.6 ± 0.7 Q4 49.9 ± 0.7 P2 0.68 <u>Verbal memory</u> Q1 50.2 ± 0.7 Q2 49.8 ± 0.7 Q3 49.6 ± 0.8 Q4 49.7 ± 0.7 P2 0.32 <u>Executive functioning</u> Q1 49.9 ± 0.7

Q2 49.5 ± 0.7
Q3 49.7 ± 0.7
Q4 50.1 ± 0.7
P2 0.60

Significant trends: A healthy and a traditional DP were identified. In the multivariate model, the healthy pattern was associated with better global cognitive function (50.1 ± 0.7 vs. 48.9 ± 0.7; P-trend = 0.001) and verbal memory (49.7 ± 0.4 vs. 48.7 ± 0.4; P-trend = 0.01).

Limitations:
Author

1. Cognitive evaluation was not available at baseline.
2. Empirically derived DP showed some limitations regarding food groupings, factor selection, and labelling.
3. Sample likely included the more compliant or health-conscious participants.
4. Residual confounding

Reviewer

1. Unclear reporting.
2. From intervention study but little detail of impact of intervention on groups

Source of funding: French National Research Agency (no. ANR-05-PNRA-010), the French Ministry of Health, Mederic, Sodexo, Ipsen, MGEN, and Pierre Fabre

Authors: Khalili P, Nilsson PM, Nilsson JA, Berglund G

Year: 2002

Citation: Journal of Hypertension 20(9): 1759-64

Country of study: Sweden

Aim of study: Examine to what degree smoking habits modulate the relationship between systolic blood pressure and risk for cardiovascular morbidity and mortality

Study design: Population-based screening study

Quality score: (++, + or -): +

Source population

Number of people: 22 444

Demographics: Not reported

Study (eligible and selected) population

Number of people: Not reported

Characteristics:

Q1
n 3249
Age (years) 42.2
Smoking habits* (%) 59.0/41.0
BMI (kg/m2) 23 (2.8)

Q2
n 6846
Age (years) 42.6
Smoking habits* (%) 51.9/48.1
BMI (kg/m2) 24 (2.9)

Q3

n 2272
Age (years) 43.0
Smoking habits* (%) 50.0/50.0
BMI (kg/m2) 25 (3.2)

Q4
n 4947
Age (years) 44.0
Smoking habits* (%) 45.9/54.1
BMI (kg/m2) 25 (3.1)

Q5
n 4215
Age (years) 46.0
Smoking habits* (%) 43.9/56.1
BMI (kg/m2) 26 (3.6)

Treated hypertensives
n 915
Age (years) 48.4
Smoking habits* (%) 38.9/61.1
BMI (kg/m2) 27 (3.9)

Location: Malmo, Sweden

Recruitment strategy: Not reported

Length of follow-up: Averaged a mean of 17 years

Response rate and loss to follow-up: Mean attendance rate 71%

Eligible population: Middle-aged men

Excluded populations: -

Exposures at midlife

Relevant exposures: Smoking

Time: Not reported

Measurement of exposure: Self-reported questionnaire

Outcomes at 55 years or over

Outcomes: Cardiovascular events

Outcome measurement: Local and national registers. A first cardiovascular event was defined as the first
recorded cardiovascular event during follow-up, including fatal and non-fatal cases of ischaemic heart disease and cerebrovascular disease

Time: End of 1996

Analysis

Analysis strategy: Calculated using direct standardization and expressed as risk ratios with 95% confidence intervals

Confounders: Age, systolic blood pressure, diastolic blood pressure, body mass index, cholesterol, triglycerides, or history of diabetes

Results, limitations, source of funding

Number: Not reported

Effect estimates:

Morbidity RR (95%CI) between smokers and non-smokers
Q1 1.9 (1.5–2.4)
Q2 2.1 (1.8–2.5)
Q3 2.3 (1.8–2.9)
Q4 1.8 (1.5–2.1)
Q5 1.7 (1.5–2.0)
tHTs 1.4 (1.1–1.8).

Mortality RR (95%CI) between smokers and non-smokers
Q1 1.8 (1.4–2.3)
Q2 2.5 (2.1–3.0)
Q3 2.7 (2.0–3.6)
Q4 2.2 (1.9–2.7)
Q5 2.5 (2.1–2.9)
tHTs 1.8 (1.3–2.5)

Significant trends: Increasing systolic blood pressure levels is associated with an increasing risk of future cardiovascular events and mortality, an association modified by smoking habits. Treated hypertensive patients were at increased risk in spite of antihypertensive drugs

Limitations:

Author: Unclear reporting

Reviewer**:** Not reported

Source of funding: Swedish Society of Medicine

Authors: Kimm H, Lee PH, Shin YJ, Park KS, Jo J, Lee Y… Jee SH

Year: 2011

Citation: Archives of Gerontology and Geriatrics 52(3): e117-22

Country of study: Republic of Korea

Aim of study: Determine the effects of vascular risk factors, such as blood pressure, diabetes and smoking in the mid-life or the late-life on dementia risk

Study design: Prospective cohort study

Quality score: (++, + or -): +

Source population

Number of people: 1,329,525

Demographics: Not reported

Study (eligible and selected) population

Number of people: 848,505

Characteristics:

Men
Number 490,445
Age at enrolment (year) 51.9 ±8.7
BMI (kg/m2) 23.3± 2.3
Alcohol drinking (g/day) 15.4 ± 32.2
Diabetes 6.8
Hypertension 42.8
Smoking status

Never smokers 21.4
Ex-smokers 22.6
Current smokers 56.0
Any alcohol use 73.1

Women
Number 358,060
Age at enrolment (year) 53.6 ±9.9
BMI (kg/m2) 23.8± 3.1
Alcohol drinking (g/day) 0.1 ± 1.4
Categorical variables (%)
Diabetes 5.1
Hypertension 35.2
Never smokers 92.4
Ex-smokers 2.5
Current smokers 5.1
Any alcohol use 13.6

Location: Korea

Recruitment strategy: Participated in at least one biennial National Health Insurance Corporation (NHIC) medical evaluation between 1992 and 1995

Length of follow-up:14 years

Response rate and loss to follow-up: 784,870 (59.0%) enrolled in 1992; 367,903 (27.7%) in 1993

98,417 (7.4%) in 1994; and 78,335 (5.9%) in 1995

Eligible population: Koreans aged 40–95 years insured by the National Health Insurance Corporation who had a biennial medical evaluation during 1992–1995

Excluded populations: 904 participants who died before January 1, 1993, were excluded, as were 75,807 participants who reported having cardiovascular disease, cancer, liver disease, or a respiratory disease at or prior to their initial visit, and 17,933 participants with missing information on body mass index or alcohol consumption, or with extremely low levels of BMI (<16 kg/m2) or height (1.30 m).

Exposures at midlife

Relevant exposures: Alcohol drinking, and smoking

Time: 1992-1995

Measurement of exposure: Self-report. Participants were classified into ‘‘current’’ smoker if they smoked currently for at least 1 year, ‘nonsmokers’ if they never smoked, and ex-smokers if they had quit smoking

Outcomes at 55 years or over

Outcomes: Dementia events

Outcome measurement: The category included dementia in AD (ICD-10 code: F00), VaD (F01), and unspecified dementia (F03). Diagnostic and statistical manual of mental disorder (DSM-IV, 4th edition), along with historical, physical, neurological, neuropsychological, laboratory and imaging evaluation

Time: January 1993 to December 2006

Analysis

Analysis strategy: Cox proportional hazard model

Confounders: Age, hypertension, total cholesterol, alcohol drinking, and smoking

Results, limitations, source of funding
Number: 3252 **Effect estimates:** HR (95% CI) Men AD Diabetes 1.6(1.3–2.0) Ex-smokers 1.0(0.8–1.2) Current smokers 1.1(0.9–3.4) Pre-hypertension 1.1(0.9–1.4) Stage 1 hypertension 1.3(1.0–1.6) Stage 2 hypertension 1.4(1.1–1.8) Borderline cholesterol. 1.2(1.0–1.4) High cholesterol 1.2(1.0–1.5) VaD Diabetes 2.0(1.5–2.8) Ex-smokers 0.9(0.7–1.3) Current smokers 1.1(0.8–1.5) Pre-hypertension 1.0(0.7–1.5) Stage 1 hypertension 1.7(1.2–2.5) Stage 2 hypertension 2.6(1.7–3.8) Borderline cholesterol. 1.3(1.0–1.6) High cholesterol 1.1(0.8–1.6) Unspec. Diabetes 1.3(1.0–1.7) Ex-smokers 0.9(0.7–1.2) Current smokers 1.2(1.0–1.5) Pre-hypertension 1.0(0.8–1.3) Stage 1 hypertension 1.2(0.9–1.5) Stage 2 hypertension 1.5(1.1–2.0) Borderline cholesterol. 0.9(0.7–1.0) High cholesterol 1.0(0.8–1.3) All Diabetes 1.6(1.3–1.8) Ex-smokers 1.0(0.8–1.1) Current smokers 1.2(1.0–1.3) Pre-hypertension 1.0(0.9–1.2) Stage 1 hypertension 1.3(1.1–1.5) Stage 2 hypertension 1.6 (1.4.–1.9) Borderline cholesterol. 1.0(0.9–1.2) High cholesterol 1.1(0.9–1.3) Women AD Diabetes 1.4(1.1–1.7) Ex-smokers 1.2(0.9–1.5) Current smokers 1.3(1.1–1.5) Pre-hypertension 1.1(0.9–1.3) Stage 1 hypertension 1.1(0.9–1.3) Stage 2 hypertension 1.2(0.9–1.4) Borderline cholesterol 1.0(0.9–1.2) High cholesterol 1.1(0.9–1.3) VaD

Diabetes 2.8(2.0–3.9)
Ex-smokers 0.9(0.5–1.5)
Current smokers 1.5(1.1–2.1)
Pre-hypertension 1.2(0.8–1.7)
Stage 1 hypertension 1.5(1.0–2.2)
Stage 2 hypertension 2.3(1.6–3.3)
Borderline cholesterol 1.1(0.8–1.4)
High cholesterol 0.9(0.7–1.3)

Unspec.
Diabetes 1.4(1.1–1.9)
Ex-smokers 0.9(0.7–1.2)
Current smokers 1.2(1.0–1.5)
Pre-hypertension 1.1(0.9–1.4)
Stage 1 hypertension 1.2(1.0–1.5)
Stage 2 hypertension 1.4(1.1–1.7)
Borderline cholesterol 1.0(0.8–1.2)
High cholesterol 1.1(0.9–1.4)

All
Diabetes 1.6(1.4–1.9)
Ex-smokers 1.1(0.9–1.3)
Current smokers 1.3(1.1–1.5)
Pre-hypertension 1.1(1.0–1.3)
Stage 1 hypertension 1.1(1.0–1.3)
Stage 2 hypertension 1.3(1.2–1.6)
Borderline cholesterol 1.0(0.9–1.1)
High cholesterol 1.0(0.9–1.2)

Significant trends: Diabetes increased the risk of either dementia in Alzheimer's disease or vascular dementia in men and women

Limitations: Accuracy of dementia data used from hospitalisation of NHIC has not been validated as for an outcome measurement

Source of funding: Seoul City R&BD program [10526]

Authors: King DE, Mainous AG 3rd, Geesey ME

Year: 2007

Citation: American Journal of Medicine 120(7): 598-603

Country of study: USA

Aim of study: Determine the frequency of adopting a healthy lifestyle in a middle-aged cohort, and determine the subsequent rates of cardiovascular disease and mortality among those who adopt a healthy lifestyle

Study design: Cohort study

Quality score: (++, + or -): +

Source population

Number of people: 15,792

Demographics: Not reported

Study (eligible and selected) population

Number of people: 15,708

Characteristics:

(n = 15,708) %

Age
45-54 52.7
55-64 47.3

Gender
Male 44.8
Female 55.2

Race
Other than African American 73.0
African American 27.0

Education
<High school 24.0
High school or trade school 40.7
College 35.3

Family Income
<$35,000/yr 57.8
>$35,000/yr 42.2

Hypertension
Yes 47.0
No 53.0

Diabetes
Yes 7.6
No 92.4

High Cholesterol
Yes 64.3
No 35.7

Coronary Heart Disease
Yes 4.9
No 95.1

Location: Four communities across the United States

Recruitment strategy: Probability sampling then selection involves sampling age-eligible persons from listings and then identifying their households

Length of follow-up: 6 years

Response rate and loss to follow-up: Not reported

Eligible population: Adults age 45-64

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Diet, smoking, physical activity

Time: 1987 to 1989

Measurement of exposure: The ARIC dietary questionnaire consisted of items regarding the frequency of consumption of various foods over the previous year. A healthy lifestyle was characterized by having all 4 of the following lifestyle characteristics: eating at least 5 fruits and vegetables daily; exercising minimum of 2.5 hours per week; BMI maintained between 18.5 and 30 kg/m2; and not smoking

For each physical activity the hours per week and the months per year are reported, and these values then were used to calculate the average number of hours per week spent on that activity over the course of the year

Current smokers identified by questionnaire during each visit.
Outcomes at 55 years or over
Outcomes: All-cause mortality and fatal or non-fatal cardiovascular disease **Outcome measurement:** State death certificates Identified participants who developed fatal or non-fatal cardiovascular disease from those whose underlying cause of death was coded as cardiovascular disease, or who had an MI, a silent MI, diagnosed coronary heart disease, a coronary heart disease procedure, or a definite or probable stroke **Time:** End of the year 1998
Analysis
Analysis strategy: Multiple logistic regression **Confounders:** Age group, gender, race, education, family income, and histories of hypertension, diabetes, elevated cholesterol, and previous coronary heart disease
Results, limitations, source of funding
Number: Not reported **Effect estimates:** Switchers to Healthy Lifestyle and Persistently Healthy Compared to Persistently Unhealthy Individuals Cardiovascular Disease Event OR (95% CI) Switched from Unhealthy to Healthy Lifestyle 0.65 (0.52-0.81) Persistently Unhealthy (<4 Healthy Factors at Both Visits) 1.00 (reference) Death OR (95% CI) Switched from Unhealthy to Healthy Lifestyle 0.60 (0.39-0.92) Persistently Unhealthy (<4 Healthy Factors at Both Visits) 1.00 (reference) **Significant trends:** Individuals who are older, female, with a college education, with family annual incomes greater than $35,000, or with no history of hypertension are more likely to have switched than others **Limitations:** Author: Misclassification via exaggerated exercise frequency or intake of fruits and vegetables Reviewer: Unclear no. of deaths **Source of funding:** Not reported

Authors: Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M… Folsom AR **Year:** 2001 **Citation:** Neurology 9;56(1): 42-8 **Country of study:** USA **Aim of study:** To determine the influence of smoking on cognitive change **Study design:** Longitudinal **Quality score: (++, + or -):** +

Source population
15,792 men and women ages 45-64 years recruited from Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD in 1987-89 using probability sample Clinical examination administered in 1987-89 with response rate of 46% in Jackson, and 65% in the other communities 13% of Forsyth County sample was black; the other sites consisted of predominantly white individuals
Study (eligible and selected) population
In 1990-92 (baseline for this study), 14,348 participants underwent cognitive evaluation with follow-up 6 years later, during which 10,963 respondents (76%) were re-tested **Sociodemographics:** 8,729 white individuals and 2,234 black individuals. 6% of subjects had less than 9th grade education **Follow-up:** 6 years follow-up since 1990-92 (baseline) **Exclusion:** Individuals with history of stroke or TIA (n=300) **Attrition:** Participants who dropped out or died were more impaired than those who returned for follow-up
Exposures at midlife
Self-reported smoking (never, former, current categories)
Outcomes at 55 years or over
Cognitive change: change in follow-up scores minus baseline scores for cognitive testing using: Delayed Word Recall (DWR) test, the Digit Symbol Subtest (DSS) of the Wechsler Adult Intelligence Scale-Revised, First Letter World Fluency (WF) test
Analysis
Analysis strategy: Linear regression was used to determine the influence of smoking on cognitive chang **Confounders:** Age, gender, race-center, education level, and use of CNS medications
Results, limitations, source of funding
Smoking was not associated with declines on any of the cognitive tests **Limitations:** Limited cognitive battery **Source of funding:** None reported

Authors: Lahti J, Laaksonen M, Lahelma E, Rahkonen O **Year:** 2010 **Citation:** Preventive Medicine 50(5-6): 246-50 **Country of study:** Finland **Aim of study:** To determine the impact of physical activity on physical health functioning **Study design:** Longitudinal **Quality score: (++, + or -):** + **External validity score: (++, + or -):**

Source population
Baseline questionnaire was administered to 13,346 employees ages 40, 45, 50, and 55 in Helsinki during 2000, 2001, and 2002 (response rate: 67%). At follow-up, in 2007, 7330 completed the survey (response rate: 83%)
Study (eligible and selected) population
Analysis restricted to **5,437** women and **1,257** men **Sociodemographics:** Mean ages of women and men were 49 and 51, respectively **Exclusion:** Participants with missing information (n=636) **Attrition:** -
Exposures at midlife
The average weekly hours of physical activity during leisure time or community during the last 12 months were used to calculate the volume of physical activity Time spent in physical activity and intensity were used to create the following participant categories: inactive, active moderate, active vigorous or vigorous activity only, very active moderate, very active vigorous, conditioning (moderate and vigorous activity or vigorous activity only)
Outcomes at 55 years or over
Physical health functioning was measured by the Short-Form 36 (SF-36) High scores on the SF-36 are related to better health The SF-36 demonstrates good construct validity, has high internal consistency and test-retest reliability
Analysis
Analysis strategy: Sex-specific proportions were calculated to determine the percentage of participants with poor or good physical health functioning at follow-up by baseline physical activity. Means were also computed **Confounders:** Age, baseline physical health functioning and limiting longstanding illness, working conditions, working overtime and BMI, smoking and alcohol consumption
Results, limitations, source of funding
• The more vigorous the physical activity, the greater the physical functioning mean scores appeared to be for both sexes • Among women, the lowest percentage of poor physical health functioning at follow-up was reported for the active vigorous group (22%, [95% CI: 19%, 25]) • Among men, the lowest percentage of poor physical health functioning was reported for the active moderate and active vigorous group (22%, [17%, 27%], and 22%, [16%, 28%], respectively) • Among women, the highest percentage of good physical health functioning at follow-up was reported for the very active moderate group (27%, [24%, 30%]), while for men it was reported for the conditioning group (29%, [24%, 35%]) **Limitations:** 1. Limited generalizability as sample consisted predominantly of relatively healthy, middle-aged, public sector female employees 2. Reverse causality may be possible as sicker participants may be less able to engage in physical

activity
3. Changes in levels or intensity of physical activity may have occurred during follow-up
4. Self-reported data

Source of funding: Ministry of Education, the Yrjö Jahnsson Foundation, the Juho Vainio Foundation, and the Academy of Finland

Authors: Laitala VS, Kaprio J, Koskenvuo M, Räihä I, Rinne JO, Silventoinen K

Year: 2009

Citation: American Journal of Clinical Nutrition 90(3): 640-6.

Country of study: Finland

Aim of study: To determine whether coffee consumption protects against cognitive decline in a sample of Finnish twins

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

13,888 same sex twin pairs born before 1958 in Finland were recruited and completed a self-administered questionnaire in 1975 and 1981 (response rates: 89% and 84%, respectively)

Twins ages 65 years or greater had their cognitive status assessed through telephone interview: monozygotic twins with both twins alive interviewed between 1999-01, same sex dizygotic twins and twins of uncertain zygosity between 2003-07

Study (eligible and selected) population

2483 twins of known zygosity (703 monozygotic twins and 1780 dizygotic twins) and **123** twins of uncertain zygosity

Overall response rate: 79%

Sociodemographics: Mean age of respondents of 46 years in 1975 and 52 years in 1981

Follow-up: Median follow-up of 28 years

Exclusion:

i) Participants not reached by phone (n=127)
ii) Declined to participate (n=412)
iii) Died (n=32)
iv) Not contacted or with incomplete interviews (n=133)

Exposures at midlife

Daily coffee drinking was assessed in 1975 and 1981

If coffee consumption was reported at both times, the mean intake was calculated

Participants were categorised into the following groups of intake: 0–3, 3.5–8, and >8 cups/d

Attrition: Participants and non-participants comparable in terms of sex, education, and alcohol use patterns

Outcomes at 55 years or over

Potential dementia cases identified through TELE screening and the Telephone Interview for Cognitive Status (TICS)

Based on these screening tests, scores of cognitive function were assigned (higher scores indicate better cognitive function) and participants were classified as demented, cognitively declined, and healthy

TELE and TICS and sensitive and specific and correlate well with the MMSE

Analysis

Analysis strategy: Multinomial logistic regression was used to assess the association between coffee intake and mild cognitive impairment or dementia, with twins being treated as individuals, not pairs (clustering taken into account). The association between cognitive performance and coffee intake was also assessed for discordant twin pairs

Confounders: Education, age at the interview, sex, BMI, binge drinking, smoking, life satisfaction, cardiovascular disease, hypercholesterolemia, hypertension, and diabetes

Results, limitations, source of funding

- The prevalence of dementia according to the TELE and TICS was: 9.8% and 7.8% (respectively) for those ages 65-69 years; 11.9% and 7.9% for those ages 70-74 years; 19.1% and 15.6% for those ages 75-79 years; 31.7% and 25.3% for those ages 80-84 years; and 53.0% and 47.0% for those older than 84 years
- Coffee consumption was not associated with dementia or mild cognitive impairment
- The twin-pair analysis of twins discordant for coffee consumption and cognitive score showed that the correlation between cognitive function and coffee drinking was not statistically significant

Limitations: Unable to assess if rate of coffee consumption affects rate of cognitive decline

Source of funding: None reported

Authors: Laitinen MH, Ngandu T, Rovio S, Helkala EL, Uusitalo U, Viitanen M… Kivipelto M

Year: 2006

Citation: Dementia & Geriatric Cognitive Disorders 22(1): 99-107

Country of study: Finland

Aim of study: To determine the association between fat intake at midlife and risk of dementia and Alzheimer's disease

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

Randomly selected participants from the survivors of population-based samples from North Karelia and Kuopio provinces; samples drawn from the national population register

At least 250 subjects of each sex and 10-year age group chosen

62.1% (n=900) and 37.9% (549) of participants were women and men, respectively

Study (eligible and selected) population

A random sample of **1449** participants examined once in 1972, 1977, 1982, or 1987 were re-examined in 1998 (ages 65-79 years)

Sociodemographics: Mean age at midlife examination was 50.4 years and 71.3 years at follow-up

Participation rate: 77%-96%

Follow-up: Mean length of follow-up 21 years

Exclusion: -

Attrition: -
Exposures at midlife
Dietary habits assessed through self-administered questionnaire Most questions were qualitative or frequency-based; consumption of milk, sour milk, eggs, coffee, tea, sugar in tea/coffee assessed quantitatively Daily number of bread slices and type of spread used and amount of spread per slice (i.e. 0, 2.5, 5, 10, 15 g) Fat intake from milk, sour milk and spreads calculated – served as indicator of total fat intake Calculated polyunsaturated [PUFA], monounsaturated [MUFA], saturated fatty acids [SFA] derived from spreads
Outcomes at 55 years or over
Cognitive status assessed using MMSE; if score <=24, invited to clinical phase for dementia diagnosis
Analysis
Analysis strategy: Logistic regression used to assess influence of fat intake and dementia and AD development **Confounders:** Midlife age, gender, education, follow-up time, milk fat and other subtypes of fats from spreads, midlife vascular risk factors including smoking status, systolic blood pressure, cholesterol and BMI, history of vascular disorders including MI, stroke, and diabetes;- effect modification of APOE4 by fat intake assessed
Results, limitations, source of funding
• 117 diagnosed with dementia, of which 76 had AD • Proportion of demented persons was higher among those having used very little or no fat (from milk and spreads) compared to moderate users (31.6% [n=37] and 24.6% [n=458], respectively; p-value=0.02) • 28.2% [n=33] and 24.8% [n=462] of demented and non-demented people consumed large amounts of fats • Odds of developing dementia were lower for those consuming moderate amounts of polyunsaturated fats from spreads compared to those consuming low amounts [OR=0.40, 95% CI: 0.17-0.94; and 2] • Odds of developing dementia and AD were higher for those consuming moderate amounts of saturated fats from spreads in comparison with those consuming low amounts [OR=2.45, (1.10-5.47), and OR=3.82, (1.48-9.87), respectively] • Among APOE4 carriers, the odds of developing dementia was lower for those with moderate PUFA intake compared to those with low PUFA intake [OR=0.29, 95% CI: 0.09-0.89]; the reverse was observed for SFA **Limitations:** 1. Limited reliability of self-reported dietary data 2. Residual confounding, i.e. intake of fat from other sources and other nutrients may influence association with dementia/AD 3. Long-term fat intake may be more likely to influence disease risk 4. Selective survival: those with high SFA intake may have died from vascular disease – may differ from survivors 5. Misclassification of dementia diagnosis by using medical records (under-diagnosis **Source of funding:** EVO grants from Kuopio University Hospital, Academy of Finland, Alzheimer

Association, EU, Finnish Cultural Foundation of Northern Savo, the Foundation of Juho Vainio, and the Gamla Tjanarinnor Foundation, the Swedish Council for Working Life and Social Research

Authors: Lajous M, Willett WC, Robins J, Young JG, Rimm E, Mozaffarian D, Hernán MA

Year: 2013

Citation: American Journal of Epidemiology 1;178(3): 382-91

Country of study: US

Aim of study: To determine whether changes in fish consumption in midlife affect the risk of coronary heart disease

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

51,529 US male health professionals ages 40-75 years enrolled in 1986 (Health Professionals Follow-up Study)

121,701 US female nurses ages 30-55 years enrolled in 1976 (Nurses' Health Study)

Study (eligible and selected) population

See 'Source population'

Follow-up:

Health Professionals Follow-up Study: 1990 until CHD diagnosis, death, censoring, or June 2008, whichever came first

Nurses' Health Study*:* Time of return of 1986 participant questionnaire to CHD diagnosis, death, censoring, or December 2008, whichever came first

Exclusion: Health professionals who **(male [n], female [n])**:

i) Did not respond or provided insufficient information for survey (n=14,485, 55,328)
ii) Died (n=779, 92)
iii) Had MI (n=432, 6)
iv) Had CVD, diabetes, cancer (n=6,300, 9,653)
v) Had missing variable data or implausible energy intake (n=4,726, 2,850)

Attrition: -

Exposures at midlife

Fish intake and red meat intake were assessed using a semi-quantitative food frequency questionnaire that was first administered to males in 1986 and females in 1984 and 1986, and both sexes every 4 years thereafter

Validated questionnaire evaluated average consumption of specific portion sizes of food items in the past year, with response options ranging from 'never or less than once a month' to '6 or more per day'

Food item intake was summed and daily nutrient intakes were based on nutrient content of specified portion and frequency of food item intake

Total nutrient and energy intake was calculated and based on the sum of nutrient intakes from different foods

Total alcohol intake was also calculated

Outcomes at 55 years or over

Total, nonfatal, and fatal CHD were assessed

Nonfatal myocardial infarctions occurring during follow-up were identified using medical records, while deaths were identified through relatives, postal authorities, or the National Death Index (medical records, death certificates, autopsies used to identify cause of death)

Analysis

Hypothetical interventions: A randomised trial of fish intake on 18-year risks of CHD outcomes in men and 22-year risks of CHD outcomes in women was emulated using observational data

The effect of the following hypothetical 'threshold' interventions was assessed: intake of fish (measured in servings/week) of: 1) 0; 2) at least 1; 3) at least 2; 4) at least 3; or 4) at least 5 (servings/week)

At each 4-year interval, fish intake is increased to the threshold for those who eat fewer fish servings than the threshold (e.g., the threshold for intervention 3) is at least 2 servings/week); otherwise, it remains unchanged

'Isocaloric' interventions were also considered in which red meat intake was replaced by fish intake to achieve the following serving amounts: 6) at least 1 (serving/week); 7) at least 2; 8) at least 3; 9) at least 5

Increase to the threshold was not undertaken if neither fish nor red meat consumption was reported

Analysis strategy: The standardised risk of CHD outcomes under hypothetical interventions was assessed using the parametric g-formula. Pooled logistic and linear regression models were used to estimate probability density functions. Monte Carlo simulations were conducted

Confounders: Age, parental history of myocardial infarction, oral contraceptive use, body mass index, smoking, menopausal status, hormone replacement therapy, physical activity, aspirin use, vitamin E supplement use, multivitamin supplement use, high blood pressure, high cholesterol, diabetes, angina or coronary artery bypass grafting, stroke, and intakes of calories, trans-fats, alcohol, cereal fibre, red meat, and fish

Results, limitations, source of funding

<u>Males</u>
No significant associations were reported for males

<u>Females:</u>
Meat replaced with fish: the lowest risk for *total coronary heart disease* was reported when meat was replaced with fish to attain >=3 servings/week (Risk ratio=0.81, [0.68, 0.95])

The lowest risk for *fatal coronary heart disease* was reported when: meat was replaced with fish to attain >=5 servings/week (Risk ratio=0.68, [0.37, 0.99]); and when >=5 fish servings/week were consumed (Risk ratio=0.66, [0.36, 0.98])

Limitations:

1. Measurement error when attempting to quantify dietary change
2. Potential residual confounding; particularly in men, as they may have been more focused on preventing CVD and making dietary changes in presence of slightly elevated BP or glucose/lipid levels

Source of funding: National Institutes of Health

Authors: Lang IA, Guralnik JM, Melzer D

Year: 2007

Citation: Journal of the American Geriatric Society 55(11): 1836-41

Country of study: US

Aim of study: To assess whether body mass index and level of physical activity are associated with impaired physical function **Study design:** Longitudinal **Quality score: (++, + or -):** +
Source population
Health and Retirement Study(HRS): 10,086 US participants ages 50-59 years at baseline in 1998 and still alive in 2004 After baseline face to face interviews, phone interviews were conducted every even-numbered year English Longitudinal Study of Aging (ELSA): 19,924 English participants born on or before February 29, 1952 were identified for cross-sectional survey in 1998, 1999, 2001 11,392 individuals recruited for ELSA study (eligible respondents 65.7%)
Study (eligible and selected) population
HRS: Analysis restricted to **8,702** participants **Sociodemographics:** 4569 were women and 1,031 had 0-9 years of full-time education, baseline mean age of 60.2 years ELSA: Analysis restricted to **1,507** out of 3,335 respondents ages 50-69 years with baseline exposure information measured in 1998-99, who participated in second ELSA wave in 2004, and had recommended weight or above and were nondisabled at baseline **Sociodemographics:** 837 were women and 134 had 0-9 years of full-time education, baseline mean age of 58 years **Median length of follow-up:** HRS: 72 months ELSA: 73 months **Exclusion:** HRS: *BMI <20 (353) *Participants with one or more mobility problems (n=1,370) ELSA: *Participants who died or were ineligible for follow-up (n=2,596) *BMI <20 (n=64) *Participants with long-term conditions (n=1,764) **Attrition:** -
Exposures at midlife
BMI In HRS, self-reported weight and height at baseline and follow-up used to calculate BMI, which was classified as: recommended weight (20-24.9), overweight (25-29.9), or obese (>=30) In ELSA, weight and height measured by clinicians at baseline and follow-up, and same BMI categories used as for HRS Physical activity In HRS, participants asked about participation in vigorous physical activity (e.g., sports) at least 3 times/week over last 12 months, with yes/no answer options

In ELSA, respondents asked about the number of days/week that they undertook activities, such as housework or gardening, manual labour, participating in vigorous sports for 30 minutes or longer, and a summary measure was subsequently created

ELSA participants were also categorized into whether or not they participated in vigorous activity at least 3 days/week

Outcomes at 55 years or over

Physical function

Mobility impairment was ascertained for HRS participants through questions on difficulty with walking or climbing stairs

Measured physical performance impairment in ELSA respondents was measured by clinician using a modified version of the Short Physical Performance Battery that assessed balance, chair stands, and grip strength; a physical performance score out of 12 was allocated to each participant (with 7 or less representing impairment)

Analysis

Analysis strategy: Logistic regression was used to assess the influence of physical activity on incident impaired physical function (ELSA) and self-reported mobility impairment (HRS) by baseline BMI category

Confounders: Age, sex, health behaviours, socioeconomic status, and baseline functional limitations, smoking, drinking

Results, limitations, source of funding

- Participants who reported being active at least three times per week had a lower incidence of physical impairment than those with lower levels of reported physical activity for each weight category in both HRS and ELSA

Limitations: Self-reported physical activity

Source of funding: National Institutes of Health Award, Intramural Research Program, National Institute on Aging, NIH

Authors: Langlois JA, Mussolino ME, Visser M, Looker AC, Harris T, Madans J

Year: 2001

Citation: Osteoporosis International 12(9): 763-8

Country of study: USA

Aim of study: To determine the influence of weight loss in middle-aged and older women and risk for hip fracture

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

US women surveyed on nutrition and weight history in 1971-75 (baseline)

14,407 individuals ages 25-74 years participated in study follow-up waves in 1982-84, 1986, 1987, and 1992

Study (eligible and selected) population

Study restricted to **2180** out of 2410 community-dwelling white women ages 50–74 years who met inclusion criteria **Follow-up:** 33,174 person-years of observation during 22 years Time from date of examination to date of hip fracture, or date of last follow-up interview, or date of death for those without a hip fracture **Exclusion:** Women with: i) A history of hip fracture at baseline (n=51) ii) Loss to follow (n=139) iii) Missing data (n=40) **Attrition:** 139 women lost to follow-up. At baseline, excluded women were older, less physically active, and weighed less than participants
Exposures at midlife
Body weight and weight history self-reported at baseline in 1971-75 Self-reported maximum lifetime weight was ascertained and the percent weight loss was calculated ([maximum weight-baseline weight / maximum weight]*100) Proportional weight loss categorized into: 1) <5%; 5% to <10% and >=10%; and 2) <10% and >=10%
Outcomes at 55 years or over
Hip fractures identified through death certificates and hospital records
Analysis
Analysis strategy: Cox proportional hazards regression was used to determine the influence of weight loss on hip fracture risk **Confounders:** Age at baseline, body mass index at maximum weight, smoking, alcohol consumption in the past year, history of chronic conditions and level of non-recreational physical activity **Stratification:** BMI, age
Results, limitations, source of funding

- 171 hip fractures identified
- Mean age at hip fracture was 71.7 years for women ages 50-64 years, and 81.1 years for women ages 65-
  74 years
- Incidence rates of hip fracture appeared to increase with increasing age and weight loss

Women aged 50-64 years at baseline:

Women with >=10% weight loss had a greater risk of hip fracture compared to women with <5% weight loss (RR=2.54, [1.10, 5.86])

Women aged 65-74 years at baseline:

Women with >=10% weight loss had a greater risk of hip fracture compared to women with <5% weight loss (RR=2.04, [1.37, 3.04])

When <10% weight loss was used as the reference category, the relative risks changed minimally for both age groups

Women with BMI <26.2 (kg/m2) at baseline:

Women with >=10% weight loss had a greater risk of hip fracture compared to women with <5% weight loss (RR=2.37, [1.32, 4.27])

Limitations:

1. Cannot generalise to other age groups, races, or older men
2. Self-reported weight (potentially bias association towards the null)
3. Weight fluctuation was not taken into account

Source of funding: None reported

Authors: Laurin D, Masaki KH, Foley DJ, White LR, Launer LJ

Year: 2004

Citation: American Journal of Epidemiology 159(10): 959-96

Country of study: USA

Aim of study: To determine the influence of midlife dietary intake of antioxidants on risk of late-life incident dementia

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

8,006 Japanese-American men, born between 1900-19, and residing in Oahu, Hawaii in 1965 were clinically evaluated and interviewed in 1965-68 when they were aged 45-68 years (examination 1), with follow-up examinations/interviews in 1968-70 (examination 2) and 1971-74 (examination 3)

3,734 people (80% of those eligible) ages 71-93 years participated in 1991-93 survey on neurodegenerative disease (examination 4) with 2 re-examinations for dementia after assessments in 1994-96 (examination 5) and 1997-99 (examination 6)

Study (eligible and selected) population

Analysis restricted to **2,459** participants free of dementia in 1991-93 and who underwent follow-up examinations until 1999

Follow-up: 30.2 years

Sociodemographics: Mean ages at examinations 1 and 4 were 51.2 and 76.3 years

Median number of years of education was 12

Exclusion: Participants with:

i) Dementia (n=226)
ii) Atypical diet (n=226)
iii) Died during follow-up (n=516)
iv) Nonresponse at examination 5 (n=307)

Attrition:

a) Excluded individuals with atypical diet were similar to participants with respect to age, education, and BMI at exam. 1 and intake of supplemental vitamins
b) Those who died during follow-up were, at exam. 1, older, less educated, reported lower energy intake and were less likely to use supplements
c) Non-responders at examination 5 were older at exam. 1, had lower intakes of beta-carotene and vitamin C, and were less likely to use supplements

Exposures at midlife

24-hour dietary recall assessed through interview in 1965-68

Participants also queried on frequency of consumption of 26 food and drink items at examinations 1 and 3

Flavonoid intake was assessed through mean intake of tea assessed at examinations 1 and 3

Intakes of beta-carotene, vitamin C, vitamin E, and flavonoids were divided into quartiles; the median energy-adjusted intakes for the first, second, third, and fourth quartiles, respectively, were: 16, 71, 296, and 1,101 µg/day for beta-carotene; 23, 69, 128, and 219 mg/day for vitamin C, 3.8, 10.7, 18.0, and 29.9 mg/day for vitamin E; and 2.0, 2.9, 4.5, and 8.2 mg/day for flavonoids

Outcomes at 55 years or over

Dementia was ascertained through screening using the Cognitive Abilities Screening Instrument and evaluated through a neurologic examination, neuropsychological testing, and an informant interview

Subjects with dementia underwent blood tests and brain imaging

Analysis

Analysis strategy: Cox proportional hazards regression was used to determine influence of midlife intake of antioxidants and risk of late-life cognitive impairment

Confounders: Age, education, smoking status, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, and apolipoprotein E e4

Results, limitations, source of funding

- 235 participants developed dementia over 30.2 years of follow-up (102 Alzheimer's disease cases, 38 cases of Alzheimer's disease with cerebrovascular disease, 44 vascular dementia cases, 51 cases due to other causes)

<u>Vitamin E intake:</u>

- Compared to the first quartile of vit. E intake, the risk for dementia and Alzheimer's disease was greater for those in the second quartile of vit. E intake (dementia RR=1.47, [1.01, 2.14] and Alzheimer's disease RR=1.84, [1.04, 3.25], respectively)
- Compared to the first quartile of vit. E intake, the risk for Alzheimer's disease with and without cerebrovascular disease was greater for those in the second and fourth quartiles of vit. E intake (RR=1.92, [1.16, 3.18], RR=1.78, [1.06, 2.98], respectively)
- There was a significant association between high intake of antioxidants and risk for Alzheimer's disease with and without contributing cerebrovascular disease (RR=1.82, [1.04, 3.21])

Limitations:

1. High nonparticipation at first follow-up and death rates
2. The short 24-hour recall period of food intake may be inaccurate in determining average intake of antioxidants

Source of funding: National Institutes of Health, the National Institute on Aging, and the National Heart, Lung, and Blood Institute

Authors: Lehto SM, Ruusunen A, Tolmunen T, Voutilainen S, Tuomainen TP, Kauhanen J

Year: 2013

Citation: Journal of Affective Disorders 5;150(2): 682-5

Country of study: Finland

Aim of study: Examine the association between dietary zinc intake and depression

Study design: Population-based prospective study

Quality score: (++, + or -): +

Source population

Number of people: Not reported

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2682

Characteristics:

Discharge diagnosis of depressive disorder
Age (years) 54.3(48.5–54.4)
HPL depression scores 2(0–3)
Living alone, n (%) 8(13.3)
Length of education (years) 8(6–10)
Smoking (cigarette-years) 0(0–287)
Alcohol consumption (g/week) 41.1(7.6–116.1)
Energy expenditure (kcal/d) 85.8(32.1–179.6)
Regular use of vitamins and trace elements, yes (%)7(11.7)
Body mass index (kg/m2) 26.8(25.0–28.5)
Total energy intake (kJ/d) 10,451(8708–12,780)
Zinc RDIe met (≥9 mg/d), n (%) 60(100.0)
Dietary zinc (energy-adjusted)(mg)14.4(12.7–16.4)

No depression
Age (years) 54.3(48.9–54.5)
HPL depression scores 1(0–2)
Living alone, n (%) 282(12.5)
Length of education (years) 8(6–10)
Smoking (cigarette-years) 0(0–173)
Alcohol consumption (g/week) 30.7(6.2–88.5)
Energy expenditure (kcal/d) 88.2(31.8–193.4)
Regular use of vitamins and trace elements, yes (%) 165(7.3)
Body mass index (kg/m2) 26.4(24.5–28.9)
Total energy intake (kJ/d) 9621 (8122–11,289)
Zinc RDIe met (≥9 mg/d), n (%) 2129 (94.3)
Dietary zinc (energy-adjusted)(mg) 14.3 (12.9–16.0)

Test statistics and P value
Age Z=−2.2 and 0.026
HPL depression scores Z=−2.7 and 0.006
Living alone $\chi2$=0.0 and 0.846
Length of education Z=0.0 and 0.968
Smoking Z=−0.5 and 0.597
Alcohol consumption Z=−0.7 and 0.467
Energy expenditure Z=0.0 and 0.993
Regular use of vitamins and trace elements, yes $\chi2$=1.60 and .204
Body mass index Z=−0.7 and 0.476
Total energy intake Z=−2.7 and 0.008
Zinc RDIe met – 0.076c
Dietary zinc Z=−0.3 and 0.795

Location: Kuopio region of eastern Finland

Recruitment strategy: Not reported

Length of follow-up: 20 years

Response rate and loss to follow-up: Not reported

Eligible population: Finnish men

Excluded populations: Individuals who at baseline had elevated depressive symptoms. Data were incomplete for 82 participants

Exposures at midlife

Relevant exposures: Diet, smoking, physical activity

Time: March 1984 and December 1989

Measurement of exposure: 4-day food recording during baseline examination

The current number of cigarettes, cigars and pipefuls of tobacco smoked daily and the duration of regular smoking in years were recorded using a self-administered questionnaire

Physical activity was assessed using the 12-month Physical Activity Questionnaire

Outcomes at 55 years or over

Outcomes: Depressive symptoms

Outcome measurement: Depression was defined as having received a hospital discharge diagnosis of unipolar depressive disorder

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, baseline depression severity, smoking, alcohol use, physical exercise and the use of dietary supplements

Results, limitations, source of funding

Number: 60 (2.7%)

Effect estimates:

Receiving diagnosis of depression and energy-adjusted dietary zinc intake
RR 1.02, 95%CI 0.96–1.08, p=0.595

Lowest tertile of energy-adjusted zinc intake and a diagnosis of depression

RR 1.06, 95%CI 0.59–1.90, p=0.856

Future hospital discharge diagnosis of depression and baseline HPL depressions core
RR 1.39, 95% CI 1.15–1.67, p=0.001

Significant trends: No association was observable between the risk of receiving a hospital discharge diagnosis of depression and the energy- adjusted dietary zinc intake as a continuous measure. No association was observed between belonging to the lowest tertile of energy-adjusted zinc intake and a future hospital discharge diagnosis of depression

Limitations:

1. Study comprised exclusively of men.
2. The number of individuals who received a hospital discharge diagnosis of depression was fairly small.
3. May not have detected the cases with milder depression

Source of funding: The authors conducted this study as part of their work, without external funding

Authors: Leosdottir M, Nilsson PM, Nilsson JA, Berglund G

Year: 2007

Citation: European Journal of Cardiovascular Prevention & Rehabilitation 14(5): 701-6

Country of study: Sweden

Aim of study: To determine whether total fat intake, saturated, monounsaturated, or polyunsaturated fat intake are risk factor for cardiovascular events

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

74,138 individuals, comprising men born between 1923-45 and women born between 1923-50 were recruited from 1991 through 1996

Study (eligible and selected) population

28,098 enrolled individuals (60.6% were women)

40% participation rate

Follow-up: Date of study entry until occurrence of cardiovascular event or end of follow in year 2002. Mean follow-up of 8.4 years

Exclusion: Individuals with history of acute coronary event or ischemic stroke (women: n=168, men: n=536)

Attrition: 100 women and 64 men lost to follow-up mainly due to out-of-country emigration.

Mortality higher in non-participants

Exposures at midlife

Dietary intake was assessed through 7-day menu diary, questionnaire assessing meal patterns, food item consumption frequencies and portion sizes, as well as interviews

Intake of fat, protein, carbohydrates, and alcohol recorded in grams/day, and relative fat intake measured as percentage of non-alcohol energy from fat

Reproducibility and validity of dietary measurement methods established

Intake divided into quartiles of total fat intake, saturated, monounsaturated, and polyunsaturated fat intake; the ratio between unsaturated and saturated fat intake was also obtained

Outcomes at 55 years or over
Fatal and nonfatal CVD event cases identified through local and national registries
Analysis
Analysis strategy: Cox proportional hazards regression used to assess influence of fat intake on risk for cardiovascular events in total, as well as risk for acute coronary events or ischemic stroke **Confounders: A**ge, smoking habits, alcohol consumption, socioeconomic status, marital status, physical activity, body mass index, fibre intake, and blood pressure; adjustments were also made for total fat intake for the ratio between unsaturated and saturated fats
Results, limitations, source of funding
1556 fatal and non-fatal events (908 acute coronary events and 648 ischemic strokes) occurred <u>Cardiovascular events:</u> • Compared to the first quartile of monounsaturated/sat. fat intake ratio, the risk for cardiovascular events was lower for women in the second quartile of monounsaturated/sat. fat intake ratio (HR=0.77, [0.61, 0.98]); similar findings were observed among women for polyunsaturated/sat. fat intake ratio (HR=0.77, [0.61, 0.97]) • Compared to the first quartile of polyunsaturated/sat. fat intake ratio, the risk for cardiovascular events was lower for women in the third quartile of polyunsaturated/sat. fat intake ratio (HR=0.78, [0.62, 0.99]); <u>Acute coronary events:</u> • Compared to the first quartile of monounsaturated/sat. fat intake ratio, the risk for acute coronary events was lower for women in the second quartile of monounsaturated/sat. fat intake ratio (HR=0.71, [0.51, 0.99]); similar findings were observed among women for saturated fat intake (HR=0.67, [0.45, 0.99] **Limitations:** 1. Residual confounding (e.g., trans-fatty acids not measured) 2. Assessment of diet at only one point in time raises issue of reliability of dietary assessment 3. Self-reported dietary assessment may lead to underreporting of energy and fat intake 4. Low participation rate 5. Possible healthy-cohort effect **Source of funding:** The Swedish Scientific Council, The Swedish Cancer Foundation, Anna Jonssons Memorial Fund, the Swedish Heart and Lung Foundation, The European Commission, and The Region of Skane, Sweden

Authors: Levitan EB, Mittleman MA, Håkansson N, Wolk A **Year:** 2007 **Citation:** American Journal of Clinical Nutrition 85(6): 1521-6 **Country of study:** Sweden **Aim of study:** Tested the hypothesis that men consuming diets high in glycemic index or glycemic load have a greater risk of cardiovascular disease **Study design:** Prospective observational study **Quality score: (++, + or -):** +
Source population

Number of people: 48,850

Demographics: Not reported

Study (eligible and selected) population

Number of people: 36,246

Characteristics:

Quartile of dietary glycemic load

Quartile 1: Age (y) 58.7 ± 9.1; BMI (kg/m2) 25.8 ± 3.3; Physical activity (min/d) 53.9 ± 42.7; Cigarette smoking (%) Never 31.4, Past 39.2, Current 29.4; Education (%) Less than high school 63.1, High school 16.0, University 20.9; Alcohol (g/d) 14.8 ± 13.2

Quartile 2: Age (y) 58.7 ± 9.3; BMI (kg/m2) 25.6 ± 3.2; Physical activity (min/d) 56.7 ± 43.2; Cigarette smoking (%) Never 37.7, Past 38.0, Current 24.4; Education (%) Less than high school 63.5, High school 16.1, University 20.5; Alcohol (g/d) 11.5 ± 9.6

Quartile 3: Age (y) 59.0 ± 9.5; BMI (kg/m2) 25.5 ± 3.2; Physical activity (min/d) 57.6 ± 43.2; Cigarette smoking (%) Never 40.1, Past 37.7, Current 22.2; Education (%) Less than high school 67.3, High school 15.0, University 17.7; Alcohol (g/d) 9.5 ± 8.7

Quartile 4: Age (y) 59.4 ± 9.7; BMI (kg/m2) 25.6 ± 3.3; Physical activity (min/d) 58.6 ± 45.3; Cigarette smoking (%) Never 40.0, Past 37.0, Current 23.1; Education (%) Less than high school 73.8, High school 12.7, University 13.5; Alcohol (g/d) 7.1 ± 7.4

Location: Vastmanland and Orebro Counties in central Sweden

Recruitment strategy: Mailed a four-page questionnaire

Length of follow-up: 6 years

Response rate and loss to follow-up: 49

Eligible population: All men in two Swedish counties aged 45–79 years

Excluded populations: Men providing incorrect national identification numbers or who did not provide national identification numbers (n=260), who returned blank questionnaires (n=92), or who had a previous diagnosis of cancer (n=2592), history of cardiovascular disease before 1 January 1998 or a history of diabetes (n=5069) determined from record linkage and self-report , those who did not report their height and weight or who reported implausible energy intakes

Exposures at midlife

Relevant exposures: Diet

Time: 1997 and 1998

Measurement of exposure: Food-frequency questionnaire

Outcomes at 55 years or over

Outcomes: Myocardial infarction, ischemic stroke, hemorrhagic stroke, and cardiovascular mortality and all-cause mortality

Outcome measurement: Inpatient, cause-of-death, and death registries

Time: 01 January 1998 until 31 December 2003 for myocardial infarction, ischemic stroke, hemorrhagic stroke, and cardiovascular mortality; until 31 December 2005 for all-cause mortality.

Analysis

Analysis strategy: Cox proportion hazard models

Confounders: Cigarette smoking, body mass index, physical activity, demographic characteristics,

and nutritional factors
Results, limitations, source of funding
Number: Myocardial infarction (n=1324), ischemic stroke (n=692), cardiovascular mortality (n=785), or all-cause mortality (n=2959), hemorrhagic stroke (n= 165) **Effect estimates:** **Relative risks (RRs) CVD and mortality by quartile of dietary GI** <u>Myocardial infarction</u> **Q1** 1, **Q2** 0.91 (0.77, 1.07), **Q3** 0.96 (0.82, 1.13), **Q4** 0.99 (0.84, 1.17), **P** 0.93 <u>Ischemic stroke</u> **Q1** 1, **Q2** 1.21 (0.97, 1.50) **Q3** 1.12 (0.89, 1.41) **Q4** 1.09 (0.85, 1.38) **P** 0.67 <u>Hemorrhagic stroke</u> **Q1** 1 **Q2** 1.11 (0.71, 1.72)**Q3** 1.04 (0.66, 1.63) **Q4** 1.19 (0.77, 1.83) **P** 0.49 <u>Cardiovascular mortality</u> **Q1** 1 **Q2** 0.98 (0.80, 1.21) **Q3** 0.93 (0.74, 1.15) **Q4** 1.09 (0.88, 1.36) **P** 0.46 <u>All-cause mortality</u> **Q1** 1 **Q2** 1.02 (0.92, 1.14) **Q3** 0.96 (0.86, 1.07) **Q4** 1.06 (0.95, 1.19) **P** 0.41 **CVD and mortality by quartile of dietary GL** <u>Myocardial infarction</u> **Q1** 1 **Q2** 0.91 (0.77, 1.08) **Q3** 1.02 (0.83, 1.25) **Q4** 1.04 (0.80, 1.34) **P** 0.65 <u>Ischemic stroke</u> **Q1** 1 **Q2** 0.94 (0.74, 1.19) **Q3** 0.95 (0.72, 1.26) **Q4** 1.05 (0.74, 1.49) **P** 0.76 <u>Hemorrhagic stroke</u> **Q1** 1 **Q2** 0.98 (0.60, 1.59) **Q3** 1.57 (1.01, 2.44) **Q4** 1.44 (0.91, 2.27) **P** 0.047 <u>Cardiovascular mortality</u> **Q1** 1 **Q2** 0.93 (0.74, 1.17) **Q3** 1.06 (0.81, 1.37) **Q4** 1.13 (0.81, 1.56) **P** 0.39 <u>All-cause mortality</u> **Q1** 1 **Q2** 0.90 (0.80, 1.00) **Q3** 0.95 (0.83, 1.08) **Q4** 0.94 (0.79, 1.11) **P** 0.54 **Significant trends:** Dietary GI and dietary GL were not associated with ischemic CVD or mortality, but dietary GL was associated with a greater risk of hemorrhagic stroke **Limitations:** 1. Misclassification of exposure 2. Follow-up in this study was relatively short **3.** Survival bias **Source of funding:** Swedish Research Council/Longitudinal Studies. EBL was supported by a grant from the Swedish Foundation for International Cooperation in Research and Higher Education (STINT) and a National Heart, Lung, and Blood Institute training grant (HL07374)

Authors: Levitan EB, Wolk A, Mittleman MA **Year:** 2009 **Citation:** European Heart Journal 30(12): 1495-500 **Country of study:** Sweden **Aim of study:** Examine if fatty fish and marine omega-3 fatty acids were associated with lower rates of heart failure **Study design:** Population-based prospective study **Quality score: (++, + or -):** +
Source population
Number of people: 48,850 **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 39,367

Characteristics:

Fatty-fish intake

Never Age (years) 58.0 + 9.8; Physical activity (MET h/day) 41.9 + 5.1; Body mass index (kg/m2) 25.7 + 3.5; Cigarette smoking Current 1605 (27.6); Past 1963 (33.8); Never 2245 (38.6); Education Less than high school 4218 (72.6), High school 773 (13.3), University 822 (14.1); Alcohol (g/day) 8.7+10.8

<1 servings/week Age (years) 59.3 + 9.6; Physical activity (MET h/day) 41.9 + 5.0; Body mass index (kg/m2) 25.6 + 3.2; Cigarette smoking Current 2675 (25.0); Past 3972 (37.1); Never 4053 (37.9); Education Less than high school 7800 (72.9), High school 1406 (13.1), University 1494 (14.0); Alcohol (g/day) 9.2 + 9.6

1 serving/week Age (years) 58.9 + 9.2; Physical activity (MET h/day) 41.4 + 4.8; Body mass index (kg/m2) 25.6 + 3.2; Cigarette smoking Current 3808 (23.0), Past 6375 (38.4), Never 6405 (38.6); Education Less than high school 10 683 (64.4), High school 2622 (15.8), University 3283 (19.8); Alcohol (g/day) 11.4 + 9.9

2 servings/week Age (years) 61.0 + 9.2; Physical activity (MET h/day) 41.5 + 4.8; Body mass index (kg/m2) 25.8 + 3.3; Cigarette smoking Current 1235 (23.1), Past 2161 (40.5), Never 1944 (36.4); Education Less than high school 3427 (64.2), High school 789 (14.8), University 1124 (21.1); Alcohol (g/day) 12.6 + 11.0

Exposures at midlife

Relevant exposures: Diet

Time: 1997 and 1998

Measurement of exposure: Food-frequency questionnaire

Outcomes at 55 years or over

Outcomes: Heart failure

Outcome measurement: Inpatient, cause-of-death, and death registries

Time: 2004

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, body mass index, physical activity, energy, alcohol, fibre, sodium, and red or processed meat consumption, education, family history of myocardial infarction at ,60 years, cigarette smoking, marital status, self-reported history of hypertension, and high cholesterol

Results, limitations, source of funding

Number: 97 (563 hospitalisations and 34 deaths)

Effect estimates

Fatty-fish intake

Never 1 (reference)

<1 serving/week 0.93 (0.72 – 1.21)

1 serving/week 0.88 (0.68 – 1.13)

2 serving/week 0.99 (0.73 – 1.33)

>3 serving/week 0.97 (0.61 – 1.55)

Quintiles of marine omega-3 fatty acids

1 1 (reference)

2 0.94 (0.74 – 1.20)

3 0.67 (0.50 – 0.90)

4 0.89 (0.68 – 1.16)

5 1.00 (0.77 – 1.29)

Significant trends: Moderate intake of fatty fish and marine omega-3 fatty acids was associated with lower rates of HF, though the association for fish intake was not statistically significant

Limitations

1. Not able to determine HF aetiology or subtype
2. As the registers only captured cases that result in hospitalization or death results may not be generalizable to less severe HF treated on an outpatient basis
3. Misclassification of intake; estimated portion sizes
4. Residual or unmeasured confounding

Source of funding: Swedish Research Council/Committee for infrastructure; Swedish Foundation for International Cooperation in Research and Higher Education (to E.B.L.); National Heart, Lung, and Blood Institute, National Institutes of Health (F32 HL091683 to E.B.L.)

Authors: Levitan EB, Mittleman MA, Wolk A

Year: 2010

Citation: Journal of the American College of Nutrition 29(1): 65-71

Country of study: Sweden

Aim of study: Assessed whether dietary glycemic index and glycemic load were associated with rates of heart failure events

Study design: Prospective observational study

Quality score: (++, + or -): +

Source population

Number of people: 90,303

Demographics: Not reported

Study (eligible and selected) population

Number of people: 36,019

Characteristics:

Quartile dietary glycemic index

1 Age (y) 60.1 (8.8); Physical activity (MET hr/d) 42.3 (4.7); Body mass index (kg/m2) 25.0 (3.9); Cigarette smoking (%) Never 47.6, Past 27.5, Current 24.9; Living alone (%) 25.8; Education (%) Less than high school 64.1, High school 9.5, University 26.3; Alcohol (g/d) 5.6 (6.4)

2 Age (y) 60.5 (8.8); Physical activity (MET hr/d) 42.4 (4.7); Body mass index (kg/m2) 24.9 (3.8); Cigarette smoking (%) Never 53.7, Past 24.5, Current 21.8; Living alone (%) 21.7; Education (%) Less than high school 68.8, High school 9.1, University 22.1; Alcohol (g/d) 4.7 (5.3)

3 Age (y) 61.8 (9.2); Physical activity (MET hr/d) 42.6 (4.7); Body mass index (kg/m2) 25.0 (3.9); Cigarette smoking (%) Never 56.9, Past 21.7, Current 21.5; Living alone (%) 21.9; Education (%) Less than high school 75.9, High school 7.5, University 16.6; Alcohol (g/d) 3.8 (4.6)

4 Age (y) 63.9 (9.4); Physical activity (MET hr/d) 42.5 (5.0); Body mass index (kg/m2) 25.0 (4.1); Cigarette smoking (%) Never 56.8, Past 18.5, Current 24.7; Living alone (%) 26.5; Education (%) Less than high school 85.1, High school 5.8, University 9.2; Alcohol (g/d) 2.7 (3.9)

Location: Västmanland and Uppsala counties in central Sweden

Recruitment strategy: Invitation to a free-of-charge mammography examination, and a mailed questionnaire on diet

Length of follow-up: 9 years

Eligible population: Women 48-83 years old without baseline HF, diabetes, or myocardial infarction. Participants in the Swedish Mammography Cohort

Excluded populations: Participants who:

i) Did not provide or provided incorrect national identification numbers
ii) Reported implausible energy intakes
iii) Had previous diagnosis of cancer or who left more than half of the food and beverage items blank
iv) Those at baseline with a history of HF, myocardial infarction (MI), or diabetes

Exposures at midlife

Relevant exposures: Diet

Time: 1998

Measurement of exposure: Self-administered food-frequency questionnaire. Asked frequency of consumption of 96 foods and beverages over the previous year. Portion sizes for most foods were not specified.

Outcomes at 55 years or over

Outcomes: Heart failure events

Outcome measurement: Swedish inpatient and cause-of-death registers

Time: 2006

Analysis

Analysis strategy: Cox proportional hazards models

Confounders: Age, education, body mass index, physical activity, cigarette smoking, living alone, postmenopausal hormone use, total energy intake, alcohol intake, fiber intake, sodium intake, saturated fat, polyunsaturated fat, protein, carbohydrate, family history of MI before 60 years, selfreported history of hypertension, and self-reported history of high cholesterol.

Results, limitations, source of funding

Number: 639

Effect estimates:

Dietary glycemic index, dietary glycemic load and incidence of heart failure hospitalization or mortality

<u>Dietary glycemic index</u>

RR (95% CI)

1 1 (reference)

2 1.01 (0.78-1.31)

3 1.14 (0.89-1.47)

4 1.12 (0.87-1.45)

p-trend 0.31

<u>Dietary glycemic load</u>

RR (95% CI)

1 1 (reference)

2 1.05 (0.80-1.38)

3 1.19 (0.87-1.62)

4 1.30 (0.87-1.93)

p-trend 0.16

Significant trends: Dietary glycemic index did not appear to be associated with incident HF events

Limitations:

1. Only cases of HF that resulted in hospitalisation or death were recorded
2. Registers do not contain information on HF etiology or subtype
3. Assessment of medical history was based on self-report
4. Exposure misclassification; residual or unmeasured confounding

Source of funding: Swedish Research Council/Committee for Infrastructure and the Committee for Medicine, Stockholm, Swedent. Dr. Levitan was supported by a grant from the Swedish Foundation for International Cooperation in Research and Higher Education (STINT), Stockholm, Sweden, and National Institutes of Health, Bethesda, MD, grant F32 HL091683

Authors: Lim SH, Tai BC, Yuan JM, Yu MC, Koh WP

Year: 2013

Citation: Tobacco Control 22(4): 235-40

Country of study: Singapore

Aim of study: To assess influence of smoking (cessation) on all-cause and cause-specific mortality

Study design: Longitudinal

Quality score: (++, + or -): -

Source population

Cohort of Hokkiens and Cantonese permanent residents or citizens of Singapore ages 45-74 years recruited between April 1993 and Dec. 1998 (baseline)

Response rate: 85%

Surviving members re-interviewed at follow-up between 1999 and 2004

Study (eligible and selected) population

63,257 people from Fujian Province and Guangdong Province interviewed at baseline, and 52,322 participants re-contacted at follow-up. Analysis restricted to **48,251** people

Follow-up:1993-98 to 09. Date of the follow-up interview to the date of death or Dec. 31, 2009, whichever came first

Exclusion: Participants who started smoking after baseline interview (n=2564) and those whose responses were inconsistent (n=1507)

Attrition: Loss to follow-up due to death, physical disability, or participants could no longer be contacted

41 lost to follow-up due to migration or other reasons

Exposures at midlife

Self-reported smoking categorised as: current smokers (smoking at baseline and f/u interview), long-term quitters (quitter at baseline and f/u interview), new quitters (baseline smoking and quitter at f/u interview), never smokers

Outcomes at 55 years or over
Mortality: all-cause, lung cancer, other cancers, coronary heart disease, stroke, chronic obstructive pulmonary disease identified using nationwide death registry Mortality data available through Dec. 31 2009
Analysis
Analysis strategy: Cox proportional hazards model used to assess influence of smoking (cessation) on all-cause mortality. The association between smoking and cause-specific mortality assessed using competing risks regression **Confounders:** Age, year, BMI, sex, dialect, education, alcohol intake, diagnosis of physical activity, hypertension, diabetes mellitus, stroke and cardiovascular disease, and cancer
Results, limitations, source of funding
• Compared with current smokers, the risk for total mortality was lower for new quitters (HR=0.84, [0.76, 0.94], long-term quitters (HR=0.61, [0.56, 0.67]), long-term quitters and never-smokers (HR=0.49, [0.46, 0.53] • Compared with current smokers, the risk of lung cancer mortality was lower for new quitters (HR=0.76 [0.57, 1.00) and long-term quitters (HR=0.44, [0.35, 0.57]) • Compared with current smokers, the risk for coronary heart disease mortality was lower for long-term quitters (HR= 0.63, [0.52,0.77]) **Limitations:** 1. Non-differential 2. Misclassification of smoking status 3. Small sample sizes for various sub-groups 4. No validation of self-reported smoking **Source of funding:** National Institutes of Health

Authors: Lin Y, Kikuchi S, Tamakoshi A, Wakai K, Kawamura T, Iso H… Ishibashi T; JACC Study Group **Year:** 2005 **Citation:** Annals of Epidemiology 15(8): 590-7 **Country of study:** Japan **Aim of study:** Examine the association between alcohol intake and the risk of all-cause mortality **Study design:** Prospective cohort study **Quality score: (++, + or -):** ++
Source population
Number of people: 110,792 **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 97,432 **Characteristics:** Men

Nondrinkers. Age (years) 59.0±10.6; Body mass index (kg/m2) 22.5±2.9; More than high school education (%) 11.9; History of hypertension (%) 14.1; History of diabetes (%) 5.1; Current smokers (%) 49.7; Exercise > 5 hours per week (%) 5.9

Ex-drinkers. Age (years) 62.4±9.5; Body mass index (kg/m2) 22.2±3.0; More than high school education (%) 12.8; History of hypertension (%) 24.5; History of diabetes (%) 11.8; Current smokers (%) 45.9; Exercise > 5 hours per week (%) 6.7

Current drinkers (alcohol intake: g/day) 0.1–22.9. Age (years) 56.3±10.3; Body mass index (kg/m2) 22.7±2.7; More than high school education (%) 18.1; History of hypertension (%) 15.8; History of diabetes (%) 5.6; Current smokers (%) 46.9; Exercise > 5 hours per week (%) 6.2

Current drinkers (alcohol intake: g/day) 23.0–45.9. Age (years) 57.2±10.1; Body mass index (kg/m2) 22.6±2.7; More than high school education (%) 14.6; History of hypertension (%) 19.6; History of diabetes (%) 5.7; Current smokers (%) 52.6; Exercise > 5 hours per week (%) 7.4

Current drinkers (alcohol intake: g/day) 46.0–68.9. Age (years) 55.5±9.3; Body mass index (kg/m2) 22.8±2.6; More than high school education (%) 12.8; History of hypertension (%) 21.0; History of diabetes (%) 4.4; Current smokers (%) 61.7; Exercise > 5 hours per week (%) 6.4

Current drinkers (alcohol intake: g/day) > 69.0. Age (years) 53.9±9.0; Body mass index (kg/m2) 22.9±2.8; More than high school education (%) 10.6; History of hypertension (%) 19.1; History of diabetes (%) 5.2; Current smokers (%) 69.3; Exercise > 5 hours per week (%) 5.8

Women

Nondrinkers. Age (years) 57.8±10.0; Body mass index (kg/m2) 22.9±3.1; History of hypertension (%) 21.0; History of diabetes (%)3.5; More than high school education (%)7.6; Current smokers (%) 3.5; Exercise > 5 hours per week (%) 3.5

Ex-drinkers. Age (years) 58.2±10.2; Body mass index (kg/m2) 23.0±3.4; History of hypertension (%) 24.8; History of diabetes (%) 7.8; More than high school education (%) 7.2; Current smokers (%) 22.8; Exercise > 5 hours per week (%) 4.8

Current drinkers (alcohol intake: g/day) 0.1–22.9. Age (years) 55.0±9.6; Body mass index (kg/m2) 22.9±2.9; History of hypertension (%) 16.9; History of diabetes (%) 2.4; More than high school education (%) 10.8; Current smokers (%) 7.6; Exercise > 5 hours per week (%) 5.4

Current drinkers (alcohol intake: g/day) 23.0–45.9. Age (years) 54.9±9.9; Body mass index (kg/m2) 23.0±3.1; History of hypertension (%) 21.8; History of diabetes (%) 2.1; More than high school education (%) 7.7; Current smokers (%) 22.2; Exercise > 5 hours per week (%) 5.9

Current drinkers (alcohol intake: g/day) 46.0–68.9. Age (years) 53.0±9.3; body mass index (kg/m2) 23.4±3.4; History of hypertension (%) 23.3; History of diabetes (%) 2.4; More than high school education (%) 7.5; Current smokers (%) 41.6; Exercise > 5 hours per week (%) 4.5

Location: 45 areas throughout Japan

Recruitment strategy: Not reported

Length of follow-up: 10 years

Response rate and loss to follow-up: Not reported

Eligible population: Japanese men and women aged 40 to 79 years

Excluded populations: Subjects who reported a history of cancer, stroke, or myocardial infarction

Exposures at midlife

Relevant exposures: Alcohol intake

Time: 1988–1990

Measurement of exposure: Self-administered questionnaire. subjects choose their drinking status from three pre-coded response categories: nondrinkers, ex-drinkers, or current drinkers

Outcomes at 55 years or over

Outcomes: All-cause mortality

Outcome measurement: Resident-registry data from the municipalities

Time: 1999

Analysis

Analysis strategy: Cox proportional-hazards models

Confounders: Age, body mass index, education, history of diabetes and hypertension, cigarette smoking, and exercise

Results, limitations, source of funding

Number: 9589 subjects (5902 men and 3687 women) died from all causes

Effect estimates:

RR (95%CI)

Death from all cause

Nondrinkers 1.00; Ex-drinkers 1.58 (1.44–1.74); Current drinkers (alcohol intake: g/day) 0.1–22.9 0.80 (0.72–0.88); Current drinkers (alcohol intake: g/day) 23.0–45.9 0.90 (0.82–0.98); Current drinkers (alcohol intake: g/day) 46.0–68.9 0.95 (0.86–1.04); Current drinkers (alcohol intake: g/day) > 69.0 1.32 (1.18–1.48)

Death from cancer

Nondrinkers 1.00; Ex-drinkers 1.50 (1.29–1.75); Current drinkers (alcohol intake: g/day) 0.1–22.9 0.82 (0.70–0.95); Current drinkers (alcohol intake: g/day) 23.0–45.9 0.96 (0.84–1.10); Current drinkers (alcohol intake: g/day) 46.0–68.9 1.05 (0.91–1.20); Current drinkers (alcohol intake: g/day) > 69.0 1.31 (1.10–1.56)

Death from cardiovascular disease

Nondrinkers 1.00; Ex-drinkers 1.79 (1.51–2.14); Current drinkers (alcohol intake: g/day) 0.1–22.9 0.86 (0.73–1.06); Current drinkers (alcohol intake: g/day) 23.0–45.9 0.89 (0.75–1.05); Current drinkers (alcohol intake: g/day) 46.0–68.9 1.09 (0.92–1.30); Current drinkers (alcohol intake: g/day) > 69.0 1.28 (1.02–1.61)

Death from injuries and external causes

Nondrinkers 1.00; Ex-drinkers 1.69 (0.92–3.08); Current drinkers (alcohol intake: g/day) 0.1–22.9 1.52 (0.90–2.58); Current drinkers (alcohol intake: g/day) 23.0–45.9 1.37 (0.83–2.26); Current drinkers (alcohol intake: g/day) 46.0–68.9 1.23 (0.71–2.13); Current drinkers (alcohol intake: g/day) > 69.0 1.99 (1.09–3.64)

P-value

Death from all cause <0.001; Death from cancer <0.001; Death from cardiovascular disease 0.01; Death from injuries and external causes 0.11

Significant trends: Risk of all-cause mortality was lowest among current drinkers with an alcohol intake of 0.1 to 22.9 g/d. Excessive mortality associated with heavy drinking was observed for cancer, cardiovascular disease and injuries and other external causes in men, while significantly reduced mortality with light drinking was seen for cancer in men and CVD in women. For men, the benefit associated with light alcohol consumption was more apparent among nonsmokers than among smokers.

Limitations:

1. Self-reported alcohol consumption
2. Low risk of total mortality among light-to-moderate drinkers may be attributable to these favorable lifestyle factors rather than to the role of alcohol consumption itself

3. We could not estimate drinking patterns such as binge drinking or drinking with meals
4. Small number of response options for frequency of drinking

Source of funding: Japanese Ministry of Education, Culture, Sports, Science and Technology

Authors: Liu S, Willett WC, Manson JE, Hu FB, Rosner B, Colditz G

Year: 2003

Citation: American Journal of Clinical Nutrition 78(5): 920-7

Country of study: US

Aim of study: To determine the influence of intake of whole grains on body weight and weight changes

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

121,700 US female registered nurses ages 30-55 years recruited in 1976 and followed-up every two years as part of the Nurses' Health Study

Study (eligible and selected) population

74,091 women that were ages 38-63 years in 1984

Exclusion:

i) Participants with daily energy intakes outside the 2514 – 14665 KF range in 1980
ii) Respondents with diabetes (n=2518), cardiovascular disease (n=690), and cancer (n=4458)

Attrition: -

Exposures at midlife

Semi-quantitative food frequency questionnaire (FFQ) administered in 1984, 1986, 1990, and 1994 to measure intake of whole-grain and refined-grain foods

Participants were asked about the mean frequency of consumption of one unit of each food item of interest over the past year, with response options ranging from 'never' to '>=6 times per day'

Average grain intake in servings/day was calculated for each participant

Reproducibility and validity of FFQ has been established; when FFQ was compared to diet records, the correlation coefficients for grain products ranged from 0.71-0.77

In the analysis, grain intake was divided into quintiles; the first quintile represented the smallest change in intake

Outcomes at 55 years or over

Body weight, BMI, and weight changes assessed

Body weight was self-reported every two years from 1984 to 1996, height was reported in 1976

Weight change was calculated as the difference in weight or BMI between: 1) 1984 and 1986, 2) 1986 and 1990, 3) and 1990 and 1994; weight change between 1984 and 1996 was also calculated

When self-reported and measured weights were compared in a sample of participants, correlation was 0.96

Analysis

Analysis strategy: Generalised estimating equations used to determine the influence of changes in intake of whole or refined grains on weight changes

Confounders: Age, changes in exercise, change in smoking status, change in hormone replacement therapy status, changes in intakes of alcohol, caffeine, and total energy, changes in intakes of saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, and protein, and BMI at baseline

Results, limitations, source of funding

- Average BMI increased over time regardless of grain intake; 6400 women became obese (BMI >=30) and 657 had a major weight gain (>=25 kg) over 12 years

Average changes in BMI or in weight in 2-4 years during follow-up:

- The average change in *BMI* increased (meaning, greater weight gain) with increasing intake of refined-grains (linear trend test p-value <0.0001)
- The average change in *BMI* decreased (less weight gain) with increasing intake of dietary fiber (trend p-value: 0.0001)
- The average change in *BMI* appeared to decrease (less weight gain) with increasing intake of whole grains (trend test p<0.0001)
- Same results as above were reported when the average change in *weight* in 2-4 years was the outcome

Average weight gain during follow-up:

- Average weight gain became greater with increasing change in intake of refined grains (trend test p-value <0.0001), while it became lower with increasing intake of dietary fiber (trend test p-value <0.0001)

Odds for obesity or weight gain during follow-up:

- There appeared to be a decreasing trend in obesity (BMI >=30) and major weight gain (>=25 kg) with larger intakes of whole grains (trend test p-values=0.0002 and 0.03, respectively); intake of refined grains appeared to be inversely related to obesity and major weight gain (trend test p-values: <0.0001 and 0.04, respectively)
- There appeared to be a decreasing trend in major weight gain with larger intake of dietary fiber (trend test p-value <0.0001)
- Women with the highest increase in intake of dietary fiber had a significantly lower risk of major weight gain compared to women with the smallest change in intake of fiber (OR=0.51, [0.39, 0.67])

Limitations:

1. Those with recent weight gain may attempt to lose weight by increasing consumption of grain products (difficult to ascertain whether increases in intake of grains prevented weight gain)
2. Participants with greater intake of whole grains and caloric restriction may be more health conscious
3. Misclassification of dietary intake may be dependent on body weight (e.g., obese people may underreport intake)
4. Residual confounding from other dietary factors

Source of funding: None reported

Authors: Liu Y, Sobue T, Otani T, Tsugane S

Year: 2004

Citation: Cancer Causes Control 15(4): 349-57

Country of study: Japan

Aim of study: To determine the influence of fruit and vegetables on lung cancer

Study design: Longitudinal

Quality score: (++, + or -): +

Source population
Two population-based cohorts of 57,591 men and 59,103 women were established through residence registries maintained by local governments and public health centres of administrative districts Cohort I comprised inhabitants ages 40-59 years in 1990 and cohort II consisted of inhabitants ages 40-69 years in 1993 Questionnaires completed by 45,452 men (response rate: 79%) and 49,924 women (response rate: 84%) from both cohorts
Study (eligible and selected) population
44,774 men and **48,566** women **Follow-up:** Study start date (Jan. 1, 1990 for Cohort I and Jan. 1, 1993 for Cohort II) until date of diagnosis of lung cancer, date of migration out of study area, date of death or end of follow-up Dec. 31, 1999 **Exclusion:** Men (n=680) and women (n=1358) with a history of cancer **Attrition:** -
Exposures at midlife
Dietary habits were assessed in 1990 for Cohort I and 1993 for Cohort II using self-administered questionnaire Food frequency questionnaires administered to both cohorts that assessed average consumption of food items (vegetables, fruit, fruit and vegetable juices) during past month, with the following response options '<1 day/week', '1-2 days/week', '3-4 days/week', and 'almost daily' (with the additional category of 'never use' for cohort II Participants reporting daily drinking of juice, the cups/day were further assessed The portion size and content of food items were taken into account when calculating amount of vegetable and fruit intakes, which was subsequently divided into and analysed as tertiles ('low', 'medium', 'high') When the questionnaire for Cohort I was compared to dietary records, correlation coefficients ranged from 0.26 to 0.52
Outcomes at 55 years or over
Incident cases of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, other histological types) identified through hospital records, population-based cancer registries, and death certificates
Analysis
Analysis strategy: Cox proportional hazards model used to assess influence of dietary intake on lung cancer risk. Relative risks of Cohorts I and II were also pooled using inverse-variance weighting (cohorts combined) **Confounders:** Age, gender, area, sports, frequency of alcohol intake, body mass index, vitamin supplement use, salted fish and meat, and pickled vegetables, smoking status, smoking duration, and number of cigarettes per day among ever smokers
Results, limitations, source of funding
• 428 lung cancer cases (177 cases from Cohort I reported during 401,382 person-years of follow-

up, and 251 cases from Cohort II during 330,588 person-years)

- Among Cohort I participants, the risk of adenocarcinoma was greater for those in the middle consumption category of fruit intake compared to the low consumption category of fruit intake (RR=2.06, [1.20, 3.54])
- Overall, there were no significant associations between vegetable and fruit consumption and incidence of lung cancer (except for the above result)

Limitations:

1. Residual confounding
2. Misclassification of intake of fruit and vegetables through use of a simple food frequency questionnaire

Source of funding: Ministry of Health and Welfare of Japan

Authors: Malmberg JJ, Miilunpalo SI, Pasanen ME, Vuori IM, Oja P

Year: 2006

Citation: Journal of Aging and Physical Activity 14(2): 133-53

Country of study: Finland

Aim of study: Associations of the ammount, frequency and intesity, and type of leisure-time physical activity with the risk of self-reported difficulty in walking and stair climbing

Study design: Population-based cohort

Quality score: (++, + or -): +

Source population

Number of people: 6,787

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1791

Characteristics:

<u>Men</u>

Age in 1981, years
40-47 98 (234/238)
48-55 92 (147/160)
56-64 80(59/74)
Marital status
Married 94 (369/394)
Single 92 (55/60)
Divorced, separated, or widowed 88 (14/16)
Living community
Urban 95 (253/267)
Rural 91 (186/204)
Education
Higher education 100 (21/21)
Secondary education 98 (119/121)
Vocational training 94 (176/187)
No education 86 (110/128)
BMI, kg/m2
<25.0 93 (175/188)
25.0-29.9 94 (219/233)
>30 89(33/37)

Smoking status
Never smoked 96 (150/157)
Past smoker 91 (179/196)
Current smoker 93 (102/110)
Alcohol use. g/cby
0 88 (67/76).
0.1-12.0 95 (250/263)
>12.0 92 (122/132)
Participant in working life
Yes 95 (404/425)
No 73 (30/41)
Occupational activity
Sitting 95 (112/118)
Light or moderate movement 97 (176/182)
Heavy or very heavy movement 93 (116/125)
Did not work 68 (19/28)
Disease or symptoms
Did not prevent participation in PA 96 (335/348)
Somewhat prevented participation in PA 85 (105/124)

Women

Age in 1981, years
40-47 93 (252/270)
48-55 91 (177/194)
56-64 77(76/99)
Marital status
Married 90 (392/434)
Single 90(44/49)
Divorced, separated, or widowed 87(67/77)
Living community
Urban 90 (310/345)
Rural 90(195/217)
Education
Higher education 97 (33/34)
Secondary education 93 (124/134)
Vocational training 93 (185/198)
No education 83 (157/189)
BMI, kg/m2
<25.0 94 (244/261)
25.0-29.9 89(199/223)
>30 73 (43/59)
Smoking status
Never smoked 89 (388/434)
Past smoker 94(43/46)
Current smoker 90(71/79)
Alcohol use. g/cby
0 86 (242/282)
0.1-12.0 94 (246/262)
>12.0 100 (15/15)
Participant in working life
Yes 91 (357/391)
No 86(146/169)
Occupational activity
Sitting 91 (122/134)
Light or moderate movement 92 (267/289)
Heavy or very heavy movement 85 (44/52)
Did not work 80 (48/60)

Disease or symptoms
Did not prevent participation in PA 93 (396/428)
Somewhat prevented participation in PA 81 (109/135)

Location: Oja, Miilunpalo, Vuori, Pasanen, Urponen. Finland

Recruitment strategy: Not reported

Length of follow-up: 16 years

Response rate and loss to follow-up: 77.5%

Eligible population: All respondents who were 40-64 years old (in 1981) and had no self-reported difficulty in walking (n=1,198) or stair climbing (n=1,000).

Excluded populations: Excluded all individuals who reponed (in 1980) that they were substantially or totally unable to participate in physical activity because of their health status or who failed to respond to 5 or more of the 13 questions concerning physical activity

Exposures at midlife

Relevant exposures: Leisure-time physical activity

Time: 1980-1981

Measurement of exposure: Three different sets of L TPA questions, two sets in 1980 and one in 1981

Used two LTPA indexes-fitness activity and commuting-to test recent evidence suggesting that energy expenditure during physical activity

The single-item self-assessment of global LTPA covered the intensity, frequency, and duration of respondents' exercise sessions as follows: .. Which of the following categories best describes your physical activity during the past 2 months?

The single-item self-assessment of global LTPA reflects the behaviour, and LTPA energy-expenditure index, the energy cost of this behaviour

Outcomes at 55 years or over

Outcomes: Mobility difficulties

Outcome measurement: Self-reported estimate of their ability to walk 2 km and climb several flights of stairs without rest

Time: 1981, 1990, and 1996

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, body-mass Index, disease or symptoms, and education, marital, living community, employment, occupational activity, smoking, and alcohol-consumption status

Significant trends:

Men: Rates for difficulty in walking and stair climbing were highest among the oldest; the obese; those not working; those who suffered from disease or symptoms that prevented them from participating in physical activity.

Women: Rates for difficulty in walking and stair climbing were highest among the oldest; the overweight or obese; those who lived in rural communities; who suffered from disease or symptoms that prevented them from participating in physical activity.

Limitations: Self-reported estimates

Source of funding: Finnish Ministry of Education, the Finnish Ministry of Social Affairs and Health, and the Yrjo Jahnsson Foundation

Results, limitations, source of funding

Number: Depending upon outcome and variable:

Walking
Men 113-118
Women 130-146

Stair
Men 116-127
Women 176-198

Effect estimates:

Relative Risks (95% CI) for Self-Reported Difficulty In Walking and Stair Climbing According to LTPA

Men

Difficulty In Walking
Global LPTA
High 1.00
Moderate 1.49 (0.77-2.88)
Low 1.60 (0.88-2.91)
p = .298

LTPA energy expenditure index
High 1.00
Moderate 1.27 0.77-2.09
Low 0.98 (0.585-1.75)
P= .531

LTPA frequency intensity
Vigorous 1.00
Moderate 1.13 0.63-2.03
Light 0.93 (0.51-1.72)
No activity 1.23 (0.67-2.28)
P=.826

Fitness activity
>3x a week 1.00
Twice 2.90 (1.09-7.70)
Once a week 4.48 (1.70-11.79)
<1 per week 3.74 (1.47-9.54)
No activity 4.15 (1.62-10.63)
P= .029

Commuting
At least once a week 1.00
No activity 0.86 (0.54-1.37)
P= .532

Difficulty in Stair Climbing
Global LPTA
High 1.00
Moderate 1.86 (0.99-3.52)
Low 2.30 (1.27-4.16)
p = .023

LTPA energy expenditure index
High 1.00
Moderate 1.04 (0.66-1.66)
Low 1.26 (0.77-2.05)

P= .633

LTPA frequency intensity
Vigorous 1.00
Moderate 0.88 (0.51-0.51)
Light 0.98 (0.56-1.73)
No activity 1.42 (0.81-2.49)
P= .393

Fitness activity
>3x a week 1.00
Twice 0.91 (0.46-1.82)
Once a week 1.38 (0.10-2.71)
<1 per week 1.34 (0.69-2.62)
No activity 1.81 (0.96-3.43)
P= .221

Commuting
At least once a week 1.00
No activity 1.08 (0.71-1.65)
P= .725

Women
Difficulty In Walking
Global LPTA
High 1.00
Moderate 0.69 (0.37-1.29)
Low 1.00 (0.61-1 .65)
p = .371

LTPA energy expenditure index
High 1.00
Moderate 0.95 (0.61-1.47)
Low 1.04 (0.65-1.66)
P=.935

LTPA frequency intensity
Vigorous 1.00
Moderate 1.01 (0.61-1.66)
Light 1.19 (0.73-1.94)
No activity 1.01 (0.57-1.76)
P= .873

Fitness activity
>3x a week 1.00
Twice 0.86 (0.49-1.52)
Once a week 0.82 (0.46-1.45)
<1 per week 0.68 (0.38-1.21)
No activity 0.71 (0.41-1.25)
P=.690

Commuting
At least once a week 1.00
No activity 0.79 (0.48-1.31)
P= .363

Difficulty in Stair Climbing
Difficulty In Walking
Global LPTA
High 1.00
Moderate 0.93 (0.56-1.53)
Low 1.49 (0.99-2.24)
p = 0.34

LTPA energy expenditure index
High 1.00
Moderate 0.92 (0.65-1.30)
Low 0.99 (0.64-1.51)
P= .869
LTPA frequency intensity
Vigorous 1.00
Moderate 0.95 (0.62-1.47)
Light 1.81 (1.20-2.73)
No activity 1.16 (0.73-1.85)
P= .009

Fitness activity
>3x a week 1.00
Twice 0.68 (0.42-1.12)
Once a week 0.97 (0.60-1.56)
<1 per week 0.98 (0.60-1.62)
No activity 0.78 (0.48-1.26)
P= .43

Commuting
At least once a week 1.00
No activity 0.92 (0.64-1.33)
P=.659

Authors: Mannami T, Iso H, Baba S, Sasaki S, Okada K, Konishi M, Tsugane S; Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease Group

Year: 2004

Citation: Stroke 35(6): 1248-53

Country of study: Japan

Aim of study: To assess the influence of smoking on fatal and nonfatal strokes

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Population-based cohort of 27,063 men and 27,435 women ages 40-59, and born between 1930 and 1949, registered in administrative districts and supervised by public health centre areas in Jan. 1, 1990

Cohort from Ninohe, Yokote, Nagano, Ishikawa

Study (eligible and selected) population

Self-administered questionnaire (capturing smoking, drinking, diet) returned by 20,665 men (76%) and 22,484 women (82%) in 1990/1992. Analysis restricted to **19,782** men and **21,500** women

Follow-up: 11 years from 1990 to 2001**.** Person-months calculated from date of return of the baseline questionnaire to the first end point, death, or January 1, 2002, whichever was first.

Exclusion:

i) Individuals with stroke, myocardial infarction, angina pectoris, cancer at baseline (n=667 men and 883 women)
ii) Those with incomplete data (n=196 men and 85 women)
iii) Loss to follow-up (n=14 men and 14 women)

Attrition: 14 men and 14 women lost to follow-up

Exposures at midlife
Self-reported smoking for both sexes categorised as never-smokers, ex-smokers, and current smokers; smoking habit for men categorized as: never-smoker, ex-smoker, current smoker, and number of cigarettes 1 to 19/d, 20 to 39/d, and >=40/d
Outcomes at 55 years or over
Fatal and nonfatal strokes assessed with medical records, death certificates
Analysis
Analysis strategy: The Cox proportional hazards model was used to assess the influence of smoking on fatal and nonfatal strokes **Confounders:** Age, alcohol intake, body mass index, history of diabetes (yes), education level, sports at leisure, frequency of fruit, vegetable, and fish servings , and public health centers
Results, limitations, source of funding
• Risks for current smokers compared with never-smokers were higher for total stroke (RR=1.27, [1.05, 1.54]), subarachnoid hemorrhage (RR=3.60, [1.62, 8.01]), ischemic stroke (1.66, [1.25, 2.20]); the respective relative risks among women were 1.98 (1.42 to 2.77), 1.53 (0.86 to 4.25), 2.70 (1.45 to 5.02), and 1.57 (0.86 to 2.87) **Limitations:** 1. Self-reported data 2. Limited generalizability of results to women and older men **Source of funding:** Ministry of Health, Labor, and Welfare of Japan

Authors: Masaki M, Sugimori H, Nakamura K, Tadera M **Year:** 2003 **Citation:** Asian Pacific Journal of Cancer Prevention 4(1): 61-6 **Country of study:** Japan **Aim of study:** Identify dietary patterns that may change stomach cancer risk **Study design:** Cohort **Quality score: (++, + or -):** +
Source population
Number of people: 200,000
Study (eligible and selected) population
Number of people: 5,644 **Characteristics:** **Vegetable and fruit** <u>Low</u> Entire cohort (%) 33.4 Mean age (years) 50.1 Mean BMI 23.1

Education (% university) 58.9
History of peptic ulcer (% yes) 17.9
Family history of stomach cancer (% yes) 10.3
Cigarette smoking (%)
Never 18.8
Past 21.2
Current 60.1
Alcohol drinking (%)
No 17.2
Light 32.4
Heavy 50.4

<u>Middle</u>
Entire cohort (%) 34.5
Mean age (years) 51.7
Mean BMI 23.2
Education (% university) 62.3
History of peptic ulcer (% yes) 20.1
Family history of stomach cancer (% yes) 8.3
Cigarette smoking (%)
Never 21.1
Past 29.3
Current 49.7
Alcohol drinking (%)
No 18.3
Light 36.3
Heavy 45.4

<u>High</u>
Entire cohort (%) 32.1
Mean age (years) 53.2
Mean BMI 23.2
Education (% university) 64.4
History of peptic ulcer (% yes) 22.3
Family history of stomach cancer (% yes) 10.9
Cigarette smoking (%)
Never 21.1
Past 34.3
Current 44.6
Alcohol drinking (%)
No 19.6
Light 38.3
Heavy 42.1

Western breakfast

<u>Low</u>
Entire cohort (%) 32.6
Mean age (years) 51.9
Mean BMI 23.4
Education (% university) 54.6
History of peptic ulcer (% yes) 20.5
Family history of stomach cancer (% yes) 10.7
Cigarette smoking (%)
Never 17.8
Past 28.6
Current 53.7
Alcohol drinking (%)
No 12.1
Light 27.9

Heavy 60.0

Middle
Entire cohort (%) 32.9
Mean age (years) 50.8
Mean BMI 23.2
Education (% university) 62.0
History of peptic ulcer (% yes) 18.0
Family history of stomach cancer (% yes) 8.6
Cigarette smoking (%)
Never 21.6
Past 26.0
Current 52.4
Alcohol drinking (%)
No 18.9
Light 34.7
Heavy 46.4

High
Entire cohort (%) 34.5
Mean age (years) 52.0
Mean BMI 23.0
Education (% university) 68.5
History of peptic ulcer (% yes) 21.6
Family history of stomach cancer (% yes) 10.0
Cigarette smoking (%)
Never 21.6
Past 29.9
Current 48.6
Alcohol drinking (%)
No 23.7
Light 43.9
Heavy 32.5

Meat

Low
Entire cohort (%) 33.7
Mean age (years) 53.4
Mean BMI 23.2
Education (% university) 63.9
History of peptic ulcer (% yes) 21.5
Family history of stomach cancer (% yes) 10.3
Cigarette smoking (%)
Never 22.4
Past 33.8
Current 43.8
Alcohol drinking (%)
No 23.2
Light 38.8
Heavy 38.0

Middle
Entire cohort (%) 35.5
Mean age (years) 51.1
Mean BMI 23.2
Education (% university) 60.0
History of peptic ulcer (% yes) 20.3
Family history of stomach cancer (% yes) 8.9
Cigarette smoking (%)

Never 19.2
Past 26.8
Current 54.0
Alcohol drinking (%)
No 15.9
Light 37.0
Heavy 47.1

High
Entire cohort (%) 30.8
Mean age (years) 50.1
Mean BMI 23.2
Education (% university) 61.7
History of peptic ulcer (% yes) 18.2
Family history of stomach cancer (% yes) 10.2
Cigarette smoking (%)
Never 19.4
Past 23.6
Current 57.1
Alcohol drinking (%)
No 15.8
Light 30.6
Heavy 53.6

Rice/snacks

Low
Entire cohort (%) 33.6
Mean age (years) 51.4
Mean BMI 23.1
Education (% university) 60.3
History of peptic ulcer (% yes) 21.4
Family history of stomach cancer (% yes) 10.0
Cigarette smoking (%)
Never 16.0
Past 27.5
Current 56.4
Alcohol drinking (%)
No 13.2
Light 33.1
Heavy 53.8

Middle
Entire cohort (%) 32.9
Mean age (years) 51.1
Mean BMI 23.2
Education (% university) 63.0
History of peptic ulcer (% yes) 18.8
Family history of stomach cancer (% yes) 9.4
Cigarette smoking (%)
Never 18.9
Past 27.4
Current 53.7
Alcohol drinking (%)
No 15.8
Light 36.5
Heavy 47.7

High
Entire cohort (%) 33.5

Mean age (years) 52.4
Mean BMI 23.2
Education (% university) 62.4
History of peptic ulcer (% yes) 20.0
Family history of stomach cancer (% yes) 10.0
Cigarette smoking (%)
Never 26.1
Past 29.6
Current 44.4
Alcohol drinking (%)
No 26.0
Light 37.4
Heavy 36.6

Exposures at midlife

Relevant exposures: Frequency of consumption of selected foods, health condition, medical history, smoking and drinking habits, exercise and leisure time, places of birth, and working situation

Time: 1988

Measurement of exposure: Self-report questionnaire

Location: Tokyo, Japan

Recruitment strategy: Not reported

Length of follow-up: 10 years of follow-up

Response rate and loss to follow-up: Subjects who had retired from their firms before the start of the study (n=8), having a past history of cancer (n=11), incomplete description of food consumption questionnaire (n=102), those identified within first year follow-up (n=71)

Eligible population: Members of the Health Insurance Society of Tokyo Stockbrokerage

Outcomes at 55 years or over

Outcomes: Stomach cancer

Outcome measurement: Detailed statements of medical care (performed for insured persons) by medical care facilities

Time: Until the dates of the events or the end of follow-up (August 31, 1998) whichever occurred first

Analysis

Analysis strategy: Cox proportional hazard regression model

Confounders: Age (10 years age groups), cigarette smoking (never, former current), alcohol drinking (no or current drinker), and history of peptic ulcer and family history of stomach cancer (yes or no).

Results, limitations, source of funding

Number: 86 incident cases of stomach cancer

Effect estimates:

Rate Ratios for Stomach Cancer According to Tertiles of Dietary Pattern

RR 95% CI

<u>Vegetable and fruit</u>
Low 1.00
Middle 1.06 (0.61-1.87)
High 0.78 (0.42-1.44)

P trend .56

Western breakfast
Low 1.00
Middle 0.59 (0.33-1.08)
High 0.71 (0.40-1.24)
P trend .20

Meat
Low 1.00
Middle 0.55 (0.29-1.01)
High 1.10 (0.64-1.89)
P trend .07

Rice/snacks
Low 1.00
Middle 0.52 (0.27-1.01)
High 1.19 (0.71-2.02)
P trend .05

Significant trends: There were no clear associations between the four major dietary patterns and stomach cancer risk

Limitations:

1. Relatively small size of cohort
2. Food consumption data in summer only
3. Case ascertainment only through medical records provided by various clinical sites
4. No data on histological classification of stomach cancer
5. Portion size and energy intake were not available

Source of funding: Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan: 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102

Authors: Meisinger C, Löwel H, Heier M, Kandler U, Döring A

Year: 2007

Citation: European Journal of Cardiovascular Prevention & Rehabilitation 14(6): 788-92.

Country of study: Germany

Aim of study: To examine sex-specific associations between sports activities in leisure time and incident myocardial infarction

Study design: Independent cross-sectional surveys

Quality score: (++, + or -): +

Source population

Number of people: 7823

Demographics: Not reported

Study (eligible and selected) population

Number of people: 3501 men and 3475 women

Characteristics:

No sports activities in leisure time

Men: Age (years) 58.5 (8.0); Education (< 12 years, %) 77.6; BMI (kg/m2) 28.1 (3.8); Regular smoking (%) 27.7; Alcohol intake 0 g/day (%) 17.7, 0.1–39.9 g/day (%) 47.0; > 40 g/day (%) 35.3;

Parental history of MI (%) 14.3 **Women:** Age (years) 58.5 (8.1); Education (< 12 years, %) 90.7; BMI (kg/m2) 28.3 (4.9); Regular smoking (%) 11.2; Alcohol intake 0 g/day (%) 52.1, 0.1–19.9 g/day (%) 33.0, > 20 g/day (%) 14.9; Parental history of MI (%) 18.4 **Low level of sports activities in leisure time** **Men:** Age (years) 57.2 (8.0); Education (< 12 years, %) 72.1; BMI (kg/m2) 27.9 (3.3); Regular smoking (%) 24.8; Alcohol intake 0 g/day (%) 14.2, 0.1–39.9 g/day (%) 48.8, > 40 g/day (%) 37.0; Parental history of MI (%) 17.2 **Women:** Age (years) 6.1 (7.3); Education (< 12 years, %) 87.6; BMI (kg/m2) 27.7 (4.5); Regular smoking (%) 16.3; Alcohol intake 0 g/day (%) 46.0, 0.1–19.9 g/day (%) 37.3, > 20 g/day (%) 16.8; Parental history of MI (%) 20.7 **Moderate level of sports activities in leisure time** **Men:** Age (years) 55.7 (7.6); Education (< 12 years, %) 59.8; BMI (kg/m2) 27.6 (3.3); Regular smoking (%) 21.0; Alcohol intake 0 g/day (%) 13.6, 0.1–39.9 g/day (%) 53.5, > 40 g/day (%) 32.8; Parental history of MI (%) 18.7 **Women:** Age (years) 55.8 (7.8); Education (< 12 years, %) 86.0; BMI (kg/m2) 26.6 (4.2); Regular smoking (%) 12.4; Alcohol intake 0 g/day (%) 41.5, 0.1–19.9 g/day (%) 38.5, > 20 g/day (%) 20.0; Parental history of MI (%)23.7 **High level of sports activities in leisure time** **Men:** Age (years) 57.2 (8.2); Education (< 12 years, %) 60.3; BMI (kg/m2) 27.3 (3.1); Regular smoking (%) 16.0; Alcohol intake 0 g/day (%) 17.7, 0.1–39.9 g/day (%) 52.5; > 40 g/day (%) 29.7; Parental history of MI (%) 19.6 **Women:** Age (years) 56.8 (7.8); Education (< 12 years, %) 81.3; BMI (kg/m2) 26.5 (4.3); Regular smoking (%) 12.4; Alcohol intake 0 g/day (%) 42.3, 0.1–19.9 g/day (%) 36.5, > 20 g/day (%) 21.2; Parental history of MI (%) 25.0 **Location:** Germany **Recruitment strategy:** Not reported **Length of follow-up:** Median of 8.6 years **Response rate and loss to follow-up:** Not reported **Eligible population:** Men and women aged 45–74 years who participated in one of the three MONICA Augsburg surveys **Excluded populations:** 248 study participants with incomplete data on any of the included variables and 599 persons with angina pectoris or prevalent MI at baseline
Exposures at midlife
Relevant exposures: Sports activities in leisure time **Time:** 1984/1985, 1989/1990 and 1994/1995 **Measurement of exposure:** Standardized interview Leisure-time physical activity was assessed by a four-level graded scale assessing leisure time activities during summer and wintertime (0, <1, 1–2 and more than 2h/week).
Outcomes at 55 years or over
Outcomes: Incidence of nonfatal MI or fatal coronary death, including sudden cardiac death **Outcome measurement:** MONICA/KORA Augsburg coronary event registry **Time:** 2002

Analysis

Analysis strategy: Cox proportional hazard models

Confounders: Physical activity, age, smoking status, alcohol intake, history of diabetes, education and parental history of MI, intermediary risk factors actual hypertension, dyslipidemia, and BMI

Results, limitations, source of funding

Number: 295 men and 91 women

Effect estimates:

No sports activities in leisure time

Men 1.0

Women 1.0

Low level of sports activities in leisure time

Men 1.01 (0.73–1.40)

Women 1.00 (0.56–1.78)

Moderate level of sports activities in leisure time

Men 0.78 (0.56–1.10)

Women 0.49 (0.24–1.00)

High level of sports activities in leisure time

Men 0.84 (0.59–1.18)

Women 0.21 (0.05–0.87)

Significant trends: Moderate or high levels of sports activities in leisure time are associated with a significantly reduced risk of MI in women, but not men from the general population

Limitations:

1. Self-reported information on physical activity
2. Focused on sports activities in leisure time only
3. Small number of cases in women of the two highest physical activity categories

Source of funding: GSF National Research Center for Environment and Health, Federal Ministry of Education, Science, Research and Technology (01 ER 9701/4) and the German Research Foundation (DFG) (TH 784/2-1)

Authors: Menotti A, Lanti M, Puddu PE

Year: 2000

Citation: Italian Heart Journal 1(11): 749-57

Country of study: Italy

Aim of study: To describe the comprehensive disease burden related to cardiovascular diseases of atherosclerotic-hypertensive origin in a population sample of middle-aged men

Study design: Prospective cohort

Quality score: (++, + or -): +

Source population

Number of people: Not reported

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1712

Characteristics:

Age (years) 49.8 ± 5.1
Cigarettes (n/day) 8.7 ± 9.5
Diabetes(%) 4.8
Corneal arcus(%) 13.9
Vital capacity (dl) 45.7 ± 8.0
Cholesterol (mmol/1) 5.21 ± 1.06
Systolic blood pressure (mmHg) 143.6 ± 21.O

Location: Crevalcore in Northern Italy and Montegiorgio in Central Italy

Recruitment strategy: Not reported

Length of follow-up: 2S-year follow-up

Response rate and loss to follow-up: 98.8%

Eligible population: Italian middle-aged men

Excluded populations: Subjects with cardiovascular diseases at entry examination

Exposures at midlife

Relevant exposures: Smoking habits

Time: 1960

Measurement of exposure: Elicited from a questionnaire allowing us to estimate the daily average consumption of cigarettes (nlday)

Outcomes at 55 years or over

Outcomes: Morbidity and mortality

Outcome measurement: Causes of death were allocated reviewing and combining together information from several sources such as death certificates, hospital and medical records, interviews with physicians, relatives of the deceased and any other witness of the fatal event.

Morbidity data obtained via a) interim quinquennial; b) information obtained in relation to causes of death; c) periodic visits to local physicians and hospitals for identification of new cases; d) home visits to subjects suspected of having developed a new CV event; e) postal questionnaire and postal clinical records in a few cases

Time: Not reported

Analysis

Analysis strategy: Log-linear model incorporating the Weibull distribution

Confounders: Age, Cigarettes, diabetes, corneal arcus, vital capacity, cholesterol and systolic blood pressure

Results, limitations, source of funding

Number: 126 for CHD, 62 for stroke, 8 for PAD, 9 for other heart diseases, 24 for lung cancer, 126 for other cancer locations, 21 for chronic bronchitis, 8 for infectious diseases, 25 for violence, and 75 for all other causes

Effect estimates:

CHD-H

Coefficient T value
Age -0.0308 -3.69
Cigarettes -0.0101 -2.60

CHD-A
Coefficient T value
Age -0.0281 -3.63
Cigarettes -0.0070 -1.89

STR-H
Coefficient T value
Age -0.0471 -5.17
Cigarettes -0.0038 -0.89

STR-A
Coefficient T value
Age -0.0471 -.5.55
Cigarettes 0.0041 -1.02

PAD
Coefficient T value
Age -0.0450 -3.27
Cigarettes 0.0276 -4.45

CVD
Coefficient T value
Age -0.0401 -6.42
Cigarettes -0.0115 -3.95

Delta for Hazard ratio, Hazard ratio, (95% CI)
Age (years) 5, 1.29, (1.19-1.39)
Cigarettes (n/day) 10, 1.16 (1.08-1.24)

Significant trends: Incidence of cardiovascular disease is higher than CHD

Limitations: Not reported

Source of funding: Personal grant to the senior author (AM) from the Association for Cardiac Research. Rome, Italy, and by a grant of the Martinson Clinical Foundation, Wayzata. Minnesota, USA.

Authors: Menotti A, Lanti M, Maiani G, Kromhout D

Year: 2006

Citation: Aging Clinical and Experimental Research 18(5): 394-406

Country of study: Italy

Aim of study: Survival and all-cause mortality in two cohorts of middle-aged men followed for 40 years

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Number of people: Not reported

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1712

Characteristics: Not reported

Location: Crevalcore in Northern Italy and Montegiorgio in Central Italy

Recruitment strategy: Not reported

Length of follow-up: 40 years

Response rate and loss to follow-up: 98.8%

Eligible population: Middle-aged men

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Physical activity, cigarette smoking, diet

Time: 1960

Measurement of exposure: Questionnaire

Outcomes at 55 years or over

Outcomes: Causes of death and morbidity

Outcome measurement: Death certificates, hospital and medical records, interviews with physicians and relatives of the deceased, and any other witnesses of fatal events.

Time: Not reported

Analysis

Analysis strategy: Proportional hazard model

Confounders: Age; father history, mother history, family history of cardiovascular diseases; marital status children; job relatedphysical activity, cigarette smoking, diet of any type followed by subjects; height, weight, body mass index (BMI), trunk/height ratio, biacromial diameter, bicrystal diameter, shoulder/pelvis shape. laterality/linearity index, tricipital skinfold thickness. subscapular skinfold thickness, arm circumference; systolic blood pressure. Diastolic blood pressure, rnean blood pressure, heart rate: vital capacity, forced expiratory volume; serum cholesterol, urine protein. urine glucose: baldness. cornealarcus. xanthelasma: diagnoses of Cardiovascular diseases, cancer. diabetes, chronic bronchitis; history of lung tuberculosis, bronchial asthma, peptic ulcer, intestinal diseases. liver diseases, gall bladder diseases. kidney stones. other genito-urinary diseases; thyroid disease;minor ECG abnormalities at rest. exercise ECG abnormalities

Results, limitations, source of funding

Number: 1434 deaths (83.8%)

Effect estimates:

Risk factor Coefficient and (SE) Hazard ratio (95% confidence) Standardized Coefficient and (rank)

Age 0.1021 (0.0064) 1.67 (1 56-1.77) 0.5152 (1)
Father history.0.1692 (0.0679) 1.18 (1.04-135) 0.0689 (10)
Mother history 0.2166 (0.0695) 1.24 (1.08-1.42) 0.0875 (7)
Physical activity -0.0986 (0.0446) 0.91 (0.83-0.09) -0.0636 (13)
Cigarette smoking 0.0194 (0.0029) 1.21 (1.15-1.29) 0.1841 (3)
Body mass index (linear) -0.1425 (0.0721) 0.57 (0.33-1.00) ---
Body mass index (quadratic) 0.0025 (0.0013) 1.65 (0.99-2.74) ---
Mid-arm circumference -0.0036 (0.0017) 0.91 (0.84-0.99) -0.0840(8}
Mean blood pressure 0.0205 (0 0024) 1.36 (1.27-1.46) 0.2764 (2)
Forced expiratory volume in 3/4 sec -0.5770 (0.1256) 0 87 (0.81-0.92) -0.1439(4}

Serum cholesterol 0.0851 (0.0271) 1.09 (1.03-1.15) 0.0908 (6)
Corneal arcus 0.1838 (0.0795) 1.20 (1.03-1.40) 0.0643 (12)
Xanthelasma 0 5550 (0.21421) 1.74 (1.14-2.65) 0.0685 (11)
Diagnosis of cardiovascular disease 0.3714 (0.1315) 1.45 (1.12-1.88) 0.0761 (9)
Diagnosis of cancer 2.1717 (0.4554) 8.77 (3.59-21 42) 0.1232(5)
Diagnosis of diabetes 0.2193 (0.1103) 1.25 (1.00-1.55) 0.0549 (14)

Significant trends: During a 40-year period 15 mainly cardiovascular risk factors were highly predictive of all-cause mortality and survival in middle-aged men

Limitations: Not reported

Source of funding: The company Medrisk of Roma, Italy, contributed financially to this analysis

Authors: Menotti A, Alberti-Fidanza A, Fidanza F

Year: 2012

Citation: Nutrition, Metabolism and Cardiovascular Diseases 22(4): 369-75

Country of study: Italy

Aim of study: To test the adequacy of the Mediterranean Adequacy Index (MAI) as a predictor of CHD mortality

Study design: Longitudinal

Quality score: (++, + or -): -

Source population

Men ages 40-59 years of two rural cohorts living in Crevalcore and Montegiorgio, Italy

Study (eligible and selected) population

1712 men (98% of the roster) were examined in 1960; of these, 1286 men were re-examined in 1965. Study restricted to **1139** men free from CHD at study entry and with complete data

Sociodemographics: Mean age of 34.5 years at baseline

Exclusion:

i) Men who died between 1960 and 1965 (n=90)
ii) Men with missing data (n=278)
iii) Men with CHD

Attrition: -

Exposures at midlife

The adequacy of the Mediterranean Adequacy Index (MAI), which captures the healthiness of a diet, was tested as a predictor of CHD mortality

<u>Mediterranean Adequacy Index (MAI)</u>

- In 1960, participant diet was captured through weighted-record method for 1 week during 3 seasons from a subsample of 28 men from Crevalcore and 34 from Montegiorgio
- In 1965, food intake of all participants was assessed through dietary-history method
- Dietary intake data was used to create the MAI:
- The MAI measures the similarity of various diets to the Reference Mediterranean Dietary Pattern, and an MAI score ranging from 0 to 100 is obtained by dividing the sum of percentages of dietary energy of healthy Mediterranean diet food groups (e.g., cereals, legumes, vegetables) by the sum of the percentages of dietary energy of other food groups not characteristic of a Mediterranean diet (e.g., milk, cheese, meat, animal fats, cakes, pies, sugar)

Outcomes at 55 years or over

CHD deaths occurring during 40 years after 1965 examination ascertained through death certificates, medical records, physical interviews, interviews with relatives or other witnesses of fatal events

Analysis

Analysis strategy: Reduced rank regression was used to derive dietary patterns with C-reactive protein, IL-6 and IL-18 as responses; partial least squares and principal components regression was also used

Confounders: Aage, survey, BMI, place of residence (urban/rural), actual hypertension (yes/no), education level (low/ high), self-reported diagnosis of diabetes, physical activity (active/not active), energy intake (kcal/day), ratio of total cholesterol and HDL cholesterol, smoking status

Results, limitations, source of funding

- 79 CHD fatal events in 20 years, and 162 in 40 years
- The coefficient of lnMAI was negative, and thus, had a protective effect against CHD mortality at 20 and 40 years (hazard ratios for 1 unit of lnMAI: HR=0.74, [0.55, 0.99], and HR=0.79, [0.64, 0.97] for each follow-up time period, respectively)
- Hazard ratio of 1 unit of lnMAI (2.7 units of MAI) was associated with a CHD mortality reduction of 26% and 21% at 20 and 40 years of follow-up, respectively

Limitations: Small sample size

Source of funding: None reported

Authors: Meyer J, Döring A, Herder C, Roden M, Koenig W, Thorand B

Year: 2011

Citation: European Journal of Clinical Nutrition 65(7): 800-7.

Country of study: Germany

Aim of study: To determine the association between dietary patterns, subclinical inflammation, incident coronary heart disease and mortality

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Three cross-sectional surveys were conducted during 1984-1995 in Southern Germany

Study (eligible and selected) population

981 males ages 45-64 years with complete data for survey 1 (n=594/899) and survey 3 (n=387/430) conducted in 1984-85 and 1994-95, respectively

Participants were on average 54.9 years at time of exposure assessment

Follow-up: 1984-1995 to 2002 for CHD case development or 2007 for CHD mortality

Median follow-up time until occurrence of acute coronary event was 16.7 and 7.9 years for CHD survey 1 and survey 3, respectively

Median follow-up time until death was 22.8 and 12.9 years for survey 1 and survey 3, respectively

Exclusion: -

Exposures at midlife
7-day dietary record completed by participants through surveys Food consumed assessed through weighing techniques and household measures
Outcomes at 55 years or over
Incidence of fatal or non-fatal myocardial infarction and all-cause mortality were study end points Deaths were identified through population registries and the underlying cause of death ascertained through death certificates, while myocardial infarctions occurring before 75 years were identified through population-based coronary event registry and questionnaire Self-reported non-fatal incident myocardial infarction cases were validated using hospital records/physicians Pro-inflammatory markers CRP, IL-6 and IL-18 measured through blood samples at the time the surveys were administered
Analysis
Analysis strategy: Reduced rank regression was used to derive dietary patterns with C-reactive protein, IL-6 and IL-18 as responses; partial least squares and principal components regression was also used **Confounders:** Age, survey, BMI, place of residence (urban/rural), actual hypertension (yes/no), education level (low/ high), self-reported diagnosis of diabetes, physical activity (active/not active), energy intake (kcal/day), ratio of total cholesterol and HDL cholesterol, smoking status
Results, limitations, source of funding
• 101 participants had an acute coronary event, and 292 died (88 died from CHD) during follow-up • High intakes of meat, soft drinks and beer and low intakes of vegetables, fresh fruit, chocolates, cake, pastries, wholemeal bread, cereals, muesli, curd, condensed milk, cream, butter, nuts, sweet bread spread and tea was associated with a *high score* of the RRR-derived pattern • A *high score* was associated with a high risk for all-cause mortality (HR=1.16, [1.00, 1.33], respectively) **Limitations:** 1. Cannot generalise to women 2. Limited study power 3. Participants may have changed dietary behaviour over time, which may attenuate association between dietary behaviour at baseline and end points **Source of funding:** Helmholtz Zentrum Munchen, the Federal Ministry of Education and Research, Berlin, German Research Foundation, Bonn, University of Ulm, the German Diabetes Center, Dusseldorf, the Federal Ministry of Health, the Ministry of Innovation, Science, Research and Technology of the state North Rhine Westphalia

Authors: Miura K, Greenland P, Stamler J, Liu K, Daviglus ML, Nakagawa H **Year:** 2004 **Citation:** American Journal of Epidemiology 15;159(6): 572-80 **Country of study:** USA **Aim of study:** Associations between food group intake and subsequent blood pressure change **Study design:** Prospective population study

Quality score: (++, + or -): +

Source population

Number of people: 5,397

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2,080

Characteristics:

Mean (SD)
Age (years) 48.5 (4.4)
Height (cm) 174.6 (6.4)
Weight (kg) 78.1 (11.0)
Body mass index (weight (kg)/height (m)2) 25.6 (3.2)
Obesity (body mass index ≥30) (%) 8.5
Current smoker (%) 53.0
No. of cigarettes per day: all 10.2 (11.0)
No. of cigarettes per day: smokers 17.8 (8.8)
Current drinker (%) 85.8
Current alcohol consumption: all (ml/day) 16.2 (20.3)
Current alcohol consumption: drinkers (ml/day) 118.8 (20.7)
Education (no. of years) 11.2 (2.5)
Total energy (kcal) 3,124 (777)
Total fat (% of kcal) 42.8 (4.2)

Location: Chicago, Illinois

Recruitment strategy: Random selection

Length of follow-up: 7 year

Response rate and loss to follow-up 67.1%

Eligible population: Men aged 40–55 years. Employed at the Hawthorne Works of the Western Electric Company in Chicago

Excluded populations: Missing baseline dietary assessments (n = 191); blood pressure (n = 72); educational attainment (n = 223); previously diagnosed diabetes mellitus (n = 31); prior myocardial infarction (n = 44), and/or fewer than three follow-up examinations between 1960 and 1966 (n = 184).

Exposures at midlife

Relevant exposures: Nutrient intake

Time: 1958-1959

Measurement of exposure: Two nutritionists using standardised interviews and questionnaires based on Burke's comprehensive dietary history method

Outcomes at 55 years or over

Outcomes: Systolic blood pressure or diastolic blood pressure

Outcome measurement: Standard mercury sphygmomanometers

Time: 1966

Analysis

Analysis strategy: Generalised estimating equation models

Confounders: Baseline age, weight at each year, height, education, smoking, alcohol consumption, daily intake of 12 nutrients

Results, limitations, source of funding

Number: Not reported

Effect estimates:

Relation between baseline food intake and adjusted average annual change in men's systolic blood pressure

Change/ year (mmHg) p value

Vegetables (cups/month)
14–42 –0.29 0.096
>42 –0.08 0.801

Fruits (cups/month)
14–42 –0.29 0.043
>42 –0.22 0.307

Fish (120-g units/month)
<4 –0.34 0.095
4–8 –0.22 0.286
>8 –0.41 0.085

Beef-veal-lamb (120-g units/month)
8–20 0.76 0.026
>20 0.80 0.022

Pork (120-g units/month)
4–8 0.55 0.002
>8 0.33 0.060

Poultry (120-g units/month)
4–8 0.21 0.072
>8 0.49 0.012

Relation between baseline food intake and adjusted average annual change in men's diastolic blood pressure

Change/ year (mmHg) p value

Vegetables (cups/month)
14–42 –0.11 0.269
>42 –0.06 0.713

Fruits (cups/month)
14–42 –0.13 0.115
>42 –0.19 0.119

Fish (120-g units/month)
<4 –0.11 0.282
4–8 –0.03 0.811
>8 –0.17 0.190

Beef-veal-lamb (120-g units/month)
8–20 0.29 0.089
>20 0.41 0.022

Pork (120-g units/month)
4–8 0.06 0.592
>8 0.04 0.735

Poultry (120-g units/month)

4–8 0.18 0.006
>8 0.25 0.031

Significant trends: Higher intakes of vegetables and of fruits were related to less of an increase in SBP and DBP over time. Men with a higher intake of red meat had a significantly greater increase in blood pressure. Men with a higher poultry intake had a significantly greater annual increase in blood pressure. Men with a higher fish intake tended to have less of an increase in blood pressure.

Limitations:
Author

1. Data collection for this study took place over 40 years ago
2. No information on dietary sodium chloride, potassium, magnesium, or fibre intakes
3. Misclassification of intake for each food.
4. Unmeasured non-dietary factors.
5. Findings may (or may not) be generalisable beyond middle-aged, non-Hispanic White males.

Reviewer: No control for medication use

Source of funding: American Heart Association and its Chicago and Illinois affiliates; the National Heart, Lung, and Blood Institute (HL 15174, HL 21010, and HL 03387); the Chicago Health Research Foundation; the Otho S. Sprague Foundation; the Research and Education Committee of the Presbyterian-St. Luke's Hospital; the Illinois Foundation; and private donors

Authors: Moayyeri A, Kaptoge S, Luben RN, Wareham NJ, Bingham S, Reeve J, Khaw KT

Year: 2009

Citation: European Journal of Epidemiology 24(5): 259-66

Country of study: UK

Aim of study: Estimates of fracture risk

Study design: Population-based cohort study

Quality score: (++, + or -): +

Source population

Number of people: 25,639

Demographics: Not reported

Study (eligible and selected) population

Number of people: 25,311

Characteristics:

Women

Fracture
n = 649
Age (years) 64.7 (8.4)
History of fracture 117 (11.1%)
Height (cm) 160.2 (6.3)
Weight (kg) 67.4 (12.4)
Body mass index (kg/m2) 26.2 (4.5)
Current smoking 64 (9.9%)
Alcohol intake (units/week) 1.5 (0.5–4.5)

No fracture
n = 13,186
Age (years) 58.1 (9.2)
History of fracture 936 (7.1%)

Height (cm) 161.0 (6.2)
Weight (kg) 68.0 (11.8)
Body mass index (kg/m2) 26.2 (4.3)
Current smoking 1,508 (11.4)
Alcohol intake (units/week) 2.5 (0.5–6.5)

P value
Age (years) \0.001
History of fracture \0.001
Height (cm) 0.002
Weight (kg) 0.2
Body mass index (kg/m2) 0.9
Current smoking 0.2
Alcohol intake (units/week) \0.001

Men

Fracture
n = 276
Age (years) 61.9 (9.7)
History of fracture 25 (9.1%)
Height (cm) 174.4 (6.4)
Weight (kg) 80.7 (11.9)
Body mass index (kg/m2) 26.5 (3.4)
Current smoking 38 (13.8%)
Alcohol intake (units/week) 7 (2–16.5)

No fracture
n = 11,200
Age (years) 59.0 (9.3)
History of fracture 654 (5.8%)
Height (cm) 174.0 (6.6)
Weight (kg) 80.4 (11.5)
Body mass index (kg/m2) 26.5 (3.3)
Current smoking 1,362 (12.2%)
Alcohol intake (units/week) 6 (2–14)

P value
Age (years) \0.001
History of fracture 0.02
Height (cm) 0.3
Weight (kg) 0.6
Body mass index (kg/m2) 0.9
Current smoking 0.4
Alcohol intake (units/week) 0.2

Location: Norfolk, East Anglia

Recruitment strategy: Age and sex registers of general practices

Length of follow-up: 11.3 years (SD = 1.5; range 9.2–14.1)

Response rate and loss to follow-up: Not reported

Eligible population: Not reported

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Smoking and alcohol

Time: 1993–1997

Measurement of exposure: Smoking status was derived from responses to the questions ‘‘Have you

ever
smoked as much as one cigarette a day for as long as a year?'' and ''Do you smoke cigarettes now?''

Alcohol consumption derived from a question ''How many alcoholic drinks do you have each week?'' with four separate categories of drinks.

Total alcohol consumption was estimated as the total units of drinks consumed in a week

Outcomes at 55 years or over

Outcomes: Osteoporotic fractures

Outcome measurement: Death certificates

Time: March 2007

Analysis

Analysis strategy: Cox proportional hazards models

Confounders: Age, sex, history of fractures, body mass index, smoking, and alcohol intake

Results, limitations, source of funding

Number: 925 incident fractures; 334 (36%) hip fractures; 154 (17%) clinical spinal fractures; 219 (24%) wrist fractures

Effect estimates:

Any incident fracture
HR (95% CI)

Women (649 cases)
Age (years)1.08 (1.07–1.09)
History of fracture 1.92 (1.57–2.36)
Body mass index (kg/m2) 0.99 (0.97–1.01)
Smoking status (current) 1.10 (0.85–1.43)
Alcohol intake (units/week) 0.98 (0.97–1.00)
C-index (95% CI)
Derivation dataset 0.70 (0.67–0.72)
Validation dataset 0.72 (0.67–0.76)

Men (276 cases)
Age (years) 1.04 (1.02–1.05)
History of fracture 1.53 (1.01–2.31)
Body mass index (kg/m2) 0.99 (0.96–1.03)
Smoking status (current) 1.19 (0.84–1.68)
Alcohol intake (units/week) 1.01 (1.01–1.02)
C-index (95% CI)
Derivation dataset 0.60 (0.55–0.64)
Validation dataset 0.63 (0.56–0.70)

Incident hip fracture
HR (95% CI)

Women (245 cases)
Age (years) 1.14 (1.12–1.16)
History of fracture 1.59 (1.14–2.20)
Body mass index (kg/m2) 0.96 (0.93–0.99)
Smoking status (current) 1.19 (0.77–1.83)
Alcohol intake (units/week) 0.99 (0.97–1.02)
C-index (95% CI)
Derivation dataset 0.78 (0.75–0.81)

Validation dataset 0.82 (0.78–0.87)

Men (89 cases)
Age (years) 1.15 (1.11–1.18)
History of fracture 1.73 (0.87–3.45)
Body mass index (kg/m2) 0.95 (0.89–1.01)
Smoking status (current) 1.38 (0.74–2.56)
Alcohol intake (units/week) 1.01 (0.99–1.03)
C-index (95% CI)
Derivation dataset 0.79 (0.74–0.85)
Validation dataset 0.79 (0.72–0.86)

Significant trends: Statistically significant differences between men and women. The 10-year probability of fracture was approximately 1% in both men and women aged 40–45 years rising to about 17% for women and 5% for men aged 75 years with a previous history of fracture.

Limitations:

1. Lack of BMD assessment at the beginning of follow-up.
2. Potential for under-registration of fracture outcomes in the cohort population.
3. Participants are likely to be healthier and have lower fracture rates

Source of funding: EPIC-Norfolk is supported by program grants from the Medical Research Council and Cancer Research UK with additional support from the Stroke Association, Research into Ageing, the Academy of Medical Sciences, British Heart Foundation, Department of Health, and the Wellcome Trust

Authors: Morgan GS, Gallacher J, Bayer A, Fish M, Ebrahim S, Ben-Shlomo Y

Year: 2012

Citation: Journal of Alzheimer's Disease 31(3): 569-580

Country of study: Wales

Aim of study: To determine the association between physical activity in mid-life and dementia in late-life

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

2,512 mostly manual class men ages 45-59 and resident in this region during 1979-1983 were identified through electoral register and recruited (89% of eligible population)

Study (eligible and selected) population

Analysis restricted to **1005** men who took part in phase 2 (1984-1988) and phase 5 (2002-2004) of study and with complete variable data

Follow-up: 16 years. Between phase 2 and phase 5, 125 people could not be traced

Exclusion: -

Attrition: 85% of subjects participating in phase 2 and 5 included (between these phases: participants had died [n=109], moved [n=86], did not wish to take part [n=295], could not be traced [n=125] or had incomplete exposure/covariate or outcome data)

Exposures at midlife

Physical activity self-reported questionnaire data assessed:

Work-related physical activity: combined score created that is indicative of occupational time spent sitting, walking, lifting, and the total number of hours spent at work

Leisure-time physical activity: total duration and frequency of participation in over thirty different leisure-time activities assessed over the past year, with each activity allocated an intensity score; finally, type, frequency, and duration of leisure-time physical activity were combined into a composite score for each participant

Outcomes at 55 years or over

Cognitive function screening using CAMCOG

Clinical assessment for case ascertainment
included use of death certificates, community mental health team for older people used for those institutionalized (those clinically assessed underwent further tests and clinical exams)

Outcome categories:
1. Cognitive impairment not dementia (CIND) [further broken down into vascular vs. non-vascular CIND]
2. Dementia [vascular dementia vs. non-vascular dementia]

Analysis

Analysis strategy: Logistic regression used to assess whether work-related and leisure-related physical activity in mid-life are related to dementia or cognitive impairment

Confounders: Age, social class, National Adult Reading Test score, smoking status, marital status, self-reported history of vascular disease, alcohol consumption, body mass index, common mental disorder, anxiety

Results, limitations, source of funding

- No association between leisure-time activity and vascular or non-vascular subtypes
- No association between work-related or leisure-related activity with dementia risk

Limitations:

1. Residual confounding, such as social networking and engagement
2. Self-report can lead to non-differential misclassification and underestimation of true associations
3. Possible that study was underpowered
4. Associations may reflect healthy survivor effect

Source of funding: Medical Research Council, Alzheimer's Society

Authors: Mursu J, Voutilainen S, Nurmi T, Tuomainen TP, Kurl S, Salonen JT

Year: 2008

Citation: British Journal of Nutrition 100(4): 890-5

Country of study: Finland

Aim of study: Investigate risk factors for CVD, atherosclerosis and related outcomes in middle-aged men from eastern Finland

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Number of people: 2682

Demographics: Not reported

Study (eligible and selected) population
Number of people: 1950 **Characteristics:** Quartiles of flavonoid intake (mg/d) Mean SD 1 (lowest) Age (years) 51.9 5.4 BMI (kg/m2) 26.7 3.4 Leisure-time physical activity (kJ/d) 482.8 636.8 Leisure-time physical activity (kcal/d) 115.4 152.2 Smokers (%) 38.2 Alcohol intake (g/week) 87.1 136.1 Total fat intake (% of total energy) 40.2 6.4 2 Age (years) 53.2 5.3 BMI (kg/m2) 26.8 3.5 Leisure-time physical activity (kJ/d) 558.6 638.9 Leisure-time physical activity (kcal/d) 133.5 152.7 Smokers (%) 32.4 Alcohol intake (g/week) 72.3 106.0 Total fat intake (% of total energy) 38.6 6.4 3 Age (years) 52.4 5.3 BMI (kg/m2) 26.7 3.5 Leisure-time physical activity (kJ/d) 670.7 825.5 Leisure-time physical activity (kcal/d) 1603 197.3 Smokers (%) 28.9 Alcohol intake (g/week) 69.7 115.7 Total fat intake (% of total energy) 37.5 6.1 4 (highest) Age (years) 52.2 5.3 BMI (kg/m2) 26.5 3.5 Leisure-time physical activity (kJ/d) 605.4 677.4 Leisure-time physical activity (kcal/d) 144.7 161.9 Smokers (%) 19.9 Alcohol intake (g/week) 60.5 95.2 Total fat intake (% of total energy) 38.1 5.6 P values Age (years) 0.001 BMI (kg/m2) 0.506 Leisure-time physical activity (kJ/d) , 0.001 Leisure-time physical activity (kcal/d) , 0.001 Smokers (%) , 0.001 Alcohol intake (g/week) 0.003 Total fat intake (% of total energy) , 0.001 **Location:** Finland **Recruitment strategy:** Not reported **Length of follow-up:** Average follow-up time of 15·2 years **Response rate and loss to follow-up:** 82.9% of those eligible. There were no losses to follow-up **Eligible population:** Not reported

Excluded populations: Men who had history of CHD or stroke were excluded from the study

Exposures at midlife

Relevant exposures: Smoking and alcohol

Time: March 1984-December 1989

Measurement of exposure: The number of cigarettes, cigars and pipefuls of tobacco currently smoked daily, duration of regular smoking in years, alcohol consumption, recorded with a self-administered questionnaire

Consumption of foods was assessed with an instructed 4 day food recording by household measures

Outcomes at 55 years or over

Outcomes: Ischaemic strokes and CVD deaths, atherosclerosis and related outcomes

Outcome measurement: 1984 and 1992 information of strokes were collected prospectively

1993 post obtained by computer linkage to the national hospital discharge and death registers

CVD deaths were ascertained by computer linkage to the national death registry using the Finnish social security number

Time: 1984 - 1992 and 1993. CVD deaths from study entry to 31 December 2004

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age and examination years, BMI, systolic blood pressure, hypertension medication, serum HDL- and LDL-cholesterol, serum TAG, maximal oxygen uptake, smoking, family history of CVD, diabetes, alcohol intake, energy-adjusted intake of folate, vitamin E, total fat and saturated fat intake (percentage of energy)

Results, limitations, source of funding

Number: 102 ischaemic strokes and 153 CVD deaths

Effect estimates:

Quartiles of flavonoid intake (mg/d)

1
Ischaemic stroke
Flavonols 1
Flavones 1
Flavanones 1
Flavan-3-ols 1
Anthocyanidins 1
Total sum of flavonoids 1

CVD mortality
Flavonols 1
Flavones 1
Flavanones 1
Flavan-3-ols 1
Anthocyanidins 1
Total sum of flavonoids 1

2
RR 95 % CI

Ischaemic stroke
Flavonols 0.68 0.40, 1.14
Flavones 1.12 0.60, 2.11
Flavanones 0.83 0.47, 1.47
Flavan-3-ols 1.24 0.73, 2.10
Anthocyanidins 0.89 0.48, 1.63
Total sum of flavonoids 1.65 0.98, 2.79

CVD mortality
Flavonols 1.22 0.77, 1.94
Flavones 0.64 0.40, 1.05
Flavanones 0.60 0.37, 0.98
Flavan-3-ols 1.29 0.82, 2.04
Anthocyanidins 0.51 0.30, 0.87
Total sum of flavonoids 1.85 1.18, 2.90

3
RR 95 % CI
Ischaemic stroke
Flavonols 0.54 0.30, 0.95
Flavones 2.05 1.15, 3.65
Flavanones 0.97 0.56, 1.71
Flavan-3-ols 1.02 0.58, 1.80
Anthocyanidins 1.58 0.91, 2.71
Total sum of flavonoids 1.00 0.55, 1.81

CVD mortality
Flavonols 1.42 0.88, 2.28
Flavones 0.64 0.40, 1.02
Flavanones 0.97 0.62, 1.50
Flavan-3-ols 1.03 0.64, 1.65
Anthocyanidins 1.17 0.74, 1.86
Total sum of flavonoids 1.05 0.63, 1.74

4 (highest)
RR 95 % CI
Ischaemic stroke
Flavonols 0.55 0.31, 0.99
Flavones 1.30 0.69, 2.47
Flavanones 0.89 0.49, 1.63
Flavan-3-ols 0.59 0.30, 1.14
Anthocyanidins 0.88 0.47, 1.62
Total sum of flavonoids 0.71 0.37, 1.37

CVD mortality
Flavonols 1.26 0.75, 2.14
Flavones 0.65 0.40, 1.05
Flavanones 0.54 0.32, 0.92
Flavan-3-ols 1.06 0.64, 1.65
Anthocyanidins 0.99 0.62, 1.85
Total sum of flavonoids 1.25 0.74, 2.11

P trend
Ischaemic stroke
Flavonols 0.027
Flavones 0.181
Flavanones 0.870
Flavan-3-ols 0.102
Anthocyanidins 0.813
Total sum of flavonoids 0.137

CVD mortality
Flavonols 0.622
Flavones 0.333
Flavanones 0.266
Flavan-3-ols 0.694
Anthocyanidins 0.193
Total sum of flavonoids 0.730

Significant trends: A high intake of flavonoids decreases the risk of ischaemic stroke and possibly CVD mortality

Limitations:

1. Could not study the main sources of flavonoids.
2. Seasonal variation in the 4d food recording

Source of funding: Juho Vainio Foundation and Finnish Cultural Foundation, North-Savo Foundation

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Authors: Nafziger AN, Lindvall K, Norberg M, Stenlund H, Wall S, Jenkins PL… Weinehall L

Year: 2007

Citation: BMC Public Health 12;7:108

Country of study: Sweden

Aim of study: Characterise who is not gaining weight during a 10 year period in Sweden

Study design: Longitudinal survey

Quality score: (++, + or -): -

Source population

Number of people: 23,863

Demographics:

Non-participants (%)
Age (years)
30 29.9%
40 39.3%
50 30.8%
Sex
Male 50.4%
Female 49.6%
Education
Low 21.8%
Medium 52.6%
High 25.6%
Smoker 30.4%
Snuff use 28.7%
Physically inactive 42.9%

Study (eligible and selected) population

Number of people: 14,867

Characteristics:

Age (years)
3023.4%
40 39.7%
50 36.9%

Sex
Male 46.6%
Female 53.4%
Education
Low 22.8%
Medium 53.9%
High 23.4%
Smoker 24.8%
Snuff use 25.6%
Physically inactive 41.5%

Location: Västerbotten, Sweden

Recruitment strategy: Not reported

Length of follow-up: 10 years

Response rate and loss to follow-up: The overall follow-up rate was 68.1%; the response rate among the eligible was 74%

Eligible population: Men and women aged 30, 40 or 50 years at baseline

Excluded populations: Participants who lacked a BMI were excluded. Participants with an initial BMI <18.5 or ≥30 kg/m2 were excluded. 1062 participants who moved out of the county, 503 individuals who died, and 7 who could not be located because of assignment of an anonymous civil number

Exposures at midlife

Relevant exposures: Physical activity, smoking and snuff use

Time: 1990-1994

Measurement of exposure: Participants completed a questionnaire that included questions use of tobacco products, physical activity. Participants were classified as smokers (yes/no) and snuff users (Swedish moist snuff (snus); yes/no)

Outcomes at 55 years or over

Outcomes: Weight gain

Outcome measurement: BMI

Time: 2000-2004

Analysis

Analysis strategy: Multivariate logistic regression model

Confounders: Not reported

Results, limitations, source of funding

Number: 9625 categorised as gainers

Effect estimates:

Odds Ratio (95% CI)

Men
30 yr 1.00
40 yr 1.13 (0.99, 1.30)
50 yr 2.24 (1.96, 2.56)

Women
30 yr 1.14 (0.98, 1.32)

40 yr 1.17 (1.03, 1.35)
50 yr 1.50 (1.16, 1.34)

Body mass index (kg/m2)
18.5–24.9 1.00
25–29.9 1.25 (1.16, 1.34)

Year of initial survey
1990 1.00
1991 1.19 (1.04, 1.36)
1992 1.38 (1.21, 1.56)
1993 1.43 (1.26, 1.62)
1994 1.74 (1.53, 1.98)

Glucose metabolism
Normal 1.00
Glucose intolerance 1.15 (0.94, 1.40)
Type 2 diabetes 1.47 (1.08, 1.99)

Snuff use
No 1.00
Yes 0.83 (0.74, 0.92)

Significant trends: Older age, being female, classified as overweight by baseline BMI, later survey year and baseline diagnosis of diabetes increased the chances of not gaining weight. Those who did not use snuff also were more likely to be non-gainers.

Limitations
Author:

1. Participation rates were not optimal.
2. Participants in this study were more likely to be of older age, women, lower education, lower baseline BMI and less likely to have cardiovascular risk factors - differences between participants and non-participants should have resulted in more conservative odds ratios

Reviewer**:** Fail to report confounders in analysis

Source of funding: AFA-Insurance Sweden

Authors: Nakamura Y, Hozawa A, Turin TC, Takashima N, Okamura T, Hayakawa T… Ueshima H; NIPPON DATA80 Research Group

Year: 2009

Citation: Gerontology 55(6): 707-13

Country of study: Japan

Aim of study: Examine the association of meat, fish and egg intake with risk of subsequent mortality and/or future decline in activities of daily living

Study design: Cohort

Quality score: (++, + or -): +

Source population

Number of people: 3,227

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1,889

Characteristics:

Men

Meat
<1/2 days
Number 375
Age, years 53.2±3.6
BMI 22.4±2.9
Smoking, % 69.9
Daily drinking, % 49.1
Professional work, % 33.7
Urban residence, % 25.3

≥1/2 days
Number 667
Age, years 52.9±3.5
BMI 22.7±2.7
Smoking, % 65.4
Daily drinking, % 52.5
Professional work, % 40.7
Urban residence, % 31.0

Fish
<1/day
Number 555
Age, years 52.9±3.5
BMI 22.5±2.9
Smoking, % 68.5
Daily drinking, % 47.9
Professional work, % 41.1
Urban residence, % 31.2

≥1/day
Number 487
Age, years 53.1±3.5
BMI 22.7±2.7
Smoking, % 65.3
Daily drinking, % 55.0
Professional work, % 34.9
Urban residence, % 26.5

Egg
<1/day
Number 599
Age, years 53.1±3.5
BMI 22.7±2.8
Smoking, % 66.9
Daily drinking, % 51.6
Professional work, % 38.7
Urban residence, % 30.4

≥1/day
Number 443
Age, years 52.9±3.5
BMI 22.4±2.9
Smoking, % 67.0
Daily drinking, % 50.8
Professional work, % 37.5
Urban residence, % 27.1

P

Meat

Age, years 0.27
BMI 0.15
Smoking, 0.13
Daily drinking, 0.29
Professional work, 0.03
Urban residence, 0.0

Fish
Age, years 0.52
BMI 0.14
Smoking, 0.28
Daily drinking, 0.02
Professional work, 0.04
Urban residence, 0.10

Egg
Age, years 0.51
BMI 0.048
Smoking, 0.97
Daily drinking, 0.80
Professional work, 0.69
Urban residence, 0.25

Women

Meat
<1/2 days
Number 573
Age, years 53.6±3.8
BMI 23.3±3.6
Smoking, % 9.8
Daily drinking, % 1.8
Professional work, % 15.4
Urban residence, % 28.5

≥1/2 days
Number 701
Age, years 53.1±3.8
BMI 23.3±3.2
Smoking, % 6.0
Daily drinking, % 2.0
Professional work, % 22.0
Urban residence, % 32.0

Fish
<1/day
Number 750
Age, years 53.1±3.7
BMI 23.4±3.4
Smoking, % 8.8
Daily drinking, % 2.3
Professional work, % 17.6
Urban residence, % 32.0

≥1/day
Number 524
Age, years 53.5±3.9
BMI 23.2±3.4
Smoking, % 6.1
Daily drinking, % 1.3
Professional work, % 21.0

Urban residence, % 28.1

Egg
<1/day
Number 877
Age, years 53.3±3.8
BMI 23.4±3.4
Smoking, % 7.8
Daily drinking, % 1.6
Professional work, % 18.5
Urban residence, % 29.8

≥1/day
Number 397
Age, years 53.3±3.7
BMI 23.2±3.3
Smoking, % 7.6
Daily drinking, % 2.5
Professional work, % 20.2
Urban residence, % 31.7

P

Meat
Age, years 0.02
BMI 0.98
Smoking, % 0.01
Daily drinking, % 0.74
Professional work, % 0.003
Urban residence, % 0.18

Fish
Age, years 0.10
BMI 0.39
Smoking, % 0.08
Daily drinking, % 0.23
Professional work, % 0.13
Urban residence, % 0.13

Egg
Age, years 0.997
BMI 0.39
Smoking, % 0.90
Daily drinking, % 0.26
Professional work, % 0.47
Urban residence, % 0.48

Exposures at midlife

Relevant exposures: Diet

Time: 1980

Measurement of exposure: A lifestyle survey was also carried out using a self-administered questionnaire which included the daily consumption of meat, eggs and fish.

Location: 300 districts

Recruitment strategy: Participants from 300 randomly selected districts in 1980

Length of follow-up: 19 years

Response rate and loss to follow-up: 75%

Eligible population: Aged 47–59 years

Excluded populations: 286 participants who had a history of coronary heart disease (CHD) or stroke (n = 39), had missing information in the baseline survey (n = 54) or were lost to follow-up (n = 193), 427 died
Outcomes at 55 years or over
Outcomes: Activities of daily living **Outcome measurement**: Participants were asked about 5 basic ADL items (modified from Katz et al.) **Time:** 1999
Analysis
Analysis strategy: Multiple adjusted logistic regression model **Confounders:** Age, BMI and cigarette smoking, alcohol drinking, hypertension and diabetes, serum albumin and total cholesterol concentrations, job type and urban residence
Results, limitations, source of funding
Number: 75 participants became dependent due to impaired ADL **Effect estimates:** **Associations of impaired ADL or death and food intake in the meat, fish and egg intake groups** Odds ratio (CI 95%) <u>Meat</u> <1/2 days 1 ≥1/2 days 0.91 (0.73–1.12) P 0.36 <u>Fish</u> <1/day 1 ≥1/day 1.08 (0.87–1.33) p 0.50 <u>Egg</u> <1/day 1 ≥1/day 1.09 (0.88–1.35) P 0.43 **Associations of death and food intake in in the meat, fish and egg intake groups** Odds ratio (CI 95%) <u>Meat</u> <1/2 days 1 ≥1/2 days 1.00 (0.80–1.25) P 0.99 <u>Fish</u> <1/day 1 ≥1/day 1.06 (0.84–1.32) P 0.65 <u>Egg</u> <1/day 1 ≥1/day 1.13 (0.90–1.42) P 0.29 **Associations of impaired ADL and food intake in the meat, fish and egg intake groups** Odds ratio (CI 95%)

Meat
<1/2 days 1
≥1/2 days 0.61 (0.38–0.99)
P 0.04

Fish
<1/day 1
≥1/day 1.25 (0.76–1.95)
P 0.42

Egg
<1/day 1
≥1/days 0.90 (0.54–1.49)
P 0.68

Significant trends: Higher intake of meat was associated with a statistically significant decrease in impaired ADL occurrence. Fish and egg intake were not associated with any difference in impaired ADL occurrence. None of the 3 foods were associated with any changes in mortality

Limitations:

1. Did not assess the baseline ADL condition.
2. No information on SES other than professional work and urban residence.
3. Diet may have changed during 19 years

Source of funding: Grant-in-Aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-Cardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare and a Health and Labor Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-chouju-046, H14-chouju-003, H17-chouju-012 and H19-chouju-014).

Authors: Nakayama T, Yokoyama T, Yoshiike N, Zaman MM, Date C, Tanaka H, Detels R

Year: 2000

Citation: Neuroepidemiology 19(4): 217-26

Country of study: Japan

Aim of study: Determined the population attributable fraction of stroke due to hypertension, atrial fibrillation and smoking - to quantify the proportion of stroke that might be prevented

Study design:

Quality score: (++, + or -): +

Source population

Number of people: 2,302

Demographics: Not reported

Study (eligible and selected) population

Number of people: 998

Characteristics: Not reported

Location: Shibata, Japan

Recruitment strategy: Not reported

Length of follow-up: 20 years

Response rate and loss to follow-up: Response rate 69%

Eligible population: All residents aged 40 years and over

Excluded populations: Those with a previous history of stroke. Non-respondents in the initial survey included 184 men and 109 women, of whom 28 men and 29 women were hospitalized or were treated at clinics and 14 men and 14 women were being cared for at home

Exposures at midlife

Relevant exposures: Smoking

Time: 1977

Measurement of exposure: Not reported

Outcomes at 55 years or over

Outcomes: Stroke

Outcome measurement: Laboratory and diagnostic imaging examined by clinicians

Time: Follow-up examination conducted annually

Analysis

Analysis strategy: Cox regression model. PAF was calculated by pd x ((RR – 1)/RR) where pd = proportion of cases exposed to the risk factor.

Confounders: BP status, Af smoking and physical activity, diabetes mellitus, obesity, drinking and age at baseline

Results, limitations, source of funding

Effect estimates:

Adjusted RRs and PAFs of stroke incidence due to hypertension, smoking and atrial fibrillation

RR 95% CI

<u>Men</u>
hypertension
controlled 0.96 (0.40–2.29)
untreated 3.94 (1.79–8.68)
uncontrolled 4.92 (2.19–11.05)
smoking 1.77 (0.96–3.27)
Af 1.94 (0.24–15.90)

<u>Women</u>
hypertension
controlled 1.35 (0.60–3.04)
untreated 3.31 (1.24–8.83)
uncontrolled 3.39 (0.99–11.64)
smoking 0.00 (0.00–0.00)
Af 92.23 (25.34–335.62)

<u>All</u>
hypertension
controlled 1.07 (0.59–1.92)
untreated 3.61 (2.01–6.50)
uncontrolled 3.69 (1.89–7.19)
smoking 1.84 (1.00–3.40)
Af 11.24 (3.72–33.97)

PAF, % (90% CI

<u>Men</u>

hypertension
controlled – –
untreated 16.6 (5.7–26.2)
uncontrolled 13.3 (4.0–21.6)
smoking 26.6 (0.7–45.7)
Af 0.9 (–2.3–4.0)

Women
hypertension
controlled 4.3 (–6.9–14.4)
untreated 10.2 (0.6–18.8)
uncontrolled 4.4 (–1.7–10.1)
smoking –
Af 6.2 (0.2–11.8)

All
hypertension
controlled 0.9 (–6.5–7.8)
untreated 13.5 (6.3–20.1)
uncontrolled 8.6 (2.9–13.9)
smoking 14.9 (2.3–26.0)
Af 3.6 (0.3–6.7)

Significant trends: Control of smoking in Japan is the most substantial single factor for reducing the incidence of stroke in middle-aged men. Lack of treatment and control of hypertension is responsible for approximately one third of strokes in the middle-aged population of Shibata.

Limitations:
Author:

1. Misclassification and change of exposure.
2. Smoking was self-reported.
3. Limited sample size

Reviewer**:** No or little reporting of patient characteristics or study methodology

Source of funding: Ministry of Health and Welfare, Japan: Nervous and Mental Disorders (grant 3A-3) from the National Center of Neurology and Psychiatry; Cardiovascular Diseases (grant 3C-2) from the National Cardiovascular Center, and a grant from the Japan Foundation for Aging and Health

Authors: Noborisaka Y, Ishizaki M, Yamada Y, Honda R, Yokoyama H, Miyao M, Tabata M

Year: 2013

Citation: Environmental Health and Preventive Medicine 18(1): 24-32

Country of study: Japan

Aim of study: Examine association between smoking and the development of chronic kidney disease

Study design: Retrospective 6-year observational study

Quality score: (++, + or -): +

Source population

Number of people: 20,782

Demographics: Not reported

Study (eligible and selected) population

Number of people: 6,998

Characteristics:

Men (n = 4,121)

Age (years)
<29 587 (14.2)
30–59 3,473 (84.3)
>60 61 (1.5)

BMI (kg/m2)
<18.4 161 (3.9)
18.5–24.9 2,920 (70.9)
25.0–29.9 928 (22.5)
>30.0 112 (2.7)

Cigarettes
Never smoked 1,028 (24.9)
Ex-smoker 904 (21.9)
Smoke up to >1 pack/day 1,540 (37.4)
Smoke >1 pack/day 649 (15.7)

Alcohol
Usually not drinking 1,246 (30.2)
Up to 69 mL/week of ethanol 1,474 (35.8)
70–209 mL/week 1,256 (30.5)
>70–209 mL/week 145 (3.5)

Occupation
Clerks 1,000 (24.3 %)
Managers/professionals 1,144 (27.8 %)
Operators/drivers 1,223 (29.7 %)
Service/sales 636 (15.4 %)
Others 118 (2.9 %)

Women (n = 2,877)

Age (years)
<29 344 (12.0)
30–59 2,484 (86.3)
>60 49 (1.7)

BMI (kg/m2)
<18.4 356 (12.4)
18.5–24.9 2,122 (73.8)
25.0–29.9 348 (12.1)
>30.0 51 (1.8)

Cigarettes
Never smoked 2,539 (88.3)
Ex-smoker 57 (2.0)
Smoke up to >1 pack/day 273 (9.5)
Smoke >1 pack/day 8 (0.3)

Alcohol
Usually not drinking 2,088 (72.6)
Up to 69 mL/week of ethanol 673 (23.4)
70–209 mL/week 108 (3.8)
>70–209 mL/week 8 (0.3)

Occupation
Clerks 1,129 (39.2 %)
Managers/professionals 600 (20.9 %)
Operators/drivers 342 (11.9 %)
Service/sales 656 (22.8 %)
Others 150 (5.2 %)

Location: Ishikawa, Japan

Recruitment strategy: Recruited from workplaces

Length of follow-up: 6-years

Exposures at midlife

Relevant exposures: Cigarette and alcohol consumption

Time: Either 2009 or 2003

Measurement of exposure: Data on cigarette and alcohol consumption were obtained by interview

Smoking habits were classified into four categories, namely, lifelong non-smokers, ex-smokers, current smokers consuming up to one pack per day, and smokers consuming more than one pack per day

Alcohol consumption was categorized into four levels, ‘‘non-drinkers’’, ‘‘mild drinkers’’, ‘‘moderate drinkers’’ and ‘‘heavy drinkers’’

Response rate and loss to follow-up: 87.9%

Eligible population: People working in 447 various kinds of workplaces

Excluded populations: Those whose data for body weight (37 men, 50 women), urinalysis (2 men, 114 women), or PG (7 men) were not available were excluded; 13 men and five women who declared a past history of primary kidney disease; 252 men and 50 women with high PG consistent DM; 28 men and 12 women who showed severe hypertension in 2003; 4,298 men and 3,096 women showing CKD signs in 2003; five men and 88 women who did not undergo urinalysis in 2009

Outcomes at 55 years or over

Outcomes: Chronic kidney disease

Outcome measurement: Categorisation in subjects based on single measurements of proteinuria and eGFR

Time: 2009

Analysis

Analysis strategy: Multiple logistic regression

Confounders: Sex, age, BMI, BP levels, alcohol consumption, the presence of IGR and dyslipidemia, and occupation

Results, limitations, source of funding

Number: 60 men (1.5 %) and 21 women (0.7 %) developed proteinuria

Effect estimates:

Proteinuria
Odds ratio (95 % CI) p
Sex (women/men) 1.06 (0.57–1.98) 0.859
Age (year) 1.02 (0.99–1.05) 0.134
BMI levels (1–4) 1.82 (1.27–2.59) 0.001
Blood pressure levels (1–5) 1.33 (1.10–1.62) 0.004
IGR 2.35 (1.19–4.65) 0.014
hChol 1.46 (0.90–2.36) 0.130
lHDLc 1.33 (0.64–2.79) 0.449
hTG 1.20 (0.68–2.13) 0.533
hGFR 1.35 (0.52–3.45) 0.538

Smoking status (vs. non-smokers) 0.002
Ex-smokers 1.29 (0.48–3.42) 0.614
Continuous smokers 2.52 (1.50–4.25) 0.001
Alcohol consumption levels (1–4) 0.87 (0.66–1.16) 0.349
Occupations (1–5) 1.01 (0.84–1.21) 0.941

Low eGFR
Odds ratio (95 % CI) p
Sex (women/men) 1.02 (0.84–1.24) 0.866
Age (year) 1.08 (1.07–1.09) <0.001
BMI levels (1–4) 1.37 (1.19–1.57) <0.001
Blood pressure levels (1–5) 0.97 (0.90–1.04) 0.347
IGR 0.84 (0.59–1.18) 0.312
hChol 1.06 (0.90–1.27) 0.480
lHDLc 0.92 (0.65–1.29) 0.625
hTG 1.44 (1.14–1.80) 0.002
hGFR 0.05 (0.01–0.22) <0.001
Smoking status (vs. non-smokers) 0.006
Ex-smokers 1.05 (0.78–1.41) 0.735
Continuous smokers 0.74 (0.60–0.90) 0.003
Alcohol consumption levels (1–4) 0.87 (0.78–0.97) 0.009
Occupations (1–5) 0.98 (0.92–1.04) 0.433

Significant trends: Continuing smokers showed a twofold or more higher risk of developing proteinuria. Discontinuation of smoking substantially reduced the risk

Limitations: The clinical definition of CKD requires CKD signs to be detectable for >3 months.

Source of funding: KAKENHI, a Grant-in-Aid for Scientific Research (C), 2010, from the Japan Society for the Promotion of Science

Authors: Nokes NR, Tucker LA

Year: 2012

Citation: American Journal of Health Promotion (2): 121-9

Country of study: US

Aim of study: To determine the influence of physical activity volume and intensity on bone mineral density (BMD) of the hip

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

268 women ages 35-45 years recruited at baseline using newspaper advertisements and flyers circulated in workplaces and churches in at least 20 cities in the Mountain West

Study (eligible and selected) population

244 participants presented to follow-up assessment 6 years later

Follow-up: 6 years

Sociodemographics: Sample 90% white

Exclusion:

i) Smokers
ii) Women who were ill according to physical activity readiness questionnaire

Attrition: 9% attrition rate.

Women who did not present to follow-up assessment were not significantly different from those who completed baseline and follow-up exams in terms of age, baseline hip BMD, baseline weight or objectively measured PA

Exposures at midlife

Physical activity (PA) volume (sum of all activity counts or total volume of movement) and physical activity intensity (variations of activity within a specified time period) measured over 7 days after baseline assessment using valid and reliable accelerometers

PA volume divided into 'low', 'moderate', and 'high'

Accelerometer activity counts within a specific time period (of 10 min.) reflected physical activity intensity

As per the 2007 American Heart Association and American College of Sports medicine guidelines, participants were required to participate in physical activity, and were categorized into the following PA intensity ranges: 1) 'vigorous': for those with at least 50,000 PA counts during at least 15 bouts (150 min.); 2) 'moderate': at least 30,000 counts during a minimum of 15 bouts; 3) 'low': at least 30,000 counts in fewer than 15 bouts

Outcomes at 55 years or over

At baseline and at 6 year follow-up, participants had their hip scanned on the valid and reliable bone densitometer to determine bone mineral density (BMD) (predicts risk of hip fracture)

BMD change was calculated by subtracting follow-up BMD score from baseline score or value of the total hip with scores divided into quartiles and participants categorized into the following groups: ' BMD loss' (<25th percentile); 'minimal BMD change' (25-75th percentile); 'BMD gain' (>75th percentile)

Analysis

Analysis strategy: Power analysis determined that 155 participants needed for effect size of 0.25 with power of 0.80. Poisson regression was used to determine influence of PA on BMD

Confounders: Age, baseline hip BMD, baseline body weight, weight change, time in study, menopause status, maternal history of osteoporosis, calcium intake, vitamin D intake

Results, limitations, source of funding

- 59% of participants lost BMD at the hip during follow-up
- Over 6 years, women with moderate to high PA volume levels were more likely to have hip BMD gains compared to women in the low PA volume group (RR=2.01, [1.05, 3.81])
- Over 6 years, women with moderate PA volume levels were more likely to gain BMD at the hip than women with low PA volume (RR=1.97, [1.02, 3.79])
- Physical activity intensity was not significant in predicting changes in BMD

Limitations:

1. Limited generalizability due to homogeneous sample
2. Not known whether PA status may have changed during follow-up and if this may have influenced outcome

Source of funding: None reported

Authors: Nooyens AC, Bueno-de-Mesquita HB, van Boxtel MP, van Gelder BM, Verhagen H, Verschuren WM

Year: 2011

Citation: British Journal of Nutrition 106(5): 752-61

Country of study: Netherlands

Aim of study: Habitual fruit and vegetable intake was studied in association with cognitive function and cognitive decline

Study design: Cohort

Quality score: (++, + or -): +

Source population

Number of people: 7769

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2613

Characteristics:

<u>Quartile 1</u>
Mean SD
N 522
Range of total fruit and vegetable intake (g) 50 – 199
Age (years) 54.3 6.6
Sex (% women) 31.2
Highly educated† (%) 48.3
Cigarette smoker at baseline (%) 35.3
Number of pack years smoked in life 22.8 15.8
Excessive consumption of alcohol (%) 24.3
Inactive (%) 32.8
Vitality 67 17
Mental health 77 16

<u>Quartile 2</u>
N 523
Range of total fruit and vegetable intake (g) 199 – 265
Age (years) 54.7 6.7
Sex (% women) 46.9
Highly educated† (%) 50.9
Cigarette smoker at baseline (%) 22.9
Number of pack years smoked in life 18.3 15.5
Excessive consumption of alcohol (%) 13.6
Inactive (%) 26.4
Vitality 67 17
Mental health 77 15

<u>Quartile 3</u>
N 523
Range of total fruit and vegetable intake (g) 265 – 334
Age (years) 55.4 7.0
Sex (% women) 54.1
Highly educated† (%) 49.1
Cigarette smoker at baseline (%) 19.9
Number of pack years smoked in life 16.7 16.0
Excessive consumption of alcohol (%) 14.2
Inactive (%)22.6
Vitality 68 18
Mental health 77 14

Quartile 4
N 523
Range of total fruit and vegetable intake (g) 334 – 415
Age (years) 55.8 7.3
Sex (% women) 57.0
Highly educated† (%) 51.1
Cigarette smoker at baseline (%) 16.3
Number of pack years smoked in life 15.8 13.8
Excessive consumption of alcohol (%) 14.9
Inactive (%) 23.7
Vitality 68 17
Mental health 77 14

Quartile 5
N 522
Range of total fruit and vegetable intake (g) 415 – 1131
Age (years) 56.0 6.8
Sex (% women) 64.4
Highly educated† (%) 55.0
Cigarette smoker at baseline (%) 15.5
Number of pack years smoked in life 14.5 13.3
Excessive consumption of alcohol (%) 12.1
Inactive (%) 19.4
Vitality 68 16
Mental health 77 14

P trends (P,0.05)
Age
Sex
Highly educated
Cigarette smoker at baseline
Number of pack years smoked in life
Excessive consumption of alcohol
Inactive

Exposures at midlife

Relevant exposures: Diet, smoking and physical activity

Time: 1995-2002

Measurement of exposure: Self-administered semi-quantitative FFQ was used to assess the habitual consumption of 178 food items during the previous year. Averaged reported intakes at baseline and follow-up

Smoking and physical activity recorded in self-report questionnaire. Smoking status defined as 'non-smoker' or 'current smoker'

Physical activity level was assessed by the EPIC questionnaire on physical activity

Location: Doetinchem

Recruitment strategy: From Doetinchem Cohort Study

Length of follow-up: 5-year

Response rate and loss to follow-up: 80%

Eligible population: 1995–7, a random sample of one-third of participants aged 45 years and older was enrolled in the study on cognitive functioning

Excluded populations: Participants who reported having experienced a stroke (n 77)

Outcomes at 55 years or over

Outcomes: Cognitive decline

Outcome measurement: Neuropsychological test battery

Time: 2003–7

Analysis

Analysis strategy: Multivariate linear regression analyses

Confounders: Age, sex, level of education, total energy intake, intake of other fruits, vegetables, legumes and juices, and the baseline level of cognitive function, physical activity, smoking, systolic blood pressure, use of blood pressure-lowering medication, serum HDL-cholesterol, waist circumference, coffee consumption, vitality and mental health

Results, limitations, source of funding

Number: Not reported

Effect estimates:

Average change in cognitive function domains:

-0.14 (SD 0.77) for memory
-0.13 (SD 0.45) for information processing speed
-0.08 (SD 0.66) for cognitive flexibility
-0.10 (SD 0.42) for global cognitive function

Baseline
β P-trend * P,0.05, ** P,0.01.
Fruits and vegetables
Memory 0.03
Speed - 0.01
Flexibility - 0.01
Global 0.03
Fruits
Memory 0.01
Speed 0.01
Flexibility 0.02
Global 0.03
Vegetables
Memory 0.03
Speed - 0.04 *
Flexibility - 0.04 *
Global 0.00
Legumes
Memory - 0.02
Speed 0.00
Flexibility 0.00
Global 0.00
Juices
Memory 0.00
Speed - 0.01
Flexibility - 0.02
Global - 0.02

Change
Fruits and vegetables
Memory 0.00
Speed 0.03

Flexibility 0.00
Global 0.02
Fruits
Memory 0.00
Speed 0.01
Flexibility - 0.01
Global 0.01
Vegetables
Memory 0.03
Speed 0.07 **
Flexibility 0.03
Global 0.05 **
Legumes
Memory 0.03
Speed - 0.02
Flexibility 0.01
Global 0.03
Juices
Memory 0.01
Speed - 0.03
Flexibility - 0.01
Global 0.00

Significant trends: Total intake of fruits and vegetables was not or inconsistently associated with cognitive function and cognitive decline. Nuts had statistically significant association between fruit consumption and cognitive decline

Limitations:
Author:

1. Baseline characteristics were different
2. Unfavourable effect of allium is not explained

Reviewer: Crude measure of habitual intake

Source of funding: Ministry of Public Health, Welfare and Sport of The Netherlands and the National Institute for Public Health and the Environment. The data up to and including 1997, including the dietary assessment method, were additionally financially supported by the Europe against Cancer programme of the European Commission

Authors: Nooyens AC, van Gelder BM, Verschuren WM

Year: 2008

Citation: American Journal of Public Health 98(12):2244-50

Country of study: Netherlands

Aim of study: Studied the effect of smoking on cognitive decline

Study design: Cohort Study

Quality score: (++, + or -): +

Source population

Number of people: 2434

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1964

Characteristics:

Age, y, mean (SD) 56.0 (7.0)
Men, % 48.5
Married, %
Lifelong cigarette smoking, pack-years, % 85.1
0 36.4
0–20 38.9
> 20 24.8
Level of education, %
Primary school 7.6
Lower vocational 26.4
Intermediate secondary 17.5
Intermediate vocational/higher secondary 24.3
Higher vocational/university 24.2
Cardiovascular risk factors
Total cholesterol, mmol/L, mean (SD) 5.9 (1.0)
Elevated serum cholesterol level, % 30.0
HDL cholesterol, mmol/L, mean (SD) 1.38 (0.39)
Systolic blood pressure, mm Hg, mean (SD) 131.1 (17.8)
Hypertension, % 35.6
Body mass index, kg/m2, mean (SD) 26.3 (3.8)
Self-reported diabetes or cardiovascular disease, % 4.1
Physically active, % 56.2
Alcohol consumption, %
No alcohol use 30.7
0–1 glass/day 27.9
1–2 glasses/day 20.0
2–4 glasses/day 16.4
> 4 glasses/day 5.0
Total energy intake, MJ/day 8.9 (2.3)

Location: Doetinchem

Recruitment strategy: From Doetinchem Cohort Study

Length of follow-up: 5 years

Response rate and loss to follow-up: 71% of the eligible population took part in the cognitive testing at baseline

Eligible population: All participants of the Doetinchem Cohort Study aged 45 years and older

Excluded populations: Participants who reported a cerebrovascular accident (n=60)

Exposures at midlife

Relevant exposures: Smoking, diet, alcohol consumption, and physical activity

Time: 1993–1997, 1998–2002, and 2003–2007

Measurement of exposure: Smoking status categorised as persistent non-smoker; ex-smoker; persistent smoker, or recent quitter, resume smoking

Alcohol consumption classified: (1) no alcohol use, (2) 0 to 1 glass per day, (3) 1 to 2 glasses per day, (4) 2 to 4 glasses per day, and (5) more than 4 glasses per day

Physical activity was dichotomised as less versus more than half an hour per day of at least moderate-intensity physical activities

Food-frequency questionnaire was used to assess the habitual consumption of 178 food items during the previous year

Outcomes at 55 years or over
Outcomes: Cognitive decline **Outcome measurement**: 1. Neuropsychological test battery 2. 15-Word Verbal Learning Test 3. Stroop Color–Word Test 4. Animal Naming Verbal Fluency Test **Time:** 1995-January 2000
Analysis
Analysis strategy: Multivariate linear regression analyses **Confounders:** Age, gender, level of education, alcohol consumption, hypertension, serum total and high-density lipoprotein cholesterol, body mass index, diabetes or cardiovascular disease,and physical activity), energy intake, total fat intake, coffee consumption, fish consumption, antioxidant intake, estrogen use, and marital status
Results, limitations, source of funding
Number: Not reported **Effect estimates:** **Effect of the Number of Cigarettes Smoked on Change in Cognitive Functions** b P Memory function (n = 1162) –0.04 .03 Speed of cognitive processes (n = 1161) –0.02 .03 Cognitive flexibility (n = 1165) –0.03 .04 Global cognitive function (n = 1146) –0.02 .06 **Significant trends:** No difference between smokers and never smokers in rates of decline in the speed of cognitive processes during follow-up. decline among smokers was 1.9 times greater for memory function, 2.4 times greater for cognitive flexibility, and 1.7 times greater for global cognitive function than among never smokers **Limitations:** No figure given for numbers of participants with cognitive decline **Source of funding:** Ministry of Health, Welfare and Sport of the Netherlands and the National Institute for Public Health and the Environment.

Authors: Osler M, Andreasen AH, Hoidrup S **Year:** 2003 **Citation:** Journal of Clinical Epidemiology 56(3): 274-9 **Country of study:** Denmark **Aim of study:** To determine the association between fish consumption and risk of all-cause mortality, and fatal and nonfatal coronary heart disease **Study design:** Longitudinal **Quality score: (++, + or -):** +
Source population
5 population studies conducted at Copenhagen County Centre for Preventive Medicine Birth cohorts of Western suburbs of Copenhagen followed since 1964

411 men and 391 women born in 1914 were examined in 1984; 436 men born in 1936 were examined in 1987; 1955 men and 1873 women sampled from 4 birth cohorts (1922, 1932, 1942, 1952) were examined in 1982; 731 men and 739 women (born 1927, 1937, 1947, and 1957) were examined in 1987; and 980 men and 981 women (born in 1922, 1932, 1942, 1952, and 1962) were examined in 1992
Study (eligible and selected) population
4,007 out of 4,513 men and **3,533** out of 3,984 women. Baseline response rate was 78% **Follow-up:** from baseline until Sept. 27, 2000 for death from all causes or until Dec. 31, 1997 for fatal and nonfatal incident CHD **Exclusion:** i) Participants with CHD diagnosed during the 5 years prior to enrolment (n=109) ii) Participants with incomplete data **Attrition:** -
Exposures at midlife
Cardiovascular risk factors assessed through clinical examinations and questionnaires (5 surveys) Dietary variables assessed through questionnaire, whereby participants were asked about frequency of consumption of fish food items, with response options ranging from 'never', 'once a month or less', 'twice a month', 'once a week', 'two to three times a week', 'once a day', 'two to three times a day', and 'four times or more daily' Questionnaire previously compared with dietary history – adequate in identifying levels of fish intake
Outcomes at 55 years or over
Data on all-cause mortality, CHD mortality, incident CHD obtained from National Board of Healths Register of Cause of Death and the National Patient Register
Analysis
Analysis strategy: Cox proportional hazards regression used to assess the influence of cardiovascular risk factors on fatal and nonfatal CHD outcome, or all-cause mortality. Analysis was repeated on a high-risk subgroup of 981 men 50+ years and 622 women 60+ years who were current smokers or current non-smokers, with serum cholesterol over 6-7 mmol/L **Confounders:** Familial predisposition, smoking status, physical activity, alcohol, educational status, healthy diet score, total cholesterol, BMI
Results, limitations, source of funding
• At end of follow-up, death occurred in 826 men and 503 women • Among men, the risk of all-cause mortality was lower for those consuming fish one time a month or less compared to those consuming fish once a week (HR=0.80, [0.65, 0.90]) • Among males and females combined, the risk of all-cause mortality was lower for those consuming fish two times a month compared to those consuming it once a week (HR=0.84, [0.73, 0.96]) • Among males and females combined, as well as the subgroup of high-risk participants, there was a significant linear trend of increasing risk in all-cause mortality with greater intake of fish (trend test p-values=0.02 and 0.03, respectively) • Among males and females combined with serum cholesterol less than 5 mmol/L, CHD risk was

lowest for those consuming fish once per week; men with cholesterol levels over 7mmol/L, the lowest CHD risk was identified for those consuming fish once per week
- Among women with lower educational levels, frequent fish intake was associated with lower risk for CHD

Limitations:

1. Low statistical power
2. Measurement bias due to self-reported dietary intake
3. Residual confounding

Source of funding: Danish Medical Research Council

Authors: Østbye T, Taylor DH, Jung SH

Year: 2002

Citation: Preventive Medicine 34(3): 334-45.

Country of study:

Aim of study: To determine the impact of smoking and other modifiable risk factors on ill health in middle-aged and older people

Study design: Longitudinal

Quality score: (++, + or -): -

Source population

At least 12,600 people born in 1931-41 were recruited for Health and Retirement Study (HRS) and interviewed along with their spouses as part of baseline survey in 1992 (wave 1), with follow-up surveys in 1994 (wave 2), 1996 (wave 3), and 1998 (wave 4)

Respondents ages 70 and older and their spouses comprised the baseline sample (wave 1, 1993) were recruited for Asset and Health Dynamics Among the Oldest Old (AHEAD), with follow-up telephone interviews conducted in 1995 (wave 2) and 1998 (wave 3)

Study (eligible and selected) population

HRS: **7,845** people ages 51-61 years

AHEAD: **5,037** people age 70+ at baseline

Exclusion: HRS participants who:

i) Were outside the age range (n=2,357)
ii) Died (n=796)
iii) Were lost to follow-up (n=1,958)

AHEAD participants who:

i) Were outside the age range (n=725)
ii) Died (n=1,853)
iii) Were lost to follow-up (n=607)

Attrition: -

Exposures at midlife

Smoking, exercise, and alcohol consumption measured at baseline for HRS and AHEAD

HRS smokers categorized as heavy (at least a pack of cigarettes/day) or light (less than one pack/day), with former smokers categorized as quit < 3 years prior to baseline, quit 3-15 years ago, or more than 15 years ago; AHEAD smokers categorized as current, former, and never smokers

HRS physical activity assessed through questions on 1. participation in light physical activity (3+

times/week, 1-2 times/week, 1-3 times/months, less than once a month, never); and 2. Participation in vigorous physical activity (same categories as for light activity)

>Based on these questions, participants were classified into ‘sedentary’ (no exercise), ‘heavy exercise’ (heavy physical activity 3+ times/week), ‘moderate exercise’ (heavy physical activity 1-2 times/week or light physical activity 3+ times/week), ‘light exercise’ (other) groups

Alcohol consumption divided into light to moderate drinking (up to 2 drinks/day), heavy drinking (2+ drinks/day), none; self-reported history of drinking problems ascertained

Outcomes at 55 years or over

Ill health outcomes: disability, impaired mobility, self-reported health, and health care utilisation, were measured at waves 2-4 for HRS and 2-3 for AHEAD

<u>Disability</u>
Disability was defined as having an impairment that limits the amount of paid work that can be accomplished; ADL or impairment in activities necessary for survival (with yes/no answer options for activities assessed), and IADL or impairment in activities necessary to manage in today’s society (with yes/no answer options for activities assessed), were identified

<u>Impaired mobility</u>
Ability to walk or climb stairs (with yes/no answer options)

<u>Self-reported health:</u>
Self-perception of health status measured with answer options of excellent, very good, good, fair or poor

<u>Health care use:</u>
Proxy for ill health
Hospitalisation in the past year or admission to nursing home with yes/no options

Analysis

Analysis strategy: Data for respondents who completed all waves for each study were entered into multivariate logistic regression models; each 'ill health' outcome (e.g. disability, impaired mobility, etc.) was assessed separately. Models with no impairment at baseline were also built

Confounders: Gender, race, marital status, age, education

Results, limitations, source of funding

<u>AHEAD (70+ years)</u>

- Compared to those who never smoked, current smokers had the highest odds for ill health in terms of IADL dependence (OR=1.46, [1.21, 1.77]), difficulty climbing stairs (OR=1.67, [1.37, 2.03]), difficulty walking (OR=2.06, [1.69, 2.49]), poor health (OR=1.55, [1.29, 1.87]), hospitalization (OR=1.28, [1.08, 1.52]), nursing home placement (OR=1.68, [1.08, 2.63]); further, the odds for ill health were greater for current smokers compared to former smokers
- Compared to those with BMI 18.5-30, those with BMI 30 or greater had the highest odds for ill health in terms of ADL dependence (OR=1.76, [1.51, 2.06]), IADL dependence (OR=1.23, [1.06, 1.43]), difficulty climbing stairs (OR=2.08, [1.77, 2.46]), difficulty walking (OR=2.27, [1.94, 2.65]), poor health (OR=1.43, [1.24, 1.65]), hospitalization (OR=1.27, [1.12, 1.46]); further, the odds for ill health were generally greater for people with BMI 30 or greater compared to those with BMI less than 18.5
- Compared to those who never drink, those with a past drinking problem had the highest odds for ill health in terms of difficulty climbing stairs (OR=1.37, [1.07, 1.75]), hospitalization (OR=1.38, [1.13, 1.68])

<u>HRS (51-64 at baseline)</u>

- Compared to those who never smoked, heavy smokers (one pack or more) and former smokers (quit less than 3 years), had the highest odds for ill health in terms of ADL dependence (OR=1.52, [1.27, 1.82]; OR=1.71, [1.29, 2.26], respectively), disability (OR=2.23, [1.84, 2.71]; OR=2.45, [1.81, 3.33], respectively), difficulty climbing stairs (OR=2.10, [1.86, 2.37]; OR=1.72, [1.41, 2.10], respectively), difficulty walking (OR=2.37, [2.05, 2.74]; OR=2.08, [1.65, 2.62], respectively), poor health (OR=2.06, [1.80, 2.36]; OR=1.99, [1.60, 2.48], respectively), hospitalization (OR=1.41, [1.24, 1.59]; OR=1.46, [1.20, 1.78], respectively); further, the odds for ill health were greater for light smokers (less than one pack), former smokers (quit 3-15 years), former smokers (quite more than 15 years) compared to non-smokers

Exercise had a beneficial effect on the odds of ill health

- Compared to those with BMI 18.5-30, those with BMI 30 or greater generally had the highest odds for ill health in terms of ADL dependence (OR=1.66, [1.45, 1.89]), disability (OR=1.48, [1.28, 1.72]), difficulty climbing stairs (OR=2.37, [2.16, 2.60]), difficulty walking (OR=2.10, [1.89, 2.34]), poor health (OR=1.70, [1.53, 1.88]), hospitalization (OR=1.38, [1.26, 1.51]); further, the odds for ill health were generally greater for people with BMI less than 18.5
- Compared to those who never drink, those with a past drinking problem had the highest odds for ill health in terms of ADL (OR=1.49, [1.20, 1.84]), disability OR=1.43, [1.15, 1.79], difficulty climbing stairs (OR=1.33, [1.13, 1.57]), difficulty walking (OR=1.32, [1.10, 1.60]), poor health (OR=1.29, [1.08, 1.53]), and hospitalization (OR=1.20, [1.02, 1.41])

Limitations:

1. Residual confounding (e.g., detailed data on nutritional and occupational information)
2. Construct overlap – for example, exercise may not be completely distinct from dependent ill health outcomes, such as those reflecting physical function (in AHEAD, there was some difficulty in identifying adequate controls when measuring exercise levels)

Source of funding: none reported

Authors: Östenson CG, Hilding A, Grill V, Efendic S

Year: 2012

Citation: Scandinavian Journal of Public Health 40(8): 730-7

Country of study: Sweden

Aim of study: Snus use predicts the risk of Type 2 diabetes incidence

Study design: Prospective population-based study

Quality score: (++, + or -): +

Source population

Number of people: 12,952

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2,383

Characteristics:

<u>Consistent never snus use</u>
N 1,431
Age: mean (95% CI) 47.2 (46.9–47.4)
BmI: mean (95% CI) 25.7 (25.5–25.8)
Physical activity during leisure time:
% sedentary (95% CI) 10.6 (9.1–12.3)
Alcohol consumption:
% highest tertile (95% CI) 28.1 (25.7–30.5)

Socioeconomic position:
% low (95% CI) 27.0 (24.7–29.4)
Current smokers among snus users/current snus users among smokers: n (%)246 (17.2)

Consistent snus use
N 301
Age: mean (95% CI) 44.8 (44.2–45.3)
BmI: mean (95% CI) 26.4 (26.0–26.8)
Physical activity during leisure time:
% sedentary (95% CI) 9.3 (6.5–13.1)
Alcohol consumption:
% highest tertile (95% CI) 47.5 (41.9–53.2)
Socioeconomic position:
% low (95% CI) 41.3 (35.8–46.9)
Current smokers among snus users/current snus users among smokers: n (%) 36 (12.0)

Former snus use
n 213
Age: mean (95% CI) 45.8 (45.2–46.4)
BmI: mean (95% CI) 25.8 (25.4–26.2)
Physical activity during leisure time:
% sedentary (95% CI) 8.0 (5.0–12.4)
Alcohol consumption:
% highest tertile (95% CI) 39.2 (32.9–46.0)
Socioeconomic position:
% low (95% CI) 41.8 (35.3–48.6)
Current smokers among snus users/current snus users among smokers: n (%) 16 (7.6)

Consistent never-smoking
N 835
Age: mean (95% CI) 46.2 (45.9–46.6)
BmI: mean (95% CI) 25.6 (25.4–25.8)
Physical activity during leisure time:
% sedentary (95% CI) 9.1 (7.3–11.2)
Alcohol consumption:
% highest tertile (95% CI) 21.7 (19.0–24.7)
Socioeconomic position:
% low (95% CI) 22.7 (20.0–25.7)
Current smokers among snus users/current snus users among smokers: n (%) 74 (8.9)

Consistent smoking
N 287
Age: mean (95% CI) 46.7 (46.1–47.3)
BmI: mean (95% CI) 25.2 (24.8–25.6)
Physical activity during leisure time:
% sedentary (95% CI) 18.5 (14.5–23.4)
Alcohol consumption:
% highest tertile (95% CI) 42.0 (36.3–47.9)
Socioeconomic position:
% low (95% CI) 41.3 (35.8–47.2)
Current smokers among snus users/ current snus users among smokers: n (%) 48 (16.8)

Former smoking
n 740
Age: mean (95% CI) 46.8 (46.4–47.1)
BmI: mean (95% CI) 26.1 (25.8–26.3)
Physical activity during leisure time:
% sedentary (95% CI) 8.1 (6.4–10.3)
Alcohol consumption:
% highest tertile (95% CI) 40.9 (37.3–44.5)

Socioeconomic position:
% low (95% CI) 36.5 (33.1–40.1)
Current smokers among snus users/current snus users among smokers: n (%) 232 (31.4)

Exposures at midlife

Relevant exposures: Snus use

Time: 1992–94

Measurement of exposure: Subjects asked if they had ever been daily users of snus, and if so, if they were current daily users

Subjects asked about daily cigarette smoking and categorised into never, former or current smokers

Location: Four municipalities within Stockholm County

Recruitment strategy: Not reported

Length of follow-up: 10 years

Response rate and loss to follow-up: 87% were reinvestigated with anthropometric measurements

Eligible population: Middle-aged Swedish men

Excluded populations: 246 control subjects and nine subjects with newly diagnosed T2D

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: Oral glucose tolerance test, homeostasis model assessment

Time: 2002-2004

Analysis

Analysis strategy: Multiple regression analysis

Confounders: Age, BMI, glucose tolerance at baseline, physical activity, alcohol consumption, socioeconomic position, family history of diabetes and smoking

Results, limitations, source of funding

Number: 99

Effect estimates:

Cases: type 2 diabetes; newly diagnosed
OR 95% CI
Consistent never snus use 1.0
Consistent snus use 1.1 0.6–2.0
Former snus use 0.5 0.2–1.2
Consistent never snus use 1.0
1-5 boxes/week 0.6 0.2–1.4
>5 boxes/week 3.3 1.4–8.1
Consistent never smoking 1.0
Consistent smoking 1.5 0.8–3.0
Former smoking 0.9 0.5–1.7
Consistent never smoking 1.0
1–15 cigarettes/day 0.8 0.3–2.1
>15 cigarettes/day 2.4 1.0–5.8

Significant trends: Men smoking at baseline and still smoking at follow-up had an increased risk of diabetes compared with never smokers

Limitations: Small number of cases developing diabetes

Source of funding: Stockholm County Council, the Swedish Research Council, the Swedish Council for Working Life and Social Research, and Novo Nordisk Scandinavia.

Authors: Otani T, Iwasaki M, Yamamoto S, Sobue T, Hanaoka T, Inoue M, Tsugane S; Japan Public Health Center-based Prospective Study Group

Year: 2003

Citation: Cancer, Epidemiology, Biomarkers & Prevention 12(12): 1492-500

Country of study: Japan

Aim of study: Examine the association of alcohol consumption and cigarette smoking with colorectal cancer

Study design: Prospective cohort

Quality score: (++, + or -): +

Source population

Number of people: 90,004

Demographics: Not reported

Study (eligible and selected) population

Number of people: Not reported

Characteristics: J-M cells

Location:

Cohort I: Iwate, Akita, Nagano, Okinawa, and Tokyo

Cohort II: Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka

Recruitment strategy: Not reported

Length of follow-up: 10-year (cohort I); 7-year (cohort II)

Response rate and loss to follow-up: Loss to follow-up 0.04%

Eligible population: Middle-aged and elderly Japanese men and women

Excluded populations: Non-Japanese (29 men and 20 women), those who had already moved away at baseline (94 men and 57 women), and those outside of the 40–59 age parameters in cohort I (2 women). self- reported medical history of cancer and with a diagnosis of colorectal cancer before the survey began (687 men and 1,363 women); incomplete alcohol and/or smoking items (2,225 men and 1,097 women)

Exposures at midlife

Relevant exposures: Smoking, alcohol consumption, dietary habits, and other lifestyle factors

Time: Cohort I – after January 1, 1990

Cohort II – after January 1, 1993–1994

Measurement of exposure:

Cohort I: Average frequency of alcohol consumption reported by: “less than 1 day/month,” “1–3 days/month,” “1–2 days/week,” “3–4 days/week,” “5–6 days/week,” and “everyday.” Subjects consuming alcoholic beverages at least once a week were also asked about types of drinks and average consumption.

Cohort II: Asked about drinking status, i.e., never-, ex-, or current drinkers. Ex- and current drinkers provided information on average frequency, types of drinks, and average consumption per day

Smoking habits included current and former smoking status, age at initiation of smoking, and average number of cigarettes smoked per day

Outcomes at 55 years or over

Outcomes: Colorectal Cancer

Outcome measurement: Cases of colorectal cancer were extracted from the JPHC cancer registry based on site codes. Mortality data from the Ministry of Health, Labor, and Welfare

Time: Until the date of diagnosis of colorectal cancer, the date of a subject's death, the date of moving from a PHC area, or December 31, 1999

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, family history of colorectal cancer, body mass index, physical exercise, smoking status, alcohol consumption, and PHC area

Results, limitations, source of funding

Number: 716

Effect estimates: N-Q cells

Significant trends: Alcohol consumption and smoking were associated with colorectal cancer in men. regular ethanol consumption was not associated with colorectal cancer in women

Limitations: None reported

Source of funding: Grant-in-Aid for Cancer Research and for the 2nd Term Comprehensive 10-Year-Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan.

Authors: Patel KV, Coppin AK, Manini TM, Lauretani F, Bandinelli S, Ferrucci L, Guralnik JM

Year: 2006

Citation: American Journal of Preventive Medicine 31(3): 217-24

Country of study: Italy

Aim of study: Test associations of past physical activity levels in midlife with objective measures of mobility in old age

Study design: Cohort

Quality score: (++, + or -): +

Source population

Number of people: 1155

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1001

Characteristics:

Age, M (SD) 74.8 (7.3)
Education, M (SD) 5.4 (3.3)
Cigarette smoking

Ever (vs never), % 40.2 Total pack-years among smokers, M (SD) 29.9 (22.0) Body mass index (kg/m2), M (SD) 27.5 (4.1) Physical Activity <u>20–40 years of age, %</u> Sedentary/minimal 0.7 Light 13.7 Moderate 55.6 Moderate/intense 16.2 Intense/strenuous 13.8 M (SD) 3.3 (0.9) <u>40–60 years of age, %</u> Sedentary/minimal 1.5 Light 22.9 Moderate 50.7 Moderate/intense 15.0 Intense/strenuous 10.0 M (SD) 3.1 (0.9) <u>In the past year, %</u> Sedentary/minimal 20.9 Light 42.5 Moderate 32.3 Moderate/intense 3.8 Intense/strenuous 0.6 M (SD) 2.2 (0.9) <u>Lifetime index to age 60, %</u> Level I 23.6 Level II 51.1 Level III 25.4 <u>Functional outcomes</u> Short Physical Performance Battery, M (SD) 9.7 (3.3) Unable to walk 400 meters, % 15.0 **Location**: Greve in Chianti and Bagno a Ripoli, Italy **Recruitment strategy:** Probability sample **Length of follow-up:** 5-8 years **Response rate and loss to follow-up:** 91.6% **Eligible population:** Not reported **Excluded populations:** -
 Exposures at midlife
Relevant exposures: Physical activity and smoking **Time:** September 1998 and March 2000 **Measurement of exposure:** Interviewer administered questionnaire; participants asked to indicate their average level of physical activity during three age periods in life: 20 to 40 years, 40 to 60 years, and the past year Mini-Mental State Examination was used to measure cognitive impairment
 Outcomes at 55 years or over
Outcomes: Mobility

Outcome measurement: Short Physical Performance Battery

Subjects asked to walk a distance of four meters at their usual pace. The quickest time out of two trials was analysed.

Subjects were asked to rise from a chair and return to the seated position five times as quickly as possible while keeping their arms folded over their chest

Subjects were asked to walk a standard 400-meter course

Time: 2005 and 2006

Analysis

Analysis strategy: Linear and logistic regression models

Confounders: Age, education, smoking behaviour, BMI, total number of medical conditions, Mini-Mental State Examination, nerve conduction velocity, leg muscle power, range of motion of hip and ankle, ankle-brachial index, and serum haemoglobin

Results, limitations, source of funding

Number: Not reported

Effect estimates:

Lifetime physical activity to age 60

Short Physical Performance Battery

Men b weight (SE)
Level I Reference
Level II 0.03 (0.24)
Level III 0.40 (0.26)
p for trend p = 0.042

Women b weight (SE)
Level I Reference
Level II 0.27 (0.19)
Level III 0.90 (0.27)
p for trend p = 0.002

Unable to walk 400 meters
Men Odds ratio (95% CI)
Level I Reference
Level II 0.76 (0.18–3.29)
Level III 0.22 (0.04–1.19)
p for trend p = 0.047

Women Odds ratio (95% CI)
Level I Reference
Level II 1.16 (0.40–3.30)
Level III 0.52 (0.13–2.08)
p for trend p = 0.434

Significant trends: Older adults who in higher levels of physical activity in midlife were significantly more likely to perform better than individuals who were less physically active

Limitations:

Author: Misclassification of previous physical activity

Reviewer: Participants retrospectively recalled their physical activity levels in midlife

Source of funding: Intramural Research Program of the National Institutes of Health, National Institute on Aging

Authors: Patja K, Jousilahti P, Hu G, Valle T, Qiao Q, Tuomilehto J

Year: 2005

Citation: Journal of Internal Medicine 258(4): 356-62.

Country of study: Finland

Aim of study: Examine effects of smoking, obesity and physical activity on the risk of type 2 diabetes

Study design: Prospective study

Quality score: (++, + or -): +

Source population

Number of people: Not reported

Demographics: Not reported

Study (eligible and selected) population

Number of people: 41,372

Characteristics:

Smoking status (men)

Never

Age (years) 41.7 (10.6); Body mass index 25.9 (3.3); Diastolic blood pressure (mmHg) 88 (12); Systolic blood pressure (mmHg) 142 (18); Education (years) 9.3 (3.9); Coffee consumption (cups) 4.6 (2.9); Alcohol drinker (%) 54.5; Low occupational physical activity (%) 30.0; Low leisure time physical activity (%) 25.8

Former

Age (years) 46.7 (10.3); Body mass index 26.9 (3.6); Diastolic blood pressure (mmHg) 89 (12); Systolic blood pressure (mmHg) 144 (19); Education (years) 9.0 (3.7); Coffee consumption (cups) 5.1 (2.9); Alcohol drinker (%) 63.8; Low occupational physical activity (%) 31.2; Low leisure time physical activity (%) 24.7

<20 cigarettes day

Age (years) 42.5 (11.0); Body mass index 25.6 (3.6); Diastolic blood pressure (mmHg) 87 (12); Systolic blood pressure (mmHg) 143 (19); Education (years) 8.8 (3.8); Coffee consumption (cups) 5.6 (3.0); Alcohol drinker (%) 71.3; Low occupational physical activity (%) 33.7; Low leisure time physical activity (%) 31.3

>20 cigarettes day

Age (years) 41.5 (10.0); Body mass index 25.9 (3.7); Diastolic blood pressure (mmHg) 88 (12); Systolic blood pressure (mmHg) 144 (18); Education (years) 8.3 (3.1); Coffee consumption (cups) 6.8 (3.5); Alcohol drinker (%) 77.6; Low occupational physical activity (%) 30.1; Low leisure time physical activity (%) 40.5

Smoking status (women)

Never

Age (years) 45.3 (10.8); Body mass index26.0 (4.7); Diastolic blood pressure (mmHg) 85 (12); Systolic blood pressure (mmHg) 141 (23); Education (years) 9.2 (3.8); Coffee consumption (cups) 4.6 (2.3); Alcohol drinker (%) 25.9; Low occupational physical activity (%) 37.0; Low leisure time physical activity (%) 39.5

Former

Age (years) 39.9 (10.5); Body mass index 26.1 (4.4); Diastolic blood pressure (mmHg) 84 (12); Systolic blood pressure (mmHg) 138 (19); Education (years) 9.5 (3.6); Coffee consumption (cups)

4.8 (2.5); Alcohol drinker (%) 45.3; Low occupational physical activity (%) 41.0; Low leisure time physical activity (%) 35.4

<20 cigarettes day

Age (years) 39.0 (10.5); Body mass index 25.5 (4.2); Diastolic blood pressure (mmHg) 83 (12); Systolic blood pressure (mmHg) 138 (20); Education (years) 9.0 (3.4); Coffee consumption (cups) 5.4 (2.6); Alcohol drinker (%) 55.8; Low occupational physical activity (%) 41.2; Low leisure time physical activity (%) 44.0

>20 cigarettes day

Age (years) 39.7 (9.7); Body mass index 25.9 (4.7); Diastolic blood pressure (mmHg) 84 (13); Systolic blood pressure (mmHg) 139 (21); Education (years) 8.6 (3.2); Coffee consumption (cups) 6.9 (3.3); Alcohol drinker (%) 65.2; Low occupational physical activity (%) 43.5; Low leisure time physical activity (%) 57.7

Location: Karelia, Kuopio, Turku-Loimaa and the Helsinki, Finland

Recruitment strategy: Randomly selected sample

Length of follow-up: Mean 21 years

Response rate and loss to follow-up: Random sample of 6.6%. Participation rate varied from 74% to 88%.

Eligible population: Middle-aged Finnish men and women aged 25–64 years born between 1913 and 1947

Excluded populations: Diagnosed with coronary heart disease or stroke (n =1444), diabetes (n = 804), subjects who had type 1 diabetes (n = 64) at baseline or during follow-up, and subjects with incomplete data on smoking or any other required factors (n=1222)

Exposures at midlife

Relevant exposures: Smoking, obesity and physical activity

Time: Karelia and Kuopio in 1972, 1977, 1982, 1987 and 1992. Turku-Loimaa 1982 and Helsinki 1992.

Measurement of exposure: Self-reported questionnaire

Classified into three smoking categories: current smokers, ex-smokers and lifelong non-smokers

Occupational and leisure time physical activity were grouped into three categories in some analyses: (i) low (ii) moderate (iii) high

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: Drug Register and the Hospital Discharge Register

Time: End of December 2002 or until death

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, study year, education, body mass index, systolic blood pressure, physical activity and coffee and alcohol drinking

Results, limitations, source of funding

Number: 2770

Effect estimates:

Hazard ratios for the incidence of type 2 diabetes according to smoking habits

Never smoking 1.00

Ex-smoking 1.09 (0.96–1.24)

Current smoker <20 cigarettes day 1.30 (1.15–1.47)

Current smoker >20 cigarettes day 1.65 (1.45–1.89)

Hazard ratios for the incidence of type 2 diabetes according to smoking habits and body mass index

Never-smoking

Body mass index <25 1.00

Body mass index 25–29.9 2.92 (2.48–3.45)

Body mass index >30 8.25 (6.98–9.74)

Ex-smoking

Body mass index <25 1.00 (0.70–1.42)

Body mass index 25–29.9 3.04 (2.46–3.77)

Body mass index >30 8.86 (7.15–10.9)

Current smoking

Body mass index <251.43 (1.15–1.78)

Body mass index 25–29.9 4.19 (3.48–5.05)

Body mass index >30 11.5 (9.46–13.9)

Hazard ratios for the incidence of type 2 diabetes according to smoking habits and physical activity

Never-smoking

High 1.00

Moderate 1.03 (0.92–1.16)

Low 1.26 (1.09–1.46)

Ex-smoking

High 1.11 (0.93–1.33)

Moderate 0.99 (0.82–1.19)

Low 1.71 (1.31–2.21)

Current smoking

High 1.32 (1.13–1.54)

Moderate 1.58 (1.37–1.82)

Low 1.72 (1.42–2.10)

Significant trends: Smoking is a risk factor for type 2 diabetes independently of BMI and physical activity

Limitations:

1. Biological markers of smoking were not measured at baseline; glucose
2. Tolerance tests were not performed during the follow-up; misclassification of exposure and outcome; did not have nutritional data; data on alcohol drinking were fairly crude

Source of funding: Finnish Academy (grants 46558, 53585, 204274, 205657)

Authors: Pelkonen M, Tukiainen H, Tervahauta M, Notkola IL, Kivelä SL, Salorinne Y, Nissinen A

Year: 2000

Citation: Thorax 55(9): 746-50

Country of study: Finland

Aim of study: Study the impact of smoking cessation on mortality over range of baseline pulmonary function

Study design: Cohort

Quality score: (++, + or -): ++

Source population

Number of people: Not reported

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1582

Characteristics: Not reported

Location: Ilomantsi, Pöytyä and Mellilä in Finland

Recruitment strategy: Not reported

Length of follow-up: 30 year

Response rate and loss to follow-up: (97.5% in 1959) and in subsequent re-examinations (90–97.7%)

Eligible population: Finnish participants in the Seven Countries Study

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Smoking

Time: Re-examinations were performed in 1964, 1969, 1974, 1984, and 1989.

Measurement of exposure: Smoking habits were recorded at the baseline and in subsequent re-examinations by a trained nurse according to a standard questionnaire developed for the Seven Countries Study

Outcomes at 55 years or over

Outcomes: Mortality

Outcome measurement: Death certificates were collected and causes of death coded

Time: 1959 and 1989

Analysis

Analysis strategy: Cox's proportional hazards regression model

Confounders: Age, BMI, diastolic blood pressure, total cholesterol and smoking

Results, limitations, source of funding

Number: 1086

Effect estimates:

All-cause mortality during 1959-89 by tertile of FEV0.75 at baseline

Hazard ratio (95% CI) p value

Tertile of FEV0.75
Low 1.56 (1.35 to 1.81) <0.001
Middle 1.08 (0.93 to 1.26) 0.295
High 1

All cause and cause specific mortality during 1964–89 among those who quit between 1959–84 compared with continuous smokers
Hazard ratio (95% CI) p value

All cause 0.71 (0.50 to 1.00) 0.049
Cardiovascular disease 0.60 (0.37 to 0.98) 0.043
Cancer 0.58 (0.30 to 1.12) 0.105
Lung cancer 0.50 (0.14 to 1.77) 0.281
Other cancer 0.62 (0.28 to 1.33) 0.220
Respiratory diseases† 2.51 (0.65 to 9.70) 0.181
Other causes 0.91 (0.38 to 2.18) 0.833

Significant trends: Smokers across the entire range of pulmonary function may increase their expectation of lifespan by giving up smoking

Reported limitations:

1. Author: Data set was too small for confident results on mortality from causes other than cardiovascular disease
2. Reviewer: Does not describe sample

Source of funding: Finnish Academy, the Finnish Lung Health Association, the Finnish Anti-Tuberculosis Association Foundation, and the National Institute on Aging, USA (grant EDC-1 1 RO1 AGO8762-01A1)

Authors: Pitsavos C, Panagiotakos DB, Chrysohoou C, Kokkinos P, Menotti A, Singh S, Dontas A; Seven Countries Study (the Corfu Cohort).

Year: 2004

Citation: Journal of Human Hypertension 18(7): 495-501

Country of study: Greece

Aim of study: Investigate the interaction between physical activity and left ventricular hypertrophy on stroke mortality

Study design: Cohort

Quality score: (++, + or -): ++

Source population

Number of people: 12,763

Demographics: Not reported

Study (eligible and selected) population

Number of people: 529

Characteristics:

Presence of LVH	
Age at baseline (years)	49 ±6
Current smoking (total)	30 (76%)
<10 cigarettes/day	14 (36%)
10–20 cigarettes/day	8 (20%)
>20 cigarettes/day	8 (20%)

Physical activity Sedentary life 12 (30%) Moderate physical activity 12 (30%) Hard physical activity 16 (40%) Body mass index (kg/m2) 23 ±4 Absence of LVH Age at baseline (years) 51 ±6 Current smoking (total) 308 (63%) <10 cigarettes/day 62 (13%) 10–20 cigarettes/day (29%) >20 cigarettes/day 104 (21%) Physical activity Sedentary life 155 (32%) Moderate physical activity 185 (38%) Hard physical activity 149 (30%) Body mass index (kg/m2) 23 ±5 P-value Age at baseline (years) 0.156 Current smoking (total) 0.070 Physical activity 0.423 Body mass index (kg/m2) 0.562 **Location:** Corfu, Greece **Recruitment strategy:** Not reported **Length of follow-up:** 40-year **Response rate and loss to follow-up:** 95.3%
Exposures at midlife
Relevant exposures: Physical activity and smoking **Time:** Since 1961 periodic visits every five years **Measurement of exposure:** Physical activity levels were assessed by self-reports of habitual, occupational and leisure-time activities Daily cigarette smoking identified by a positive response on a standardised questionnaire **Eligible population:** Corfu cohort from the Seven Countries Study **Excluded populations:** -
Outcomes at 55 years or over
Outcomes: Stroke mortality **Outcome measurement:** Causes of death were obtained from: previous clinical records filled out by the study's research group, or by hospital records, or by necroscopy records, or by information from family or hospital doctors, other specialists, family or relatives, friends and any other witnesses, or from the police, in case of violent causes or death occurred suddenly in public places or un-witnessed **Time:** 2001
Analysis
Analysis strategy: Cox proportional hazard model **Confounders:** Age, body mass index, total cholesterol, glucose, smoking and blood pressure levels

Results, limitations, source of funding
Number: 74 deaths **Effect estimates:** **Estimates from a backward stepwise Cox model predicting 40-year stroke mortality as a function of baseline risk factors, by LVH level** HR (95% CI) <u>Presence of LVH</u> Physical activity status Sedentary (reference group) 1.00 — Moderate 0.70 (0.50–0.97) Hard 0.75 (0.52–1.09) Age (per 1 year) 1.12 (0.94–1.33) Systolic blood pressure (per 10 mmHg) 1.01 (0.73–1.62) Total serum cholesterol (per 1 mmol/l) 0.86 (0.69–1.07) <u>Absence of LVH</u> Physical activity status Sedentary (reference group) 1.00 — Moderate 0.64 (0.45–0.91) Hard 0.72 (0.51–1.02) Age (per 1 year) 1.12 (1.07–1.180 Systolic blood pressure (per 10 mmHg) 1.21 (1.10–1.480 Total serum cholesterol (per 1 mmol/l) 0.80 (0.47–1.22) **Significant trends:** Physical activity was associated with a lower risk of stroke. LVH had 5.8-fold the risk of stroke among sedentary and 4.5-fold the risk among physically active men. Moderate physical activity decreased the risk of stroke by 49% in men with LVH as compared to sedentary without LVH. Hard exercise did not confer any significant reduction in stroke risk. **Limitations:** 1. Mortality data were available from this specific cohort - could not provide predictors for stroke incidence. 2. The imbalance of the sample sizes between men with and without LVH. 3. Inability to segregate thrombotic from haemorrhagic strokes. 4. Physical activity level of the active group at baseline is likely to decline with advancing age. The physically inactive group at baseline could either stay physically inactive or increase their physical activity level. **Source of funding:** National Heart, Lung and Blood Institute Grants HE 04697, HE 6090 and HE00278

Authors: Preis SR, Stampfer MJ, Spiegelman D, Willett WC, Rimm EB **Year:** 2010 **Citation:** American Journal of Clinical Nutrition 92(5): 1265-72 **Country of study:** USA **Aim of study:** Examine the association between dietary protein and risk of ischemic heart disease **Study design:** Prospective study **Quality score: (++, + or -):** ++
Source population
Number of people: 51,529 **Demographics:** Not reported

Study (eligible and selected) population
Number of people: 43,960 **Characteristics:** Q1 Age (y) 53 ± 10 Smoking status [n (%)] Never 3993 (45.2) Past 3405 (38.6) 1–14 cigarettes/d 262 (3.0) 15–24 cigarettes/d 334 (3.8) 2:25 cigarettes/d 390 (4.4) Unknown no. of cigarettes/d 105 (1.2) Missing 337 (3.8) Exercise (METs) 20.9 ± 30.1 BMI (kg/m2) 25.1 ± 3.2 Calories (kcal/d) 2137 ± 664 Alcohol (% of energy) 5.9 ± 7.4 Alcohol (g/d) 17.5 ± 22.0 Q3 Age (y) 53 ±6 9 Smoking status [n (%)] Never 4007 (47.5) Past 3336 (39.5) 1–14 cigarettes/d 216 (2.6) 15–24 cigarettes/d 294 (3.5) 2:25 cigarettes/d 214 (2.5) Unknown no. of cigarettes/d 72 (0.9) Missing 301 (3.6) Exercise (METs) 20.8 ± 27.4 BMI (kg/m2) 25.5 ± 3.3 Calories (kcal/d) 2024 ± 597 Alcohol (% of energy) 3.9 ± 4.8 Alcohol (g/d) 10.9 ± 13.5 Q5 Age (y) 55 ± 9 Smoking status [n (%)] Never 4409 (44.9) Past 4126 (42.1) 1–14 cigarettes/d 251 (2.6) 15–24 cigarettes/d 276 (2.8) 2:25 cigarettes/d 209 (2.1) Unknown no. of cigarettes/d 96 (1.0) Missing 446 (4.5) Exercise (METs) 21.1 ± 29.1 BMI (kg/m2) 25.9 ± 3.6 Calories (kcal/d) 1780 ± 574 Alcohol (% of energy) 2.7 ± 3.6 Alcohol (g/d) 6.8 ± 9.1 P for linear trend Age (y) <0.0001 Smoking status [n (%)] Never Referent Past 0.009

1–14 cigarettes/d 0.07
15–24 cigarettes/d <0.0001
2:25 cigarettes/d <0.0001
Unknown no. of cigarettes/d 0.14
Missing 0.03
Exercise (METs) 0.89
BMI (kg/m2) <0.0001
Calories (kcal/d) <0.0001
Alcohol (% of energy) <0.0001
Alcohol (g/d) <0.0001

Location: Not reported

Recruitment strategy: Not reported

Length of follow-up: 18 years

Response rate and loss to follow-up: Not reported

Eligible population: Men aged 40–75 y at baseline in 1986

Excluded populations: Those who reported a history of myocardial infarction, angina, coronary artery bypass graft, other heart conditions, stroke, pulmonary embolism, or cancer on the baseline questionnaire. those who had an implausible caloric intake derived from the baseline or had >70 missing responses to food items

Exposures at midlife

Relevant exposures: Smoking status, diet and physical activity

Time: 1986 and in 1990, 1994, 1998, and 2002

Measurement of exposure: Every four years, participants are sent a food-frequency questionnaire to assess their diet composition

Outcomes at 55 years or over

Outcomes: Nonfatal myocardial infarction and fatal ischemic heart disease

Outcome measurement: Nonfatal MI was assessed biennially with a mailed questionnaire

Deaths ascertained by contact with family members or through the National Death Index. Fatal IHD was confirmed from the medical records or autopsy reports or if IHD was listed as the cause of death on the death certificate and there was evidence of previous IHD in the records

Time: 1986 and 31 January 2004

Analysis

Analysis strategy: Cox proportional hazards regression model

Confounders: Age and quintiles of percentage of energy from saturated fat, monounsaturated fat, polyunsaturated fat, trans fat, and calories, fibre, folate, vitamin C, magnesium, total omega-3 fatty acids, glycemic index, physical activity, family history of myocardial infarction, BMI, cigarette smoking, alcohol use, and multivitamin use, status of hypertension, hypercholesterolemia and diabetes

Results, limitations, source of funding

Number: 2959

Effect estimates:

Relative risks (RRs) and 95% CIs for total ischemic heart disease according to quintile of percentage of energy from protein

Q1
Total protein 1.00 (referent)
Animal protein 1.00 (referent)
Vegetable protein 1.00 (referent)

Q2
Total protein 1.03 (0.91, 1.16)
Animal protein 1.05 (0.93, 1.16)
Vegetable protein 0.96 (0.85, 1.08)

Q3
Total protein 1.07 (0.94, 1.21)
Animal protein 1.02 (0.90, 1.16)
Vegetable protein 0.94 (0.82, 1.08)

Q4
Total protein 1.03 (0.90, 1.16)
Animal protein 1.03 (0.90, 1.17)
Vegetable protein 0.94 (0.80, 1.09)

Q5
Total protein 1.08 (0.95, 1.23)
Animal protein 1.11 (0.97, 1.28)
Vegetable protein 0.93 (0.78, 1.12)

P for trend
Total protein 0.30
Animal protein 0.18
Vegetable protein 0.49

Relative risks (RRs) and 95% CIs for nonfatal myocardial infarction and fatal ischemic heart disease according to quintile

Q1

Total protein:
Non-fatal MI 1.00 (referent)
Fatal IHD 1.00 (referent)

Animal protein:
Nonfatal MI 1.00 (referent)
Fatal IHD 1.00 (referent)

Vegetable protein:
Non-fatal MI 1.00 (referent)
Fatal IHD 1.00 (referent)

Q2

Total protein:
Non-fatal MI 1.01 (0.86, 1.18)
Fatal IHD 1.05 (0.86, 1.28)

Animal protein:
Nonfatal MI 1.01 (0.86, 1.18)
Fatal IHD 1.12 (0.91, 1.37)

Vegetable protein:
Non-fatal MI 1.07 (0.91, 1.25)
Fatal IHD 0.84 (0.69, 1.02)

Q3

Total protein:
Non-fatal MI 1.05 (0.90, 1.23)
Fatal IHD 1.08 (0.88, 1.33)

Animal protein:
Nonfatal MI 0.99 (0.84, 1.16)
Fatal IHD 1.08 (0.87, 1.33)

Vegetable protein:
Non-fatal MI 1.03 (0.86, 1.24)
Fatal IHD 0.84 (0.68, 1.05)

Q4

Total protein:
Non-fatal MI 1.02 (0.87, 1.20)
Fatal IHD 1.02 (0.83, 1.25)

Animal protein:
Nonfatal MI 1.05 (0.89, 1.23)
Fatal IHD 0.98 (0.79, 1.21)

Vegetable protein:
Non-fatal MI 1.09 (0.89, 1.33)
Fatal IHD 0.76 (0.59, 0.96)

Q5

Total protein:
Non-fatal MI 1.10 (0.92, 1.30)
Fatal IHD 1.05 (0.85, 1.30)

Animal protein:
Nonfatal MI 1.12 (0.94, 1.33)
Fatal IHD 1.10 (0.88, 1.37)

Vegetable protein:
Non-fatal MI 1.18 (0.93, 1.48)
Fatal IHD 0.66 (0.49, 0.88)

P for trend

Total protein:
Non-fatal MI 0.30
Fatal IHD 0.79

Animal protein:
Nonfatal MI 0.18
Fatal IHD 0.71

Vegetable protein:
Non-fatal MI 0.18
Fatal IHD 0.005

Significant trends: No association between dietary protein and risk of total IHD in this group of men

Limitations:

1. Self-administered questionnaires.
2. Study population consisted of white male health professionals

Source of funding: National Institutes of Health (HL35464 and CA55075) and by the Kirschstein-NRSA Aging Training Grant (AG000158)

Authors: Qiao Q, Tervahauta M, Nissinen A, Tuomilehto J

Year: 2000

Citation: European Heart Journal 21(19):1621-6

Country of study: Finland

Aim of study: Risk of early and late death in relation to smoking and ex-smoking

Study design: Cohort

Quality score: (++, + or -): +

Source population

Number of people: 1711

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1673

Characteristics: Not reported

Location: Finland

Recruitment strategy: Not reported

Length of follow-up: 35-year

Response rate and loss to follow-up: Not reported

Eligible population: Men born between 1900 and 1919

Excluded populations: Subjects known to have coronary heart disease at baseline

Exposures at midlife

Relevant exposures: Smoking

Time: 1959 to 1989

Measurement of exposure: Smoking habits was collected using a standardised questionnaire developed for the Seven Countries Study

Outcomes at 55 years or over

Outcomes: Mortality

Outcome measurement: Review of death certificates, collection of medical information and clinical records from hospitals, and interviews with physicians and relatives of the deceased or any other witnesses of fatal events. After the 15th year of follow-up, only the reviewing and coding of official death certificates was performed.

Time: End of 1994

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, area of residence, body mass index, systolic blood pressure, serum cholesterol at baseline

Results, limitations, source of funding

Number:

CHD mortality (n = 1463)
Total mortality (n = 1673)

Effect estimates:

Smoking status at baseline

Total mortality

10-year mortality
Non-smoker 1
Ex-smoker 1.74 (1.07–2.83)
Current smoker 2.16 (1.44–3.25)

35-year mortality
Non-smoker 1
Ex-smoker 1.13 (0.93–1.36)
Current smoker 1.62 (1.40–1.88)

CHD mortality

10-year mortality
Non-smoker 1
Ex-smoker 7.37 (1.66–32.70)
Current smoker 6.80 (1.64–28.22)

35-year mortality
Non-smoker 1
Ex-smoker 1.39 (1.00–1.94)
Current smoker 1.63 (1.24–2.13)

Baseline cigarettes consumption (number per day)

Total mortality

10-year mortality
Non-smoker 1
Ex-smoker
1–9 1.94 (1.01–3.74)
10–19 2.05 (1.10–3.80)
>20 1.45 (0.77–2.74)

Current smoker
1–9 1.74 (1.02–2.98)
10–19 2.26 (1.45–3.52)
>20 2.56 (1.62–4.06)

35-year mortality

Non-smoker 1
Ex-smoker
1–9 0.98 (0.72–1.33)
10–19 1.09 (0.82–1.44)
>20 1.29 (1.01–1.65)

Current smoker
1–9 1.15 (0.93–1.42)
10–19 1.76 (1.48–2.09)
>20 1.98 (1.65–2.37)

CHD mortality

10-year mortality
Non-smoker 1
Ex-smoker
1–9 8.18 (1.48–45.09)
10–19 7.32 (1.34–40.08)
>20 7.91 (1.59–39.41)

Current smoker
1–9 7.13 (1.51–33.69)
10–19 8.28 (1.92–35.76)
>20 7.16 (1.60–31.95)

35-year mortality

Non-smoker 1
Ex-smoker
1–9 1.21 (0.73–2.03)
10–19 1.47 (0.93–2.32)
>20 1.60 (1.06–2.41)

Current smoker
1–9 1.13 (0.77–1.66)
10–19 1.82 (1.33–2.48)
>20 1.96 (1.42–2.72)

Hazard ratios (95% CI) of deaths from all-cause and coronary heart disease in relation to the changes in smoking status between 1959 and 1969

Total mortality
Non-smoker 1
Persistent former smoker 0.97 (0.76–1.22)
Smoked in one of three examinations 1.13 (0.87–1.47)
Smoked in two of three examinations 1.18 (0.93–1.51)
Persistent current smoker 1.84 (1.54–2.19)

CHD mortality
Non-smoker 1
Persistent former smoker 1.12 (0.77–1.65)
Smoked in one of three examinations 1.07 (0.67–1.70)
Smoked in two of three examinations 1.08 (0.71–1.65)
Persistent current smoker 1.84 (1.36–2.48)

Significant trends: Men smoking persistently were most at risk, while those who persisted in quitting had no increased risk of death compared with non-smokers

Limitations

1. Author: None reported
2. Reviewer: Not reporting demographic characteristics of participants

Source of funding: Yrjo Jahnsson's Foundation, Academy of Finland, the Sandoz Foundation for Gerontological Research and the National Institute of Health (AG-08762)

Authors: Qiu D, Mei J, Tanihata T, Kawaminami K, Minowa M

Year: 2003

Citation: Journal of Epidemiology 13(3): 149-56

Country of study: China

Aim of study: Clarify the risk factors of CVD deaths in rural areas

Study design: Cohort study

Quality score: (++, + or -): +

Source population

Number of people: 50,252

Demographics: Not reported

Study (eligible and selected) population

Number of people: 50,069

Characteristics:

No. of subjects 50252

Age group(%)
40-49 years 41.1
50-59 23.0
60-69 20.8
70-79 12.3
80+ 2.8
Mean age (years) ± SD 55.3 ±11.8
Cigarette smoking status(%)
Non-smoker 57.1
Ex-smoker 3.0
Current smoker 39.9
Alcohol drinking status(%)
Non- drinker 57.2
Ex-drinker 2.0
Current drinker 40.8
Mean body mass index (kg/m') ± SD 20.1 ± 2.5

Location: Sixi, Lixi, Luoping, Putian, Luxi, Shinao, Meizhuang, and Ertang Townships in Shanggao, Wuning, Jinxian, and Gaoan Counties in Jiangxi Province, China.

Area (%):
Wuning 39.7
Shanggao 19.7
Gaoan 19.6
Jinxian 21.0

Recruitment strategy: Door-to-door

Length of follow-up: Six years

Response rate and loss to follow-up: 99.6%

Eligible population: Door-to-door

Excluded populations: 183 cases with a previous history of CVD, 632 CVD deaths. Inpatients were excluded from the study.

Exposures at midlife

Relevant exposures: Frequency of food intake, liking for fatty foods and salty foods, cigarette smoking, alcohol drinking

Time: September 01, 1994 and June 30, 1996

Measurement of exposure: Door-to-door survey

Outcomes at 55 years or over

Outcomes: CVD death

Outcome measurement: Village physicians who lived in the same village as cohort subjects filled out follow-up reports and submitted them to the township hospitals every 10 days

Time: Death from causes other than CVD, or December 31, 2000, whichever came first

Analysis

Analysis strategy: Cox proportional hazard model

Confounders: Sex, age group, area, cigarette smoking status, alcohol drinking status, blood pressure, BMI, marital status, fatty foods, salty foods, frequency of Chinese pickles intake, frequency of meat intake, sleeping hours per day

Results, limitations, source of funding
Number: 671 **Effect estimates:** Hazard ratios of cerebrovascular disease mortality HR (95% CI) (Age group) 40-49 years 1.00 50-59 2.14 (1.52- 3.01) 60-69 5.13 (3.79- 6.94) 70-79 11.38 (8.34- 15.54) 80+ 19.85 (13.65- 28.87) p for trend <0.01 (Cigarette smoking status) Non-smoker 1.00 Ex-smoker 1.40 (0.98- 2.00) Current smoker 1.08 (0.87- 1.34) p for trend 0.59 (Alcohol drinking status) Non-drinker 1.00 Ex-drinker 1.55 (1.04- 2.31) Current drinker 1.12 (0.93- 1.34) p for trend 0.23 (Blood pressure) Normal 1.00 High-normal 1.38 (1.09- 1.74) Hypertension 2.06 (1.72- 2.47) p for trend <0.01 (Body mass index) <18.5 1.00 18.5-23.9 1.12 (0.94- 1.33) >24.0 1.03 (0.68- 1.58) p for trend 0.33 (Marital status) Married 1.00 Never married 1.25 (0.59- 2.65) Divorced 0.95 (0.42- 2.13) Widowed 1.16 (0.96-1.41) p for trend – (Fatty foods) Dislike 1.00 Normal 1.24 (0.72- 2.15) Like 1.33 (0.78- 2.29) p for trend 0.23 (Salty foods) Dislike 1.00 Normal 1.40 (1.13- 1.73) Like 1.46 (1.10- 1.95) p for trend <0.01 (Frequency of Chinese pickles intake) Never or seldom 1.00 Once or twice per month 0.91 (0.74- 1.13) More than once per week 0.79 (0.63- 0.98)

p for trend 0.03

(Frequency of meat intake)
Never or seldom 1.00
Once or twice per month 10.75 (0.62- 0.91)
More than once per week
p for trend 0.13

(Sleeping hours per day)
6 hours or less 1.00
7 to 8 hours 0.86 (0.68- 1.09)
9 hours or more 1.01 (0.78- 1.31)
p for trend 0.65

Significant trends: CVD mortality significantly increased in parallel with age, blood pressure and salty foods

Limitations:

Author: None reported

Reviewer:

1. Misclassification and change of exposure.
2. Behaviours are self-reported

Source of funding: Not reported

Authors: Räikkönen K, Matthews KA, Kuller LH

Year: 2001

Citation: Hypertension 38(4): 798-802.

Country of study: USA

Aim of study: Test the hypotheses that the trajectory of psychological risk increases the risk for the development of hypertension and that blood pressure levels fluctuate with psychological changes

Study design: Began as a prospective study

Quality score: (++, + or -): +

Source population

Number of people: Not reported

Demographics: Not reported

Study (eligible and selected) population

Number of people: 541

Characteristics:

Hypertensives
Mean±SD (coefficient of variation)
Age at baseline, y 48.0±1.5
Age at the time of menopause, y 52.6±3.1
BMI, kg/m2 26.8±5.2 (5.6)
Physical activity, kJ/wk 4847±5010 (262)
Alcohol consumption, g/d 9.0±12.6 (88.1)
Current smoking (yes), n (%) 24 (32)
Cigarettes among smokers, n/d 20.5±11.6 (77.6)

Normotensives
Age at baseline, y 47.6±1.6

Age at the time of menopause, y 52.6±2.6
BMI, kg/m2 24.4±4.3 (5.2)
Physical activity, kJ/wk 6217±7276 (229)
Alcohol consumption, g/d 8.4±10.0 (92.2)
Current smoking (yes), n (%) 123 (28.5)
Cigarettes among smokers, n/d 19.3±12.0 (74.9)

Location: USA

Recruitment strategy: Driver's license list

Length of follow-up: 9.2 years; SD, 3.4 years; range, 1 to 14 years

Response rate and loss to follow-up: -

Eligible population: Middle-aged women

Excluded populations: -

Exposures at midlife

Relevant exposures: Physical activity, alcohol use, and cigarette smoking

Time: 1983-1984

Measurement of exposure: Cigarette smoking defined as the number of cigarettes smoked per day

Alcohol intake defined as the amount of current alcohol intake per day converted into grams of absolute alcohol

Outcomes at 55 years or over

Outcomes: Hypertensive

Outcome measurement: Use of antihypertensive medication and/or had elevated systolic BP or diastolic BP on two consecutive exams

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards

Confounders: Age, race, years of education, parental history of hypertension, baseline blood pressure, body mass index, physical activity, alcohol use, and cigarette smoking

Results, limitations, source of funding

Number: 75

Effect estimates:

Biological and Health Behaviour Predictors of Hypertension Incidence
Predictor, b, P, Hazards Ratio (95% CI)

Race (white/African American) 0.16, 0.67, 1.18 (0.57–2.44)
Parental history (no/yes) 0.76, 0.005, 2.15 (1.26–3.66)
Age at baseline (y) 0.12, 0.14, 1.12 (0.96–1.31)
Education (y) -0.04, 0.13, 0.96 (0.78–1.19)
BMI (kg/m2) 0.05, 0.04, 1.05 (1.01–1.10)
Physical activity (kJ/wk) -0.45, 0.12, 0.64 (0.36–1.13)
Alcohol consumption (g/d) 0.84, 0.17, 2.31 (0.71–7.54)
Smoking status (no/yes) 0.40, 0.19, 1.50 (0.83–2.72)

Significant trends: Increasing levels of anger, decreasing levels of social support, and high anxiety increase the likelihood of women's development of hypertension in midlife

Limitations:

1. Bias due to unavailability of follow-up
2. Missing data for BP or for prescription of antihypertensive medication, and psychological changes occurring between the available data points.
3. Participants had a different number of evaluations (range, 2 to 8 visits) across the follow-up

Source of funding: National Institutes of Health grant HL-28266, the Pittsburgh Mind-Body Center (HL-65111 and HL-65112), and the John D. and Catherine T. MacArthur Foundation Research Network on Socioeconomic Status and Health

Authors: Rantakömi SH, Laukkanen JA, Sivenius J, Kauhanen J, Kurl S

Year: 2013

Citation: Acta Neurologic Scandinavica 127(3): 186-91

Country of study: Finland

Aim of study: Examine the association between hangover and the risk of stroke

Study design: Longitudinal population-based study

Quality score: (++, + or -): +

Source population

Number of people: 2682

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2466

Characteristics:

Age, years 52.9 (5.3); BMI, kg/m2 26.8 (3.6); Current smokers, % 31.4; Current smoking, pack-years 8.2 (16.1); Alcohol consumption, g/week 74.3 (126.4); Systolic blood pressure, mmHg 133.9 (16.9); Diastolic blood pressure, mmHg 88.6 (10.4); Serum HDL-cholesterol, mM 1.3 (0.3); Serum LDL cholesterol, mM 4.0 (1.0); Symptomatic CHD or CHD history, % 76.0; CHD in family, % 48.6; C-reactive protein, mg/l 2.4 (4.1); Diabetes, % 5.2; Atrial fibrillation, % 1.3; Cardiac failure, % 6.9

Location: Kuopio, Finland

Recruitment strategy: Participants of the Kuopio Ischemic Heart Disease Risk Factor Study

Length of follow-up: 15.7 years

Response rate and loss to follow-up: Not reported

Eligible population: Men aged 42, 48, 54, 60 years at baseline and living in the town of Kuopio and surrounding rural communities

Excluded populations: Individuals with strokes prior to the baseline investigation were excluded

Exposures at midlife

Relevant exposures: Alcohol consumption

Time: March 1984 and December 1989

Measurement of exposure: Nordic alcohol consumption inventory

Outcomes at 55 years or over

Outcomes: Stroke

Outcome measurement: 1984 and 1992 ascertained through the Finnish part of the WHO MONICA stroke register. Incidence between 1993 and 2004 obtained by computerised linkage to the Finnish national hospital discharge registry and death certificate registers

Time: March 1998 and February 2001

Analysis

Analysis strategy: Cox proportional hazards regression model

Confounders: Age, current smoking, serum high density lipoprotein cholesterol, serum low density lipoprotein cholesterol, BMI, SBP, myocardial ischemia during exercise, symptomatic CHD and CHD in family, CRP, diabetes, and total alcohol consumption, atrial fibrillation and cardiac failure

Results, limitations, source of funding

Number: 206 (167 ischemic strokes)

Effect estimates:

RR (95%CI) P-value

Risk of any stroke according to Hangover

Hangover <1 1.00

Hangover >1 1.86 (0.91–3.81)

P 0.091

Risk of ischemic stroke according to Hangover

Hangover <1 1.00

Hangover >1 2.45 (1.18–5.12)

P 0.017

Significant trends: At least one hangover a year is related to an increased risk of ischemic stroke in men

Limitations:

1. Absence of women and elderly from the cohort
2. Misclassification of exposure

Source of funding: Juho Vainio Foundation and Yrjo Jahnsson Foundation, Helsinki; Finland

Authors: Ravona-Springer R, Schnaider-Beeri M, Goldbourt U

Year: 2013

Citation: Neurology 30;80(18): 1677-83

Country of study: Israel

Aim of study: Analyse the relationship between body weight variability and dementia

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Number of people: 11,876

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1,620

Characteristics:

BMI category, kg/m2

Group I: Age, 47.9; BMI in 1963 18.8; Ever smoked, % 82; Diabetic,% 2.0; SES rank (mean 0–4) 2.07

Group II: Age, 49.0; BMI in 1963 23.1; Ever smoked, % 70; Diabetic,% 4.1; SES rank (mean 0–4) 2.57

Group III: Age, 49.3; BMI in 1963 27.1; Ever smoked, % 66; Diabetic,% 4.3; SES rank (mean 0–4) 2.68

Group IV: Age, 49.6; BMI in 1963 31.5; Ever smoked, % 68; Diabetic,% 8.2; SES rank (mean 0–4) 2.36

Location: Israel

Recruitment strategy: Stratified sampling

Length of follow-up: 34-35 years

Response rate and loss to follow-up: 86.2%

Eligible population: Civil servants and municipal employees aged 40 years and above

Excluded populations: 173 men born outside six predefined geographical areas

Exposures at midlife

Relevant exposures: Leisure time physical activity

Time: 1965

Measurement of exposure: Subjects asked: "What degree of leisure time physical activity to you practice?": 1) almost no physical activity 2) inconsistent physical activity, 3) daily physical activity, 4) daily effortful physical activity

Outcomes at 55 years or over

Outcomes: Dementia

Outcome measurement: Hebrew version of the Modified Telephone Interview for Cognitive Status. Clinical assessment included the Dementia Questionnaire, Mini-Mental State Examination, Global Deterioration Scale, and Hachinski Ischemic Scale. Dementia was diagnosed using DSM-IV criteria.

Israel Mortality Registry

Time: 1999/2000

Analysis

Analysis strategy: Logistic regression

Confounders: Age, diabetes mellitus, body height, and SES

Results, limitations, source of funding

Number: 307 had dementia, 175 had CIND

Effect estimates:

Group of baseline BMI

OR (95%CI) p

I 1.43 (0.75–2.71) NS

III 1.05 (0.79–1.40) NS

IV 1.25 (0.73–2.14) NS

Significant trends: Midlife variations in weight may antecede late-life dementia

Limitations:

1. Lack of information on the incidence of dementia in subjects from original study reported dead before follow-up
2. Brain imaging not performed in dementia assessment

Source of funding: NIA R01 AG034087 and the Graubard 431 Fund (M.S.-B.), the American Federation for Aging Research (AFAR), Young Investigator Award 2011, and NIRG-11-205083 Alzheimer's Association, 2012 (R.R.-S.).

Authors: Risérus U, Arnlöv J, Berglund L

Year: 2007

Citation: Diabetes Care 30(11): 2928-33

Country of study: Sweden

Aim of study: To identify predictors of insulin sensitivity

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

2,322 men age 50 years from Uppsala, Sweden were invited and participated in baseline investigation in 1970-73

1,221 out of 2,322 men (73% of survivors) participated at re-examination in 1991-95

Study (eligible and selected) population

Analysis restricted to **770** men with complete data

Follow-up: 20 yrs (1970-73 to 1991-95)

Exclusion:

i) 124 subjects taking glucose-lowering medication or who had diabetes
ii) Subjects treated with drugs for cardiovascular disease (n=251)
iii) Non-participants (n=460)
iv) Subjects with incomplete data (n=76)

Attrition: 422 men died and 219 moved

Exposures at midlife

Self-reported smoking and physical activity

Smoking categorised as smoking versus non-smoking

Physical activity assessed using validated questionnaire and participants categorized into 'sedentary', 'moderate', 'regular', and 'athletic' groups

Outcomes at 55 years or over

Insulin sensitivity of men at age 70 was calculated as glucose infusion rate using hyperinsulinemic – euglycemic clamp

Analysis

Analysis strategy: Multivariate regression was used to identify independent predictors of insulin sensitivity

Confounders: BMI, triglycerides, HDL cholesterol, glucose, blood pressure, physical activity, saturated fat biomarkers, and socioeconomic status, baseline fasting insulin

Results, limitations, source of funding

- Smoking did not significantly predict insulin sensitivity
- Physical activity significantly predicted insulin sensitivity (beta=0.25, [0.08, 0.42])

Limitations:

1. Lack of clamp measurements at baseline
2. Survival bias with unhealthy men (high insulin resistance) more likely to die follow-up
3. Residual confounding (e.g. abdominal obesity)
4. Cannot generalise to younger age groups, women, ethnicities other than Caucasians

Source of funding: The Swedish Society for Medical Research

Authors: Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH… White LR

Year: 2000

Citation: Journal of the American Medical Association 283(20): 2674-2679

Country of study: USA

Aim of study: To explore the association of coffee and dietary caffeine intake with risk of Parkinson Disease

Study design: Prospective cohort

Quality score: (++, + or -): +

Source population

Number of people: 8006

Demographics: Not reported

Study (eligible and selected) population

Number of people: 8004

Characteristics: Not reported

Location: Oahu, Hawaii

Recruitment strategy: Not reported

Length of follow-up: 30 years

Response rate and loss to follow-up: Not reported

Eligible population: Enrolled in the Honolulu Heart Program

Excluded populations: Two prevalent cases of PD

Exposures at midlife

Relevant exposures: Diet

Time: 1968 to 1971,1971 to 1974, 1991 to 1993, and 1994 to 1996

Measurement of exposure: Interviews, 24-hour dietary recall and physical evaluation

Outcomes at 55 years or over
Outcomes: Parkinson Disease **Outcome measurement:** Pre-91 review of all cohort members' hospitalisation records; death certificates; medical records After 1991, the diagnosis of PD was based on complete re-examinations of the entire cohort **Time:** From 1991 to 1993 and 1994 to 1996
 Analysis
Analysis strategy: Cox proportional hazards regression model **Confounders:** Age and pack-years of cigarette smoking
 Results, limitations, source of funding
Number: Not reported **Effect estimates:** Nondrinker 5.1 (1.8-14.4) 4 to 8 2.7 (1.0-7.8) 12to 16 2.5 (0.9-7.3) 20 to 24 2.0 (0.6-6.4) >28 Reference Test for trend P<.001 Nondrinkers vs drinkers 2.2 (1.4-3.3) **Significant trends:** Higher coffee and caffeine intake is associated with a significantly lower incidence of Parkinson Disease **Limitations:** Author: 1. Population is Japanese-American men with older age at diagnosis 2. Generalisations to younger-onset cases, women, and other ethnic groups cannot be made with certainty Reviewer: No characteristics provided **Source of funding:** United States Department of the Army grant DAMD17-98-1-8621; National Institutes of Health, National Institute on Aging contract N01-AG-4-2149; National Heart, Lung, and Blood Institute contract N01-HC-05102; and VA Medical Research funds

Authors: Rovio S, Kåreholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, Soininen H… Kivipelto M **Year:** 2005 **Citation:** Lancet Neurology 4(11): 705-711 **Country of study:** Finland **Aim of study:** Investigate the association between leisure-time physical activity at midlife and the subsequent development of dementia and Alzheimer’s disease **Study design:** Population-based cohort **Quality score: (++, + or -):** +

Source population
Number of people: 2000 **Demographics:** Not reported
 Study (eligible and selected) population
Number of people: 1449 **Characteristics:** <u>Active:</u> Age at midlife (years) 50.8 (6.1); Men: women 228 (44.3%): 287 (55.7%); Re-examination measurements Alzheimer's disease 10/510 (2.0%); History of stroke 32 (6.2%); Smokers 234 (45.4%); Alcohol drinkers 380 (73.8%); Dementia 15 (2.9%); Education (years) 8.7 (3.6); Age at re-examination (years) 71.5 (4.0) <u>Sedentary:</u> Age at midlife (years) 49.5 (5.8); Men: women 265 (36.0%) : 471 (64.0%); Re-examination measurements (late-life); Alzheimer's disease 31/729 (4.3%); History of stroke 61 (8.3%); Smokers 325 (44.2%); Alcohol drinkers 532 (72.3%); Dementia 38 (5.2%); Education (years) 8.7 (3.4); Age at re-examination (years) 70.9 (3.9) **Location:** North Karelia and Kuopio, Finland **Recruitment strategy:** Randomly selected from the survivors of a population-based cohort **Length of follow-up:** Follow-up time (years): Active 20·7 (5·0) Sedentary 21·3 (4·7) **Response rate and loss to follow-up:** 72.5% **Eligible population:** Individuals aged 65–79 years by the end of 1997. Participants of the Cardiovascular risk factors, Aging and Incidence of Dementia study. **Excluded populations:** Not reported
 Exposures at midlife
Relevant exposures: Leisure-time physical activity **Time:** 1972, 1977, 1982, or 1987 **Measurement of exposure:** Self-administered questionnaire
 Outcomes at 55 years or over
Outcomes: Dementia and AD **Outcome measurement:** APOE genotypes by use of PCR and HhaI Digestion. Diagnostic and Statistical Manual of Mental Disorders. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria **Time:** 1998
 Analysis
Analysis strategy: Multiple logistic regression **Confounders:** Age at re-examination, sex, education, follow-up time, and locomotor disorders, APOE e4 genotype, midlife body-mass index, systolic blood pressure, cholesterol, and history of myocardial infarction, stroke, and diabetes mellitus, smoking status and alcohol drinking
 Results, limitations, source of funding

Number: 117 persons had dementia and 76 had AD

Effect estimates:

<u>Odds ratio (95% CI) for active vs sedentary group</u>

Dementia 0·47 (0·25–0·90)

Alzheimer's disease 0·35 (0·16–0·80)

Significant trends: Leisure-time physical activity at midlife is associated with a decreased risk of dementia and AD later in Life

Limitations:

1. Survival bias
2. Dementia cases may have been lost because of cut-off
3. Reliability of physical activity data

Source of funding: EVO 5772720 from Kuopio University Hospital, grant IIRG-04–1345 from Alzheimer Association, Academy of Finland grants 103334 and 206951, the Gamla Tjänarinnor Foundation, and the SADF

Authors: Rovio S, Kareholt I

Year: 2007

Citation: Journal of Geriatric Psychiatry 22: 874–882.

Country of study: Finland

Aim of study: Clarify the association between work-related physical activity and dementia/AD

Study design: Prospective cohort study

Quality score: (++, + or -): +

Source population

Number of people: 2000

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1449

Characteristics:

<u>Active</u>: Age at midlife (years) 48.6 (47.9–49.4); Age at re-examination (years) 70.4 (70.0–70.8); Education (years) 8.7 (3.4); Men 272 (37.6); Women 452 (62.4); Body mass index (kg/m2) 26.2 (3.5); Physically active during leisure- time 267 (36.9); Persons employed in manual work 233 (32.2); Persons having low income 309 (42.7); Commuting physical activity: Sedentary 482 (66.6), Moderately active 184 (25.4), Active 58 (8.0); Smokers 303 (41.9)

<u>Sedentary:</u> Age at midlife (years) 51.2 (50.2–52.1); Age at re-examination (years) 70.6 (70.0–71.0); Education (years) 9.1 (3.7); Men 180 (41.5), Women 254 (58.5); Body mass index (kg/m2) 26.7 (3.8); Physically active during leisure- time 207 (47.7); Persons employed in manual work 81 (18.7); Persons having low income 179 (41.2); Commuting physical activity: Sedentary 202 (46.5), Moderately active 218 (50.2), Active 14 (3.2); Smokers 208 (47.9)

Location: Kuopio or Joensuu, Sweden

Recruitment strategy: Random recruitment

Length of follow-up:

Active 22.1 (4.2)

Sedentary 19.6 (5.3)

Response rate and loss to follow-up: 73%

Eligible population: Participants of the Cardiovascular risk factors, Aging and Dementia Study. Aged 65–79 years by the end of the year 1997

Excluded populations: 22 persons (one with AD) with missing data about occupational physical activity

Exposures at midlife

Relevant exposures: Occupational and commuting physical activity

Time: 1972, 1977, 1982, or 1987

Measurement of exposure: Self-report questionnaire.

'How physically heavy is your work?'

'How many minutes do you walk, bicycle or have some other physical activity when you are going to and from work?'

Outcomes at 55 years or over

Outcomes: Dementia and Alzheimer's dementia

Outcome measurement: Cognitive status was screened with the Mini-Mental State Examination. Participants scored <24 referred for further neurological, cardiovascular and neuropsychological examinations.

Diagnosed demented according to the DSM-IV or NINCDS-ADRDA

Time: 1998

Analysis

Analysis strategy: Multiple logistic regression model

Confounders: Age, sex, education, follow-up time, locomotor symptoms, main occupation during life, income at midlife, leisure-time physical activity, socio-economic status, other subtype of work-related physical activity, BMI, total serum cholesterol, SBP, the ApoE e4 genotype and vascular disorders

Results, limitations, source of funding

Number:

61 DSM-IV

48 NINCDS-ADRDA

Effect estimates:

Association between occupational physical activity and the risk of dementia and Alzheimer's disease

<u>Sedentary</u>

Dementia 1

Alzheimer's 1

<u>Active</u>

Dementia 1.45 (0.66–3.17)

Alzheimer's 1.90 (0.73–4.95)

Association between commuting physical activity and the risk of dementia and Alzheimer's disease

Sedentary

Dementia 0.58 (0.26–1.28)

AD 0.36 (0.13–0.96)

Moderately active

Dementia 1

AD 1

Active

Dementia 0.46 (0.10–2.17)

AD 0.48 (0.09–2.58)

Significant trends: Neither occupational nor commuting physical activity were sufficient to protect against dementia and AD later in life

Limitations

Author:

1. Survival bias
2. Residual confounding

Reviewer: Self-reported physical activity

Source of funding: EVO 5772720 from Kuopio University Hospital, grant IIRG-04-1345 from Alzheimer Association, Academy of Finland grants 103334 and 206951, the Gamla Tjanarinnor Foundation, the SADF, Juho Vainio Foundation and Finnish Cultural Foundation

Authors: Ruder EH, Thiébaut AC, Thompson FE, Potischman N, Subar AF, Park Y… Cross AJ

Year: 2011

Citation: American Journal of Clinical Nutrition 94(6): 1607-1619

Country of study: USA

Aim of study: To assess the influence of midlife (and adolescent) diet on colorectal cancer risk

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

Prospective cohort study of men and women ages 50-71 years living in California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, Texas, Arizona, Atlanta (GA), Detroit (MI)

Baseline questionnaire completed in 1995-1996 by 617,119 people

Study (eligible and selected) population

Cohort for this study included **292,797** participants (171,171 men and 121,626 women)

92.8% and 58.5% of participants were white and male

Mean age of 62.8 years at administration of risk factor questionnaire

Follow-up: Follow-up from receipt of risk factor questionnaire (1995-1996) until censoring at the end of 2006 or when the participant moved out of the cancer registry areas, had a cancer diagnosis, or died, whichever came first. 5% lost to follow-up as a result of moving out of 10 states

Exclusion: Excluded people for whom either the baseline [n=6959] or the risk factor questionnaire [n=3424] was completed by proxy respondents, those with prevalent cancer at the administration of the baseline [14,565] or risk factor [n=4297] questionnaires, those who had a death only report for any cancer [n=983], those with 0 PY of follow-up [n=19], and those in the extremes of energy intake for diet in the previous 12 months [n=2334]

Attrition: -

Exposures at midlife

Baseline questionnaire completed in 1995-1996

6 months later, risk factor questionnaire assessing dietary intake 10 years previously (when participants were around 40-61 years) was administered - comprised 37-item food-frequency questionnaire (FFQ)

Databases used to capture information on energy, carbohydrate, protein, calcium

9 categories of frequency of consumption ranging from ‘never’ to ‘2 or more times per day’

Diet 10 years before baseline: portion size estimated using the median sex-specific portion size from NHANES III; energy and nutrient intakes (carbohydrate, total fat protein, calcium, vitamins A and C) based on NHANES III

Exposures assessed: carbohydrate, total fat, protein, fibre, calcium, vitamin A, vitamin C, grains, vegetables, fruit, milk, red meat, processed meat, solid fat, sweet baked goods

Outcomes at 55 years or over

Colorectal cancer (primary diagnoses of adenocarcinoma identified through state cancer registries)

Analysis

Analysis strategy: Cox proportional hazards regression used to estimate the influence of midlife diet on colorectal cancer risk

Confounders for assessment of intake of energy and nutrients: Energy at ages 12-13 years, energy in recent adulthood, nutrient of interest in recent adulthood, age at completion of risk-factor questionnaire, sex, BMI, race, education, physical activity, alcohol consumption, smoking, use of nonsteroidal anti-inflammatory drugs, use of HRT, self-report of a first-degree relative with a history of colon cancer

Confounders for assessment of food group intake: Same as above with the addition of use of aspirin and ibuprofen

Results, limitations, source of funding

- 3773/292,797 people had colorectal cancer
- Those in the highest intake category 10 y previously for calcium (HR: 0.83; 95% CI: 0.73, 0.94), vitamin A (HR: 0.81; 95% CI: 0.71, 0.92), vitamin C (HR: 0.83; 95% CI: 0.72, 0.95), fruit (HR: 0.84; 95% CI: 0.73, 0.97), and milk (HR: 0.78; 95% CI: 0.67, 0.90) had a lower risk of colon cancer, but a higher risk of colon cancer was observed for total fat (HR: 1.15 ; 95% CI: 1.01, 1.30), red meat (HR: 1.31; 95% CI: 1.12, 1.53), and processed meat (HR: 1.24; 95% CI: 1.06, 1.45). For rectal cancer, milk was inversely associated (HR: 0.75; 95% CI: 0.58, 0.96) with risk

Limitations:

1. Self-reported data leading to possible misclassification
2. Fibre values from NHANES 1999-2000 possible source of error

Source of funding: None reported

Authors: Rusanen M, Kivipelto M, Quesenberry CP Jr, Zhou J, Whitmer RA

Year: 2011

Citation: Archives of Internal Medicine 28;171(4): 333-9

Country of study: USA **Aim of study:** To assess influence of midlife smoking on dementia, AD, and VaD **Study design:** Longitudinal **Quality score: (++, + or -):** +
Source population
33,108 members ages 50-60 years of Kaiser Permanente Medical Care Program of Northern California participated in health examination in 1978-85
Study (eligible and selected) population
Analysis restricted to **21,123** surviving participants who were members of health plan in 1994 Mean age in 1994 (at onset of outcome follow-up) of participants was 71.6 years **Follow-up:** For cases, person-years calculated since Jan 01, 1994. Censoring at dementia diagnosis, date of death, date of end of Kaiser membership, or end of follow-up in July 31, 2008 **Exclusion:** i) People with missing data (n=1045) ii) Individuals with dementia diagnosis other than outcomes assessed **Attrition:** -
Exposures at midlife
Self-reported smoking assessed using interview Participants categorised as never smokers; former smokers; current smokers, which were further categorized into: less than 0.5 packs/day, 0.5-1 pack/day, 1-2 packs/day, 2+ packs/day
Outcomes at 55 years or over
Dementia, Alzheimer's disease (AD), vascular dementia (VaD) assessed using electronic health records from Jan. 1, 1994 to July 31, 2008
Analysis
Analysis strategy: Cox proportional hazards model used to assess influence of midlife smoking on dementia, AD, and VaD **Confounders:** Age, sex, education, race, marital status, midlife BMI, hyperlipidemia, diabetes, hypertension, heart disease, and stroke during the follow-up, alcohol intake
Results, limitations, source of funding
• Compared to non-smokers, the risk of dementia was higher among those smoking: more than 2 packs per day (HR=2.14, [1.65, 2.78]), 1-2 packs per day (HR=1.44, [1.26, 1.64]), and 0.5-1 packs per day (HR=1.37, [1.23, 1.52]) • There was no association between smoking and AD risk • Those smoking more than 2 packs per day in midlife were almost 3 times (HR=2.72, [1.20, 6.18]) more likely to develop VaD later in life than the non-smoking individuals **Limitations:** 1. Possible outcome misclassification (e.g. of dementia diagnosis) 2. AD or VaD cases may have been missed in those who died prior to 1994 resulting in selective survival effect

3. Influence of smoking cessation on dementia risk was not assessed

Source of funding: The National Graduate School of Clinical Investigation, EVO grants from Kuopio University Hospital, and grants from the Juho Vainio Foundation and Maire Taponen Foundation; Kaiser Permanente Community Benefits Grant and National Institute of Health and Academy of Finland

Authors: Ruusunen A, Virtanen JK, Lehto SM, Tolmunen T, Kauhanen J, Voutilainen S

Year: 2011

Citation: European Journal of Nutrition 50(2): 89-96

Country of study: Finland

Aim of study: Investigate whether serum n - 3 polyunsaturated fatty acids or n – 6 to n - 3 ratio is associated with risk of severe depression

Study design: Prospective follow-up

Quality score: (++, + or -): +

Source population

Number of people: 2682

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2077

Characteristics:

Age (years) 52.9 (5.2); Marital status: living alone (%) 11.8; Socio-economic status (points) 9.1 (4.6); Smoking (%) 31; Body mass index (kg/m2) 26.9 (3.4); HPL depression score 1.3 (1.3); Alcohol consumption (grams/week) 71 (126)

Location: Kuopio, Finland

Recruitment strategy: Not reported

Length of follow-up: 18 years

Response rate and loss to follow-up: Cohort II 85.6%

Eligible population: Men aged 42–60 years at baseline

Excluded populations: Men without information on serum fatty acids (n = 155), men with missing dietary data (n = 41), those with significant depressive symptoms at baseline (n = 321) and a history of mental illness (n = 88)

Exposures at midlife

Relevant exposures: Diet

Time:

Cohort I: 1984 and 1986

Cohort II: 1986 and 1989

Measurement of exposure: Dietary intake of foods, beverages and nutrients was quantitatively assessed by a 4-day food recording. Fatty acids from one gas chromatographic run without pre-separation

Outcomes at 55 years or over

Outcomes: Depression

Outcome measurement: Diagnosed by a physician. Computer linkage to the national hospital discharge register, which covers every hospitalisation in Finland

Time: End of 2007

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, examination year, baseline socioeconomic status, alcohol consumption, smoking, maximal oxygen uptake and body mass index

Results, limitations, source of funding

Number: 46

Effect estimates:

Relative risk and (95% CI) of severe depression according to tertiles of serum fatty acids

n – 3 (EPA + DHA + DPA)

1 1 (ref)

2 0.41 (0.19; 0.91)

3 0.71 (0.38; 1.43)

n - 6

1 1 (ref)

2 0.96 (0.45; 2.04)

3 1.25 (0.59; 2.65)

EPA

1 1

2 0.55 (0.26; 1.12)

3 0.62 (0.31; 1.25)

DHA

1 1 (ref)

2 0.96 (0.47; 1.96)

3 0.99 (0.48; 2.04)

Linoleic acid

2 0.67 (0.29; 1.51)

3 1.43 (0.70; 2.91)

Alpha-linolenic acid

2 1.16 (0.54; 2.51)

3 1.60 (0.75; 3.43)

Arachidonic acid

1 1 (ref)

2 0.77 (0.39; 1.53)

3 0.62 (0.30; 1.29)

n - 6/n - 3 ratio

1 1 (ref)

2 0.77 (0.37; 1.62)

3 0.97 (0.49; 2.00)

P value

n – 3 (EPA + DHA + DPA) 0.33

n - 6 0.55

EPA 0.17

DHA 0.98

Linoleic acid 0.28

Alpha-linolenic acid 0.22

Arachidonic acid 0.20

n - 6/n - 3 ratio 0.98

Significant trends: Neither serum n – 3 PUFA concentration nor n - 6/n - 3 ratio was associated with risk of severe depression

Limitations:

1. Number of depressed subjects was relatively small
2. Study was limited to subjects with severe depression requiring hospitalisation
3. Lack of power
4. Use of a single measurement of these fatty acids may underestimate the association

Source of funding: Finnish Graduate School of Psychiatry, Juho Vainio Foundation and Yrjo Jahnsson Foundation

Authors: Ruusunen A, Lehto SM, Tolmunen T, Mursu J, Kaplan GA, Voutilainen S

Year: 2010

Citation: Public Health Nutrition 13(8): 1215-20

Country of study: Finland

Aim of study: Assess the association between coffee, tea and caffeine and the risk of depression

Study design: Population-based cohort study

Quality score: (++, + or -): +

Source population

Number of people: 2682

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2232

Characteristics:

Mean or % (SD)

Age (years) 53.0 (5.2); Marital status: living alone (%) 12; Smoking (%) 31; BMI (kg/m2) 26.8 (3.5); Socio-economic status (points) 9.18 (4.6); HPL depression score (points) 1.3 (1.3); Coffee consumption (ml/d) 565 (293); Tea consumption (ml/d) 105 (183); Alcohol intake (g/week) 71.8 (133.6)

Location: Kuopio, Finland

Recruitment strategy: Not reported

Length of follow-up: 11 years

Response rate and loss to follow-up: Not reported

Eligible population: Men not found to be depressive at the baseline examinations and had no previously diagnosed psychiatric disorder

Excluded populations: -

Exposures at midlife

Relevant exposures: Diet

Time: 1984 and 1989

Measurement of exposure: Dietary intake of foods, beverages and nutrients was quantitatively assessed by a four-day food recording, including cups of coffee and tea

Outcomes at 55 years or over

Outcomes: Depression

Outcome measurement: Diagnosed by a physician. Computer linkage to the national hospital discharge register, which covers every hospitalisation in Finland

Time: 2006

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, examination years, socio-economic status, smoking, alcohol consumption, maximal oxygen uptake, BMI and daily intakes of folate, PUFA, marital status, medical comorbidity, leisuretime activity, energy intake, the energy-adjusted daily intakes of eicosapentaenoic and docosahexaenoic acids, use of dairy products and HPL Depression Scale scores

Results, limitations, source of funding

Number: 49

Effect estimates:

<u>Coffee intake</u>

None 1 (ref)

Light 0.29 (0.08, 0.98)

Moderate 0.48 (0.17, 1.36)

Heavy 0.25 (0.07, 0.91)

P value 0.035

<u>Non-tea drinker</u> 1 (ref)

<u>Tea drinker</u> 1.40 (0.78, 2.51)

<u>P value</u> 0.252

Significant trends: Coffee consumption may decrease the risk of depression, whereas no association was found for tea and caffeine intake

Limitations:

<u>Author</u>

1. The number of cases was relatively low
2. Limited to participants with severe depression requiring hospitalisation
3. Measuring changes in coffee drinking habits

Reviewer

1. Survival bias
2. Residual confounding
3. Self-reported physical activity

Source of funding: Finnish Graduate School of Psychiatry, the Juho Vainio Foundation and the Yrjo Jahnsson Foundation

Authors: Sabia S, Guéguen A, Berr C, Berkman L, Ankri J, Goldberg M, Zins M, Singh-Manoux A

Year: 2011

Citation: Addiction 106(1): 93-101

Country of study: France

Aim of study: To assess association between alcohol intake and cognitive function by occupational position

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Cohort of 20,625 employees ages 40-50 years for men and 35-50 years for women of France's national electricity and gas company established in 1989

In 2002-04, 10,537 participants (9,399 men) over the age of 55 years were invited and were eligible for cognitive testing

Study (eligible and selected) population

Analysis restricted to **4,073** out of 4,525 men (denominator represents 48.2% of target population) who underwent cognitive testing and had complete data

Follow-up: Approximately 10 years

Exclusion: Participants with incomplete data (n=452)

Attrition: -

Exposures at midlife

Self-reported alcohol intake assessed annually using validated questionnaire

Frequency and daily consumption of alcoholic beverages in the week preceding questionnaire administration were used to calculate units of alcoholic drinks consumed in a week (with 1 unit=10-12 g alcohol)

Mean alcohol consumption and change in alcohol intake over 10 years prior to cognitive testing assessed

Participants were classified into the following drinking categories: no alcohol consumption, 1–3 drinks/week (occasional drinkers), 4–14 drinks/week (light drinkers), 15–21 drinks/week (moderate drinkers), and more than 21 drinks/week (heavy drinkers)

Alcohol data was extracted from 1992-2001 for those who underwent cognitive screening in 2002, from 1993-2002 for those screened in 2003, and from 1994-2003 for those screened in 2004

Outcomes at 55 years or over

Cognitive performance assessed in 2002-04 using Digit Symbol Substitution Test (DSST), which measures psychomotor speed, sustained attention and logical reasoning

Analysis
Analysis strategy: ANCOVA used to assess association between alcohol intake and cognitive performance by occupational position **Confounders:** Age, screening centre, marital status, and smoking history
Results, limitations, source of funding
• Among those with low occupational position, participants consuming more than 21 drinks/week had a mean score on the DSST that was 2.1 points lower (95% CI: −3.9, −0.3) than those consuming 4–14 drinks/week • Associations between DSST and alcohol consumption were observed only in the lower educational group • Compared to stable alcohol • Consumption, great increase and decrease in alcohol consumption were both associated with lower DSST score only in the low occupational group (−3.9 points (95% CI: −6.1, −1.7) and −3.5 points (95% CI: −6.2, −0.7) respectively for high increase and decrease compared to stable alcohol consumption); *p* for interaction=0.003 **Limitations:** 1. Unable to distinguish regular alcohol intake from binge drinking 2. Possible bias due to missing data 3. Cannot generalise to women and unemployed people **Source of funding:** European Science Foundation, National Institute on Aging

Authors: Sabia S, Nabi H, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A **Year:** 2009 **Citation:** American Journal of Epidemiology 15;170(4): 428-37 **Country of study:** England **Aim of study:** To assess the influence of unhealthy or high risk behaviours on poor executive function and memory **Study design:** Longitudinal **Quality score: (++, + or -):** +
Source population
10,308 London-based office staff, ages 35-55 years initially examined in 1985-88
Study (eligible and selected) population
Analysis restricted to **5,123** participants Mean age at baseline in 1997-99 was 56 years **Follow-up:** 1997-99 to 02-04 **Exclusion:** - **Attrition:** During the 17-year follow-up, 50% of original cohort lost to follow-up
Exposures at midlife
Self-reported health behaviours at baseline (alcohol, smoking, physical activity, diet):

Self-reported alcohol units in last 7 days, with 1unit=8 g ethanol; intake categorized as no alcohol, 1–14 units, and

15 or more units of alcohol per week ('high risk' behaviour defined as abstinence from alcohol)

Self-reported smoking ('high risk' behaviour defined as current smoker)

Self-reported frequency and duration of physical activity used to compute hours per week of activity intensity level ('low risk' behaviour defined as more than 2.5 hours per week of moderate physical activity or more than 1 hour per week of vigorous physical activity)

Self-reported dietary behaviour including frequency of fruit and vegetable intake ('low risk' behaviour defined as eating fruits and vegetables 2 or more times per day)

Outcomes at 55 years or over

Cognitive function tests used to measure executive function (reasoning, verbal fluency measures) during clinical examination in 2002-04

Analysis

Analysis strategy: Logistic regression to assess the influence of unhealthy or high risk behaviours on poor executive function and memory

Confounders: Age, sex, socio-economic status

Results, limitations, source of funding

- The odds for poor executive function were higher among current smokers compared to non-smokers (OR=1.30, [1.01, 1.67]), non-drinkers compared to those who consumed 1-14 units/week (OR=1.71, [1.39, 2.10]), those with high levels of physical activity compared to low levels (OR=1.19, [1.01, 1.39]), those who consumed fruits and vegetables >=2 times per day compared to those who consumed less than this amount (OR=1.60, [1.36, 1.89])
- The odds for poor memory were higher among non-drinkers compared to those who consumed 1-14 units/week (OR=1.34, [1.08, 1.66]), those who consumed fruits and vegetables >=2 times per day compared to those who consumed less than this amount (OR=1.35, [1.14, 1.59])
- The odds of poor executive function were higher among those with all four unhealthy behaviours (in terms of diet, physical activity, alcohol, smoking) compared to those with no unhealthy behaviours (OR=5.12, [2.46, 10.70])

Limitations:

1. Limited generalizability
2. High loss to follow-up
3. Frequency, and not amount, of fruit and vegetable intake assessed

Source of funding: British Medical Research Council; the British Heart Foundation; the British Health and Safety Executive; the British Department of Health; the National Heart, Lung, and Blood Institute; the National Institute on Aging; the Agency for Health Care Policy and Research; and the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health

Authors: Sabia S, Marmot M, Dufouil C, Singh-Manoux A

Year: 2008

Citation: Archives of Internal Medicine 168(11): 1165–1173

Country of study: England

Aim of study: Used to assess the association between smoking status and cognitive function

Study design: Longitudinal

Quality score: (++, + or -): +
Source population
10,308 London-based civil servants (6895 men and 3413 women) ages 35-55 years recruited in 1985 73% response rate Baseline examination undertaken in 1985-88 (phase 1); subsequent phases of data collection undertaken (e.g., phase 5 in 1997-99; phase 7 in 2002-04
Study (eligible and selected) population
Analysis restricted to **5,388** participants ages 35-55 years **Follow-up:** 1985-88 to 97-99**.** Mean of 17.1 years of follow-up **Exclusion:** Non-responders (n=2204) **Attrition:** Individuals who had died (n=274)
Exposures at midlife
Self-reported smoking status, age at smoking initiation or stopping if ex-smoker, and mean number of cigarettes/cigars, ounces of tobacco smoked per week assessed using questionnaire Smoking categories created: never smoker (those who never smoked), current smoker at phase 5, long-term ex-smoker (those who stopped before phase 1), and recent ex-smoker (stopped smoking between phase 1 and phase 5) Grams of tobacco smoked per day (1 cigarette=1g and 1 cigar-3g) used to calculate smoking pack-years
Outcomes at 55 years or over
Cognitive function at phase 7 assessed (memory, reasoning, vocabulary, semantic and phonemic fluency) using battery of tests: 20-word free recall test, Alice Heim AH4 Group Test of General Intelligence, Mill Hill Vocabulary Test, verbal fluency tests
Analysis
Analysis strategy: Cox proportional hazards regression models used to assess the association between smoking status at phase 1 and cognitive function at phases 5 and 7 **Confounders:** Age, sex, marital status, education, socioeconomic position, alcohol use, frequency of fruit and vegetable intake, physical activity
Results, limitations, source of funding
Odds ratio of being in the lowest quintile of change in cognitive function between phase 5 (1997-99) and phase 7 (2002-04): Compared to never smokers, current smokers (OR=1.40, [1.11, 1.75]) and recent ex-smokers (OR=1.38, [1.07, 1.77]) were more likely to show a decline in reasoning **Odds ratio of being in the lowest Quintile of Cognitive Function at phase 5 as a function of smoking status (1997-1999):** Compared to never smokers, current smokers were more likely to show a decline in memory (OR=1.37, [1.10, 1.73]) Compared to never smokers, recent ex-smokers were less likely to show a decline in vocabulary, phonemic fluency, and semantic fluency (OR=0.73, [0.60, 0.87]; OR=0.73, [0.61, 0.87]; and OR=0.75,

[0.63, 0.89], respectively); similar findings were reported for recent ex-smokers

Limitations:

1. Self-reported smoking habits (social desirability)
2. Limited generalizability due to homogeneity of cohort
3. Useful to include additional study phases to better study intra-individual change

Source of funding: British Medical Research Council; the British Heart Foundation; the British Health and Safety Executive; the British Department of Health; the National Heart, Lung, and Blood Institute; the National Institute on Aging; the Agency for Health Care Policy and Research; and by the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health

Authors: Sairenchi T, Iso H, Nishimura A, Hosoda T, Irie F, Saito Y, Murakami A, Fukutomi H

Year: 2004

Citation: American Journal of Epidemiology 15;160(2): 158-62

Country of study: Japan

Aim of study: To assess influence of smoking on the development of type 2 diabetes mellitus

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

192,125 Japanese individuals (63,379 men and 128,746 women) ages 40-79 years underwent health check-ups in 1993

Study (eligible and selected) population

Analysis restricted to **39,528** men and **88,613** women

Follow-up: 1994 to 2002. nAnual follow-up examinations until diagnosis of diabetes mellitus or end of 2002

Exclusion:

i) 3,614 men and 3,645 women with fasting plasma glucose greater than 7 mmol/L or a non-fasting plasma flucose level greater than 11.1 mmol/L
ii) 1,333 men and 1,646 women with history of diabetes mellitus at baseline
iii) Non-participants of 1994 survey (18,904 men and 34,842 women)

Attrition: 28% of participants lost to follow-up

Exposures at midlife

Self-reported never smokers, ex-smokers, current smokers of <20 cigarettes/day, or current smokers of >=20 cigarettes/day

Outcomes at 55 years or over

Incident type 2 diabetes diagnosed when fasting plasma glucose level was greater than 7 mmol/L or a non-fasting plasma glucose level of greater than 11.1 mmol/L and/or person had begun to receive diabetes treatment

Analysis

Analysis strategy: Cox proportional hazards regression was used to assess influence of smoking on

the development of type 2 diabetes mellitus **Confounders:** Age, alcohol intake, body mass index, systolic blood pressure, antihypertensive medication use, fasting status, plasma glucose level, serum total cholesterol level, high density lipoprotein cholesterol level, and log-transformed triglyceride level
Results, limitations, source of funding
3,704 incident cases of type 2 diabetes mellitus among men and 4,286 cases among women Men: • Among those 40-59 years of age, current smokers had greater risk of type 2 diabetes compared to never smokers (RR=1.37, [1.18, 1.60]) • Among those 60-79 years, current smokers had higher risk for type 2 diabetes compared to never smokers (RR=1.20, [1.08, 1.34]) Women: • Among those 40-59 years of age, current smokers had greater risk of type 2 diabetes compared to never smokers (RR=1.45, [1.18, 1.79]) • Among those 60-79 years, current smokers had higher risk for type 2 diabetes compared to never smokers (RR=1.34, [1.09, 1.66]) **Limitations:** 1. Incomplete follow-up 2. Residual confounding by physical activity and dietary habits **Source of funding:** None reported

Authors: Samieri C, Sun Q, Townsend MK, Chiuve SE, Okereke OI, Willett WC… Grodstein F **Year:** 2013 **Citation:** Annals of Internal Medicine 159(9): 584-91 **Country of study:** USA **Aim of study:** Examine the association between dietary patterns in midlife and prevalence of healthy aging. **Study design:** Observational study **Quality score: (++, + or -):** +
Source population
Number of people: 121,700 **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 10,670 **Characteristics:** Healthy Agers: Mean age (SD), 58.6 (2.5); Education Associate's degree 74, Bachelor's degree 17, Graduate degree 9; Husband's education, High school degree or less 46, College degree 29, Graduate school 24; Marital status Married 92, Widowed 5, Separated/divorced 3; BMI <22 kg/m2 35, 22–24 kg/m2 38, 25–29 kg/m2 23, >30 kg/m2 3; Smoking Never 54, Former 35, Current 12; Mean physical activity (SD), MET h/wk 19.4 (21.7); Mean energy intake (SD), kcal/d 1692 (472) Usual Agers: Mean age (SD), 59.1 (2.5); Education Associate's degree 78, Bachelor's degree 15, Graduate degree 6; Husband's education High school degree or less 52, College degree 28, Graduate

school 21; Marital status Married 93, Widowed 5, Separated/divorced 3; BMI <22 kg/m2 22, 22–24 kg/m2 33, 25–29 kg/m2 32, >30 kg/m2 13; Smoking Never 47, Former 36, Current 17; Mean physical activity (SD), MET h/wk 14.1 (19.8); Mean energy intake (SD), kcal/d 1743 (477)

Location: USA

Recruitment strategy: No reported

Length of follow-up: Average of 15 years

Response rate and loss to follow-up: Not reported

Eligible population: Women from Nurses' Health Study

Excluded populations: 2585 with a history of the 11 chronic diseases as of 1986, 2621 because of a lack of dietary data in 1984 and 1986. 44 nurses who did not complete the SF-36; 289 women who skipped more than 2 items on the mental health index or more than 5 items on the physical function scale; and 637 women who were missing data for education, 1665 who were missing BMI data, and 904 who were missing physical activity data

Exposures at midlife

Relevant exposures: Diet

Time: 1984 and 1986

Measurement of exposure: Averaged information from the 1984 and 1986 FFQs. Food intake converted into nutrient intake by multiplying the consumption of each food by its nutrient content, using the U.S. Department of Agriculture database

Outcomes at 55 years or over

Outcomes: "Healthy" and "usual" aging

Outcome measurement: Biennial questionnaires

Considered persons free of 11 chronic diseases, with no impairment in cognition, no physical disabilities, and intact mental health as healthy agers

Remaining classified as usual agers

Time: 2000

Analysis

Analysis strategy: Logistic regression models

Confounders: Age; education; husband's education; marital status; parents' occupations when the nurse was aged 16 years; family history of diabetes, cancer, and myocardial infarction; physical activity; smoking; multivitamin and aspirin use; body mass index; history of high blood pressure; and hypercholesterolemia

Results, limitations, source of funding

Number: Healthy Agers (n=1171); Usual Agers (n=9499)

Effect estimates:

Quintile 1 AHEI-2010 score 1 (Reference); A-MeDi score 1 (Reference)

Quintile 2 AHEI-2010 score 0.87 (0.70–1.09); A-MeDi score 1.25 (1.01–1.55)

Quintile 3 AHEI-2010 score 1.20 (0.97–1.48); A-MeDi score 1.24 (1.00–1.53)

Quintile 4 AHEI-2010 score 1.37 (1.12–1.69); A-MeDi score 1.28 (1.03–1.60)

Quintile 5 AHEI-2010 score 1.34 (1.09–1.66); A-MeDi score 1.46 (1.17–1.83)

P Value for Trend

AHEI-2010 score 0.001; A-MeDi score 0.002

Significant trends: Better diet quality at midlife seems to be strongly linked to greater health and wellbeing in persons surviving to older ages

Limitations:

1. Could not exclude participants with impaired cognition, mental health, and physical function in midlife
2. Followed participants until age 70 years rather than through death or onset of a condition that would classify them as no longer healthy
3. Measurement error in the assessment of dietary patterns
4. Residual confounding
5. Included female, mostly white health care professionals

Source of funding: National Cancer Institute, National Institutes of Health

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Authors: Satoh H, Nishino T, Tomita K, Saijo Y, Kishi R, Tsutsui H

Year: 2006

Citation: Internal Medicine 45(5): 235-9

Country of study: Japan

Aim of study: Elucidate the relationship between risk factors and the coronary artery disease

Study design: Follow-up study

Quality score: (++, + or -): +

Source population

Number of people: 2,867

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2,764

Characteristics:

CAD: Age 41.2 ± 2.7; Smokers (%) 89.7; BMI 25.6 ± 3.2

No-CAD: Age 42.6 ± 2.8; Smokers (%) 66.8; BMI 23.5 ±2.8

Location: Hokkaido, Japan

Recruitment strategy: Not reported

Length of follow-up: 10 years

Response rate and loss to follow-up: Not reported

Eligible population: Men working in a company in Hokkaido, Japan

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Diet

Time: 1995

Measurement of exposure: Blood samples

Outcomes at 55 years or over

Outcomes: Coronary artery disease

Outcome measurement: Examination of each subject's clinical chart

Time: 2005

Analysis

Analysis strategy: Cox Proportional hazard model

Confounders: Age, body mass index, smoking habit, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, and triglyceride

Results, limitations, source of funding

Number: 35 cases of CAD during the follow up; 25 myocardial infarctions and 10 angina pectoris

Effect estimates:

Hazard Ratios for Coronary Artery Disease with Confidence Intervals for Risk Factor

HR (95% CI) p-value

Age 0.92 (0.82-1.03) 0.16

Smoking 2.47 (0.86-7.10) 0.09

BMI 1.10 (0.98-1.23)

SBP 1.10 (0.91-1.35) 0.33

Total cholesterol 1.24 (1.12-1.36) <0.01

HDL-cholesterol 0.42 (0.28-0.63) <0.01

Fasting plasma glucose

1.14 (1.05-1.24) <0.01

Triglyceride (Log) 0.98 (0.37-1.94) 0.70

Significant trends: Total cholesterol, high-density lipoprotein cholesterol and fasting plasma glucose were found to be important risk factors for CAD, and the combination of these risk factors was associated with CAD

Limitations:

1. Could not determine the occurrence of CAD events in 78 subjects
2. Only male workers in a single company; power might not be adequate

Source of funding: Not reported

Authors: Seccareccia F, Alberti-Fidanza A, Fidanza F, Farchi G, Freeman KM, Mariotti S, Menotti A

Year: 2003

Citation: Annals of Epidemiology 13(6): 424-30

Country of study: Italy

Aim of study: Examine prospectively the relationship between vegetable consumption and long-term survival

Study design: Observational study

Quality score: (++, + or -): +

Source population

Number of people: 1,712

Demographics: Not reported
Study (eligible and selected) population
Number of people: 1536 **Characteristics:** Age (years) 54.7 Smokers/Non-smokers (ratio) 1.36 No. cigarettes/day (all subjects) 8.7 Physical activity: Light (%) 14.1, Moderate (%) 25.3, Heavy (%) 60.7 **Location:** Crevalcore and Montegiorgio, Italy **Recruitment strategy:** Not reported **Length of follow-up:** 30 years **Response rate and loss to follow-up:** Not reported **Eligible population:** Italian males of the Seven Countries Study, aged 45–65 years **Excluded populations:** 28 subjects due to missing data
Exposures at midlife
Relevant exposures: Diet **Time:** 1960 **Measurement of exposure:** Staff visited participants' homes to observe eating habits and interview subjects using a dietary history interview sheet. Also inc. 7-day food-use diary
Outcomes at 55 years or over
Outcomes: Total and cause-specific mortality **Outcome measurement:** Official death certificates, hospital physicians, relatives of the deceased and other witnesses **Time:** 1965–1995
Analysis
Analysis strategy: Cox proportional hazards model **Confounders:** Age, daily energy intake, smoking, physical activity, systolic blood pressure, total cholesterol, body mass index and fruit consumption
Results, limitations, source of funding
Number: 1096 deaths (308 coronary heart disease, 325 from cancer, 158 from cerebrovascular disease and 305 from all other causes **Effect estimates:** Vegetables (g/day) (HR for every additional 20 g/day) 0.97 (0.94–0.99) **Significant trends:** There is a positive association between vegetable intake and life expectancy **Limitations:** Author: None reported Reviewer:

1. Survival bias
2. Residual confounding
3. Some observational data but largely self-reported diet

Source of funding: Study was carried out within the Italian section of the FINE (Finland, Italy, the Netherlands Elderly) Study, partly supported by "Il Progetto CUORE—Epidemiology and Prevention of Ischaemic Heart Disease" of the Italian Ministry of Health

Authors: Shaper AG, Wannamethee SG, Walker M

Year: 2003

Citation: Journal of Epidemiology 32(5): 802-8

Country of study: UK

Aim of study: Quantify the effects of primary and secondary pipe and cigar smoking on major cardiovascular events, cancer incidence, and all-cause mortality

Study design: Prospective study

Quality score: (++, + or -): ++

Source population

Number of people: 7735

Demographics: Not reported

Study (eligible and selected) population

Number of people: 7121

Characteristics:

Never Mean age (years) 48.6; Smoking (years) 0; Tobacco usage (g/day) 0; % Manual 45.3; % 'Active' 48.0; % Heavy drinkers 5.3; % Obese 8.8; BMI (kg/m2) 25.65

Ex-cigarette smoker Mean age (years) 50.7; Smoking (years) 19.3; Tobacco usage (g/day) 0; % Manual 54.8; % 'Active' 40.0; % Heavy drinkers 9.4; % Obese 9.8; BMI (kg/m2) 26.06

Primary pipe/cigar Mean age (years) 49.9; Smoking (years) 26.7; Tobacco usage (g/day) 11.5; % Manual 34.2; % 'Active' 44.7; % Heavy drinkers 6.0; % Obese 6.0; BMI (kg/m2) 25.27

Secondary pipe/cigar Mean age (years) 50.4 Smoking (years) 31.7; Tobacco usage (g/day) 14.7; % Manual 50.9; % 'Active'41.8; % Heavy drinkers 11.0; % Obese 7.5; BMI (kg/m2) 25.49

Cigarettes 1–19/day Mean age (years) 50.5; Smoking (years) 32.5; Tobacco usage (g/day) 10.4; % Manual 67.0; % 'Active' 38.1; % Heavy drinkers 10.7; % Obese 5.8; BMI (kg/m2) 25.00

Cigarettes 20/day Mean age (years) 50.4; Smoking (years) 33.0; Tobacco usage (g/day) 20.0; % Manual 66.8; % 'Active' 30.0; % Heavy drinkers 13.0; % Obese 5.6; BMI (kg/m2) 24.92

Cigarettes 21+/day Mean age (years) 49.7; Smoking (years) 33.2; Tobacco usage (g/day) 30.9; % Manual 66.9; % 'Active' 25.4; % Heavy drinkers 21.0; % Obese 7.5; BMI (kg/m2) 24.93

Location: 24 British towns

Recruitment strategy: Age-sex registers of one general practice in each town

Length of follow-up: Mean 21.8 years

Response rate and loss to follow-up: 78%

Eligible population: Men aged 40–59 years

Excluded populations: Men with missing data on smoking

Exposures at midlife

Relevant exposures: Pipe and cigar smoking

Time: 1978-1989

Measurement of exposure: Self-report questionnaire

Outcomes at 55 years or over

Outcomes: Major coronary heart disease and stroke events, cancer incidence, and deaths from all causes

Outcome measurement: Men were asked whether a doctor had ever told them that they had CHD, stroke, diabetes, and a number of other disorders.

Information on death was collected through the established 'tagging' procedures provided by the National Health Service registers

Cancer morbidity is based on follow-up until December 1997. Cancer cases were ascertained by death certificates, the cancer registry, and by questionnaires on recall of doctor diagnoses sent to survivors in 1992, 1996, and in 1998.

Time: December 2000

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, social class, body mass index, physical activity, systolic blood pressure, serum total cholesterol, alcohol intake, and anti-hypertensive treatment

Results, limitations, source of funding

Number: 1133 major CHD events and 440 stroke events, 919 new cancers and 1994 deaths

Effect estimates:

<u>Major CHD events</u>

Never 1.00

Ex-cigarette smoker 1.10 (0.91, 1.36)

Primary pipe/cigar 1.59 (1.05, 2.39)

Secondary pipe/cigar 1.72 (1.32, 2.22)

Cigarettes 1–19/day 1.85 (1.49, 2.30)

Cigarettes 20/day 2.12 (1.69, 2.67)

Cigarettes 21+/day 2.30 (1.86, 2.84)

<u>Major stroke events</u>

Never 1.00

Ex-cigarette smoker 1.13 (0.82, 1.56)

Primary pipe/cigar 1.83 (0.98, 3.42)

Secondary pipe/cigar 1.55 (1.02, 2.37)

Cigarettes 1–19/day 1.91 (1.35, 2.68)

Cigarettes 20/day 1.78 (1.22, 2.61)

Cigarettes 21+/day 2.12 (1.50, 2.99)

Significant trends: Pipe and cigar smoking, whether primary or secondary, carries significant risk of smoking-related ill health

Limitations:

1. Number of primary pipe/cigar smokers is relatively small
2. Residual confounding

Source of funding: Department of Health (England)

Authors: Sobue T, Yamamoto S, Hara M, Sasazuki S, Sasaki S, Tsugane S; JPHC Study Group

Year: 2002

Citation: International Journal of Cancer 10;99(2): 245-51

Country of study: Japan

Aim of study: Update the findings of relative risk associated with cigarette smoking for lung cancer by histologic type

Study design: Population-based cohort study

Quality score: (++, + or -): ++

Source population

Number of people: 91,738

Demographics: Not reported

Study (eligible and selected) population

Number of people: 57,591 men (26,998 in Cohort I and 30,593 in Cohort II) and 59,103 women (27,397 in Cohort I and 31,706 in Cohort II)

Characteristics: Not reported

Location:

Cohort I: Ninohe in Iwate Prefecture, Yokote in Akita Prefecture, Saku in Nagano Prefecture, Ishikawa in Okinawa Prefecture and Katsushika in the Tokyo Metropolitan area

Cohort II: Mito in Ibaraki Prefecture, Kashiwazaki in Niigata Prefecture, Chuohigashi in Kochi Prefecture, Kamigoto in Nagasaki Prefecture, Miyako in Okinawa Prefecture and Suita in Osaka Prefecture

Recruitment strategy: Population registries maintained by the local city, town or village office

Length of follow-up: Various

Response rate and loss to follow-up: 34 persons were lost to follow-up within the study period

Eligible population: Inhabitants in the study areas, aged 40–59 years old in Cohort I and 40–69 years in Cohort II at the beginning of the each study

Excluded populations: 123 men and 79 women were found to be ineligible for the study cohort (no Japanese nationality 49, late reports of out-migration before the start of the follow-up 151 and wrong birthday 2). 4,656 persons moved out of the study area

Exposures at midlife

Relevant exposures: Smoking

Time:

1990 for Cohort I

1993 for Cohort II

Measurement of exposure: Self-report questionnaire

Outcomes at 55 years or over

Outcomes: Lung cancer

Outcome measurement: Local major hospitals and the from population-based registries

Time: Up to December 31, 1999

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age and area

Results, limitations, source of funding

Number: 422

Effect estimates:

All incident cases

<u>Men</u>

Non-smoker 1.0

Former smoker 2.2 (1.4–3.4)

Current smoker 4.5 (3.0–6.8)

<u>Women</u>

Non-smoker 1.0

Former smoker 3.7 (1.4–10.2)

Current smoker 4.2 (2.4–7.2)

Squamous cell + small cell carcinoma

<u>Men</u>

Non-smoker 1.0

Former smoker 5.1 (1.8–14.6)

Current smoker 12.7 (4.7–34.7)

<u>Women</u>

Non-smoker 1.0

Former smoker 10.8 (1.2–94.4)

Current smoker 17.5 (4.9–62.1)

Adenocarcinoma

<u>Men</u>

Non-smoker 1.0

Former smoker 1.3 (0.7–2.5)

Current smoker 2.8 (1.6–4.9)

<u>Women</u>

Non-smoker 1.0

Former smoker 4.3 (1.3–13.8)

Current smoker 2.0 (0.8–5.0)

Significant trends: Lung cancer risk in men rose with increasing cigarette smoking, especially the

duration of smoking among current smokers and decreased after the cessation of smoking among former smokers **Limitations:** <u>Author</u> 1. Limited number of small cell carcinomas 2. Baseline data may not represent the lifelong patterns <u>Reviewer</u>: Misclassified exposure **Source of funding:** Ministry of Health, Labour and Welfare of Japan.

Authors: Song Y, Manson JE, Buring JE, Liu S **Year:** 2004 **Citation:** Diabetes Care 27(9): 2108-15 **Country of study:** USA **Aim of study:** Prospectively assess the relation between red meat intake and incidence of type 2 diabetes **Study design:** Randomised, double-blind, placebo-controlled trial **Quality score: (++, + or -):** ++
Source population
Number of people: 39,876 **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 37,309 **Characteristics:** **Total meat** <u>Quintile 1</u> Median intake (servings/day) 0.63; Age (years) 54.6±7.5; Smoking (%) Current 11.4; Never 51.3, Past 37.4; Exercise (%) Rarely/never 36.5, <1/week 17.2; 1–3/week 32.2; >4/week 14.2; Alcohol consumption (%) Rarely never 49.2, 1–3 drinks/month 12.8, 1–6 drinks/week 28.7, >1 drink/day 9.29; Postmenopausal hormone use (%) Never 46.0, Past 10.7, current 43.4; Mean BMI (kg/m2) 24.8±4.3 <u>Quintile 5</u> Median intake (servings/day) 2.27; Age (years) 53.5±6.7; Smoking (%) Current 15.3, Never 51.5, Past 33.2; Exercise (%) Rarely/never 40.7, <1/week 22.5, 1–3/week 29.2, >4/week 7.65; Alcohol consumption (%) Rarely never 45.9, 1–3 drinks/month 12.4, 1–6 drinks/week 31.3, >1 drink/day 10.4; Postmenopausal hormone use (%) Never 49.3, Past 10.8, Current 440.0; Mean BMI (kg/m2) 227.1±5.5 **Location:** USA **Recruitment strategy:** Not reported **Length of follow-up:** 8.8 years **Response rate and loss to follow-up:** Not reported **Eligible population:** Participants in the Women's Health Study aged >45 years who were free of cardiovascular disease, cancer, and type 2 diabetes **Excluded populations:** Individuals with >70 items left blank in their SFFQ and with energy intake outside the range of 2,514 kJ (600 kcal) and 14,665 kJ (3,500 kcal), with reported diabetes at baseline, and with completed data on meat consumption

Exposures at midlife

Relevant exposures: Diet

Time: 1993

Measurement of exposure: 131-item semi-quantitative food frequency questionnaire. Four categories for red meat and total processed meat (1/week, 1/week, 2-4/week and5/week)

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: Contacted 473 women with self-reported diabetes who provided a blood sample.

The American Diabetes Association diagnostic criteria confirmed self-reported diagnosis of diabetes in 406 (91%) of 446 women who responded via telephone interview.

A random sample of 147 women with self-reported diabetes was mailed a supplemental diabetes questionnaire, also using the ADA criteria to parallel the telephone interview.

124 women were classified as having type 2 diabetes by the supplemental questionnaire. 113 of the 124 women gave permission to contact their primary care physician.

Time: Not reported

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age, BMI, total energy intake, exercise, alcohol intake, cigarette smoking, and family history of diabetes, intakes of dietary fibre, magnesium, glycemic load, and total fat

Results, limitations, source of funding

Number: 1558

Effect estimates:

Red meat

<1 time/week 1.00

1 time/week 1.16 (0.85–1.58)

2–4 times/week 1.09 (0.83–1.43)

>5 times/week 1.25 (0.94–1.67)

P for trend 0.07

Total processed meat

<1 time/week 1.00

1 time/week 1.03 (0.91–1.18)

2–4 times/week 1.17 (1.01–1.36)

>5 times/week 1.38 (1.11–1.71)

P for trend 0.003

Significant trends: Higher consumption of total red meat, especially various processed meats, may increase risk of developing type 2 diabetes in women

Limitations:

1. Residual confounding
2. Participants might change their diets after developing some diseases

3. High degree of statistical collinearity
4. Limited variation of intakes could lead to insufficient statistical power
5. Unable to assess levels of specific chemicals added or produced in different food preparation methods

Source of funding: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases Grant DK-02767

Authors: Song Y, Sesso HD, Manson JE, Cook NR, Buring JE, Liu S

Year: 2006

Citation: American Journal of Cardiology 15;98(12): 1616-21

Country of study: USA

Aim of study: Assess the hypothesis that magnesium intake is beneficial in the primary prevention of hypertension

Study design: Randomised, double-blind, placebo-controlled trial

Quality score: (++, + or -): ++

Source population

Number of people: 39,876

Demographics: Not reported

Study (eligible and selected) population

Number of people: 28,349

Characteristics:

Q1 Median intake (mg/d) 253; Mean age (yrs) 53; Mean body mass index (kg/m2) 26; Alcohol consumption (g/d) 4.8; Current smoker 18%; Vigorous exercise (>4 times/wk) 6.3%

Q3 Median intake (mg/d) 320; Mean age (yrs) 54; Mean body mass index (kg/m2) 25; Alcohol consumption (g/d) 5.0; Current smoker 14%; Vigorous exercise (>4 times/wk) 11%

Q5 Median intake (mg/d) 400; Mean age (yrs) 55; Mean body mass index (kg/m2) 25; Alcohol consumption (g/d) 4.2; Current smoker 10%; Vigorous exercise (>4 times/wk) 19%

Location: USA

Recruitment strategy: Not reported

Length of follow-up: Median follow-up of 9.8 years (mean 8.0)

Response rate and loss to follow-up: Not reported

Eligible population: Female United States health professionals aged >45 years with complete data on magnesium intake and other major lifestyle variables and without hypertension at baseline

Excluded populations: Those with previous myocardial infarction, stroke, transient ischemic attack, or cancer

Exposures at midlife

Relevant exposures: Diet

Time: 1992

Measurement of exposure: 131-item semi-quantitative food frequency questionnaire.

Outcomes at 55 years or over

Outcomes: Hypertension

Outcome measurement: Self-reported BP, treatment, and/or physician diagnosis

Time: Not reported

Analysis

Analysis strategy: Cox proportional-hazards models

Confounders: Age, randomized treatment, family history of MI before 60 years of age, exercise, alcohol use, postmenopausal hormone use, multivitamin use, smoking, total energy intake, body mass index, history of diabetes mellitus, high cholesterol, dietary intakes of saturated fat and cholesterol, glycemic load, and sodium intake

Results, limitations, source of funding

Number: 8,544

Effect estimates:

Quintile of Magnesium Intake

Total magnesium intake

1 1.00; 2 1.02 (0.95–1.10); 3 1.02 (0.95–1.10); 4 0.96 (0.89–1.03); 5 0.93 (0.86–1.02); P trend 0.03

Dietary magnesium intake

1 1.00; 2 1.00 (0.93–1.07); 3 1.02 (0.95–1.10); 4 0.89 (0.83–0.97); 5 0.91 (0.83–0.99); P trend 0.002

Significant trends: Higher intake of dietary magnesium may have a modest effect on the development of hypertension in women

Limitations:

1. Measurement errors of dietary intakes
2. Diet was assessed once
3. Magnesium coexisted with many nutrients in the diet
4. Residual confounding
5. Included only female health professionals who were predominantly white

Source of funding: Grants DK66401, DK62290, CA-47988, HL-43851, and HL-65727 from the National Institutes of Health, Bethesda, Maryland

Authors: Stevens RJ, Roddam AW, Spencer EA, Pirie KL, Reeves GK, Green J, Beral V; Million Women Study Collaborators

Year: 2009

Citation: International Journal of Cancer 15;124(10): 2400-5

Country of study: England and Scotland

Aim of study: To assess influence of risk factors on incident or fatal pancreatic cancer

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

13 million middle-aged women invited for breast cancer screening in England and Scotland were recruited for study in 1996-01

Study (eligible and selected) population

1.29 million women

Follow-up: 96-01 to 2005-07.

Mean yrs of follow-up: 7.2 for cancer incidence; 8.9 for cancer mortality

Incidence of pancreatic cancer: participants followed from date of recruitment to date of pancreatic cancer diagnosis, date of death, or last date of follow-up, whichever came first

Pancreatic cancer mortality: follow-up from recruitment until death from pancreatic cancer, death from other cause, or study end

Date of follow-up for cancer incidence was Dec. 31 2002- Dec. 31 2006, and for mortality Dec. 31, 2007

Exclusion: Women with cancer other than non-melanoma skin cancer before recruitment

Attrition: -

Exposures at midlife

Self-reported smoking (never, former, current categories), alcohol consumption in units/week, strenuous exercise (enough to cause sweating/rapid heartbeat), any exercise

Outcomes at 55 years or over

Incident and fatal pancreatic cancer identified through National Health Service Central Register (deaths and cancer registrations)

Analysis

Analysis strategy: Cox proportional hazards model used to assess influence of risk factors on incident or fatal pancreatic cancer

Confounders: Age, region, socioeconomic status, smoking, body mass index and height

Results, limitations, source of funding

- Current smokers had a high risk of incident pancreatic cancer compared to never smokers (RR 2.39, 95% CI 2.10–2.73)
- The incidence of pancreatic cancer increased with increasing BMI; the risk of incidence among obese women (BMI>= 30.0 kg/m2) was higher compared to women with BMI 22.5–25.0 kg/m2 (RR=1.34, [CI 1.13–1.57])

Limitations: Self-reported exposure measurements

Source of funding: None reported

Authors: Strand BH, Langballe EM, Hjellvik V, Handal M, Næss O, Knudsen GP>… Bjertness E; GENIDEM-Group

Year: 2013

Citation: Journal of Neurological Sciences 15;324(1-2): 124-30.

Country of study: Norway

Aim of study: Investigate the association of midlife vascular disease risk factors with dementia death

Study design: Cohort study

Quality score: (++, + or -): ++

Source population

Number of people: Not reported

Demographics: Not reported

Study (eligible and selected) population

Number of people: 48,793

Characteristics:

Mean age (sd) and High edu.

Oppland 42.7 (4.4) 50%

Sogn og Fjordane 42.5 (4.2) 57%

Finnmark 42.4 (4.3) 42%

Location: Finnmark, Sogn og Fjordane, and Oppland, Norway

Recruitment strategy: Not reported

Length of follow-up:

Person-yrs

Oppland 765,891

Sogn og Fjordane 416,700

Finnmark 322,008

Response rate and loss to follow-up: 88%

Eligible population: Participated in the baseline NCS screening in 1974–78 and age 35–50 years at the time of screening

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Physical activity and smoking habits

Time: 1974-78

Measurement of exposure: Physical examination and a questionnaire with self-reported questions

Outcomes at 55 years or over

Outcomes: Dementia death

Outcome measurement: Cause of Death Registry

Time: 2009

Analysis

Analysis strategy: Cox proportional-hazards models

Confounders: Age at screening, county, education, history of CVD, history of diabetes, physical inactive, smoking, BMI and cholesterol

Results, limitations, source of funding

Number: 486 dementia deaths (187 Alzheimer's; 299 non-Alzheimer's dementia)

Effect estimates:

History of CVD 0.98 (0.68, 1.43), Overall p-value 0.925 **History of diabetes** 2.38 (1.30, 4.34), Overall p-value 0.005 **Physical inactive** 1.14 (0.92, 1.43), Overall p-value 0.238; **Smoking** Non-smoker 1.00, Current < 15 1.03 (0.83, 1.28), Current 15 + 1.18 (0.88, 1.58), Overall p-value 0.550 **BMI** (kg/m2) < 20 1.84 (1.20, 2.81), 20–25 1.00, 25–30 1.03 (0.84, 1.26), ≥ 30 1.09 (0.78, 1.54), Overall p-value 0.079 **Systolic blood pressure** (mm Hg) < 140 1.00, 140–159 0.86 (0.67, 1.09), ≥ 160 0.89 (0.60, 1.30), Overall p-value 0.446 **Diastolic blood pressure** (mm Hg) < 90 1.00, 90–94 0.91 (0.68, 1.21), ≥ 95 1.15 (0.84, 1.58), Overall p-value 0.446 **Cholesterol** (mmol/l) < 5.20 1.00, 5.20–6.49 1.52 (1.08, 2.12), 6.50–7.79 1.53 (1.08, 2.16), ≥ 7.80 1.92 (1.30, 2.84); Overall p-value 0.009

Significant trends: People suffering from high cholesterol levels, diabetes or underweight in midlife are at increased risk of dying from or with dementia later in life

Limitations

1. Misclassify the cause of death and self-reported exposures
2. Measurement errors in exposures
3. Changes during follow-up

Source of funding: Not reported

Authors: Strandberg AY, Strandberg TE, Pitkälä K, Salomaa VV, Tilvis RS, Miettinen TA

Year: 2008

Citation: Archives of Intern Medicine 13;168(18): 1968-74.

Country of study: Finland

Aim of study: Evaluates the long-term effect of smoking in midlife on health-related quality of life in old age

Study design: Prospective cohort study

Quality score: (++, + or -): +

Source population

Number of people: 2464

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1131

Characteristics:

Neversmokers Age in 1974, y 47.2 (0.2)

Body mass index c 25.5 (0.1)

Alcohol consumption, median (interquartile range), g/wk 84 (28-140)

Ex-smokers Age in 1974, y 48.1 (0.2)

Body mass index c 26.2 (0.1)

Alcohol consumption, median (interquartile range), g/wk 136 (56-238)

Current Smokers, Cigarettes/d 1-10 Age in 1974, y 47.7 (0.4)

Body mass index c 26.1 (0.3)

Alcohol consumption, median (interquartile range), g/wk 140 (81-266)

Current Smokers, Cigarettes/d 11-20 Age in 1974, y 47.9 (0.4)

Body mass index c 25.9 (0.3)

Alcohol consumption, median (interquartile range), g/wk 126 (63-278)

Current Smokers, Cigarettes/d >20 Age in 1974, y 47.5 (0.3)

Body mass index c 25.6 (0.2)

Alcohol consumption, median (interquartile range), g/wk 210 (98-308)

Location: Finland

Recruitment strategy: Not reported

Length of follow-up: 26 years

Response rate and loss to follow-up: 87.9%

Eligible population: White men born 1919-1934 of similar socioeconomic status who were participating in the Helsinki Businessmen Study. All participants were white businessmen or executives with similar socioeconomic and job status.

Excluded populations: 581 men with any chronic disease or who were taking regular prescription medication and 160 men who reported smoking cigars or pipes

Exposures at midlife

Relevant exposures: Smoking

Time: 1974

Measurement of exposure: Mailed questionnaires

Outcomes at 55 years or over

Outcomes: Health-related quality of life and mortality

Outcome measurement: Mailed questionnaires and the Finnish national registers

Time: 2000

Analysis

Analysis strategy: Spearman rank coefficients

Confounders: Age and subjective health in 1974, body mass index, one-hour–postload glucose level, and alcohol consumption

Results, limitations, source of funding

Number: 372 died

Effect estimates:

Amount of daily cigarettes predicted mortality in a graded manner (P<.001).

Large differences were seen for the scales of physical functioning and role limitations owing to physical health; never-smokers gained 13.7 and 11.7 higher points, denoting a difference of 17% and 16%, respectively, compared with those smoking >20 cigarettes a day

The physical component summary score showed a graded deterioration of HRQoL with an increasing number of cigarettes smoked daily (global P=.01)

Significant trends: HRQoL deteriorated with an increase in daily cigarettes smoked in a dose-dependent manner. Never-smokers lived longer than heavy smokers, and their extra years were of better quality

Limitations:

1. High cessation rate
2. Did not update of the changes in participants' smoking habits between 1974 and 2000
3. Could not measure the baseline HRQoL with RAND-36/SF-36 in 1974

Source of funding: The Academy of Finland, the Sohlberg Foundation, the Ida Montin Foundation, Helsinki University Central Hospital, and the Finnish Foundation for Cardiovascular Research.

Authors: Strandhagen E, Hansson PO, Bosaeus I, Isaksson B, Eriksson H

Year: 2000

Citation: European Journal of Clinical Nutrition 54(4): 337-41

Country of study: Sweden

Aim of study: Investigate the long-term effect of fruit and vegetable consumption on mortality, cardiovascular disease, cardiovascular death, cancer morbidity and cancer death among middle-aged and elderly men

Study design: Prospective cohort study

Quality score: (++, + or -): ++

Source population

Number of people: 792

Demographics: Not reported

Study (eligible and selected) population

Number of people: 730

Characteristics:

Pieces of fruit (Means)

0-1 Body weight (kg) 76.3; Body mass index 25.0; Smoking (%) 64

2-3 Body weight (kg) 75.7; Body mass index 24.6; Smoking (%) 60

4-5 Body weight (kg) 76.7; Body mass index 25.1; Smoking (%) 51

6-7 Body weight (kg) 77.5; Body mass index 25.2; Smoking (%) 46

Location: Goteborg, Sweden

Recruitment strategy: Sample was drawn from the population register consisting of all men born in 1913 on a day divisible by three (i.e. the third, sixth, ninth day of each month) and living in the city of Goteborg

Length of follow-up: 26±5 years

Response rate and loss to follow-up: 92%

Eligible population: Included in The Study of Men Born in 1913

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Diet and smoking

Time: 1967

Measurement of exposure: Self-report food frequency questionnaire

Outcomes at 55 years or over

Outcomes: Mortality, cardiovascular disease, cardiovascular death, cancer morbidity and cancer death

Outcome measurement: Death certificates, autopsy reports and medical records were studied for those who died. Information on cancer incidence was obtained from the official Swedish Cancer register

Time: 31 December 1993

Analysis

Analysis strategy: Stepwise Cox's proportional hazard model

Confounders: Smoking, hypertension and S-cholesterol

Results, limitations, source of funding

Number: Not reported

Effect estimates:

RR (95% CI) P

Fruit 0.92 (0.84 - 1.00) 0.051

Smoking 1.30 (1.21 - 1.41) < 0.001

Hypertension 1.48 (1.23 – 1.79) < 0.001

S-cholesterol 1.13 (1.04 - 1.22) 0.005

Significant trends: Daily fruit consumption seems to have positive effect on long-term survival independently of other traditional cardiovascular risk factors like smoking, hypertension and cholesterol

Limitations:

Author: None reported

Reviewer:

1. Misclassify the cause of death and self-reported exposures
2. Measurement errors in exposures
3. Changes during follow-up

Source of funding: Swedish Medical Research Council (K98-274-06276-17) King Gustav V and Queen Victoria's Foundation, and the Goteborg University

Authors: Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, Grodstein F

Year: 2010

Citation: Archives of Internal Medicine 25;170(2): 194-201.

Country of study: USA

Aim of study: Explore the relation between mid-life physical activity, including walking, and successful aging

Study design: Prospective cohort study

Quality score: (++, + or -): ++

Source population

Number of people: 121,700

Demographics: Not reported

Study (eligible and selected) population

Number of people: 13,535

Characteristics:

Successful survivor Age at baseline (year) 60.1±2.5; Age at cognitive function assessment (year)

73.7±2.1; Physical activity (METs, hr/wk) 19.1±22.0; Walking activity (METs, hr/wk) 9.5±11.5; BMI (kg/m2) 23.8±3.3; Alcohol intake (g/d) 7.1±9.9; Red meat (serving/d) 1.0±0.5, Fruits and vegetables (serving/d) 5.4±2.0; Smoking status (%) Never smoked 53.5, Past smoker 34.8, Current smoke 1–14 cigarettes/d 5.7, Current smoke 15–24 cigarettes/d 4.3, Current smoke ≥25 cigarettes/d 1.7; Education (%) Registered nurse 74.0, Bachelor 17.3, Master 8.0, Doctorate 0.7

Usual survivors Age at baseline (year) 60.6±2.5; Age at cognitive function assessment (year) 74.2±2.3; Physical activity (METs, hr/wk) 14.1±19.7; Walking activity (METs, hr/wk) 7.2±9.7; BMI (kg/m2) 25.5±4.4; Alcohol intake (g/d) 6.7±9.9; Red meat (serving/d) 1.1±0.5, Fruits and vegetables (serving/d) 5.2±2.0; Smoking status (%) Never smoked 46.4, Past smoker 36.2, Current smoke 1–14 cigarettes/d 6.3, Current smoke 15–24 cigarettes/d 6.9, Current smoke ≥25 cigarettes/d 4.2; Education (%) Registered nurse 79.0, Bachelor 14.9, Master 5.8, Doctorate 0.4

Location: USA

Recruitment strategy: Not reported

Length of follow-up: 14 years

Response rate and loss to follow-up: Not reported

Eligible population: Nurses' Health Study participants who were free of major chronic diseases at baseline in 1986 and had survived to age 70 years or older as of 1995–2001

Excluded populations: History of any of the 11 (cancer, diabetes, myocardial infarction, coronary artery bypass graft surgery, congestive heart failure, stroke, kidney failure, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis) chronic diseases at baseline (n=2,361); who had missing physical activity data at baseline (n=2,724); those who skipped more than 2 items on the mental health scale at age 70 years or older, or more than 5 items on the physical function scale in the SF-36 (n=795)

Exposures at midlife

Relevant exposures: Physical activity

Time: 1986

Measurement of exposure: Self-report questionnaire. Asked average time per week in the past year spent on leisure-time physical activities.

Medical Outcomes SF-36 Health Status Survey

Outcomes at 55 years or over

Outcomes: Successful aging

Outcome measurement: No history of 11 major chronic diseases and no cognitive impairment, physical impairment, or mental health limitations

Time: 2000

Analysis

Analysis strategy: Multivariate logistic regression

Confounders: Age at baseline, education, husband's education, marital status, postmenopausal hormone use, smoking status, family history of heart disease/diabetes/cancer, polyunsaturated to saturated fat ratio, intakes of trans fat, alcohol, and cereal fiber, and intakes of fruits and vegetables and red meat

Results, limitations, source of funding

Number: 1,456 sucessful agers

Effect estimates:

METs, hr/wk

Total Physical Activity, Quintiles

1 (Lowest) 1.0

2 0.96 (0.78, 1.18)

3 1.30 (1.08, 1.57)

4 1.25 (1.03, 1.51)

5 1.76 (1.47, 2.12)

P for trend <0.0001

Walking, Quintiles

1 (Lowest) 1.0

2 0.99 (0.80, 1.22**)**

3 1.15 (0.94, 1.40)

4 1.42 (1.17, 1.72

5 1.37 (1.10, 1.67)

P for trend 0.0003

Significant trends: Higher levels of physical activity associated with better health status. Physical activity improves overall health

Limitations:

1. Limited to women
2. Successful survival as of age 70 years
3. Self-reported physical activity levels
4. Residual confounding
5. Did not assess physical and mental health status at baseline

Source of funding: AG13482, AG15424, and CA40356 from the National Institutes of Health and the Pilot and Feasibility program sponsored by the Boston Obesity Nutrition Research Center (DK46200)

Authors: Sun Q, Townsend MK, Okereke OI, Rimm EB, Hu FB, Stampfer MJ, Grodstein F

Year: 2011

Citation: PLoS Medicine 8(9): e1001090

Country of study: USA

Aim of study: To assess the influence of alcohol intake on the odds of successful aging

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

121,700 female registered nurses recruited in 1976 for Nurses' Health Study and followed every two years thereafter

Study (eligible and selected) population

Analysis restricted to **13,894** participants who survived to 70+ years of age through to year 2000

Sociodemographics: Median age of 58 years at midlife for participants

Follow-up: 1980-84 through to 2000. Biennial follow-up rate ranged from 99.2% in 1986 to 94.6% in 2000

Exclusion:

i) Heavy drinkers (>45g/day) at midlife (n=268)
ii) Those diagnosed with chronic conditions included in the successful aging definition prior to baseline in 1984 (n=2,196)
iii) Those with insufficient/missing data (n=2253)
iv) Individuals reporting previous diagnosis of alcohol dependence or chronic liver disease (n=130) or with past alcohol problems (n=674)

Attrition: -

Exposures at midlife

Midlife alcohol use was identified using averaged reports from the 1980 and 1984 validated food frequency questionnaires (FFQ)

Self-reported average total alcohol intake in grams per day over a year was assessed with response options ranging from 'almost never' to '6+ servings per day'

Alcohol consumption based on frequency of alcohol intake and alcohol content in beverages (e.g., 13.2 g alcohol for 1 bottle of beer, 10.8 g for 1 glass of wine, 15.1 g for 1 drink of liquor)

High level of reproducibility and validity of alcohol measurement on the FFQ

Correlation coefficient between FFQ and diet records ranged from 0.84-0.90

To assess drinking patterns of alcohol, 1986 FFQ was used in determining the number of drinking days/week

Outcomes at 55 years or over

Successful aging defined as being free of 11 major chronic diseases and having no major cognitive impairment, physical impairment, or mental health limitations, and survival until at least age 70 years

Outcomes assessed using medical record review, pathology report review, telephone interview, questionnaires

Telephone Interview for Cognitive Status (TICS) used to assess cognitive function (1995-2001); TICS has high reliability (r=0.97) and validity

SF-36 used to assess physical function and mental health

Analysis

Analysis strategy: Logistic regression used to assess the influence of alcohol intake on the odds of successful aging

Confounders: Age at baseline; body mass index; physical activity; smoking status; education; husband's education; marital status; postmenopausal hormone use; family history of heart disease; family history of diabetes; family history of cancer; history of hypertension; history of high cholesterol; use of aspirin; and intakes of fruits and vegetables, whole grains, fish, and red meat

Results, limitations, source of funding

- 1,491 participants aged successfully
- The odds of successful aging to age 70+ were higher among those consuming 5.1-15.0 g/day and 15.1-30.0 g/day alcohol compared to nondrinkers (OR=1.19, [1.01, 1.40], and OR=1.28, [1.03, 1.58], respectively)
- Similar findings were observed when drinking pattern at midlife in 1986 was assessed in relation to odds of successful aging (e.g., higher odds of successful aging with greater alcohol use)

Limitations:

1. Cannot generalise to other ethnic groups (sample consisted predominantly of participants of

European ancestry) and men
2. High-risk participants may have died early (selection bias)
3. Residual confounding

Source of funding: None reported

Authors: Szoeke CE, Cicuttini FM, Guthrie JR, Clark MS, Dennerstein L

Year: 2006

Citation: Bone 39(5): 1149-1155

Country of study: Australia

Aim of study: To determine the factors associated with the development of radiological osteoarthritis

Study design: Population-based prospective study

Quality score: (++, + or -): +

Source population

Number of people: 438

Demographics: Not reported

Study (eligible and selected) population

Number of people: 224

Characteristics:

Age (years) 49.66 (2.47)

Weight (kilograms) 68.62 (13.59)

BMI (kg/m2) 25.92 (4.84)

Current smoker 33 (15.7%)

Daily physical activity 56 (24.90%)

Weekly physical activity 94 (41.80%)

Infrequent physical 27 (12.00%)

No physical activity 46 (20.40%)

Location: Melbourne, Australia

Recruitment strategy: Not reported

Length of follow-up: 11 years

Response rate and loss to follow-up: Not reported

Eligible population: Participants in the Melbourne Women's Midlife Health Project

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Physical activity and smoking

Time: 1991

Measurement of exposure: Self-administered and face-to-face questionnaires

Outcomes at 55 years or over

Outcomes: Osteoarthritis

Outcome measurement: X-Ray

Time: 2002

Analysis

Analysis strategy: Multiple logistical regression

Confounders: Age, BMI and physical activity, smoking and hormone use

Results, limitations, source of funding

Number: 28 women (56%) radiological OA. 49 (21.6%) knee osteoarthritis. 101 (44.5%) hand osteoarthritis

Effect estimates:

Hand OA

RR (95.0% CI)

Age (years) 1.01 (0.9–1.2); Mean BMI (kg/m2) over 11 years 1.02 (0.9–1.1); Never used hormone therapy 2.33 (1.0–1.1); Physical activity at 20–29 Trend; Smoking ever 1.01 (1.0–5.7)

P Age (years) 0.90; Mean BMI (kg/m2) over 11 years 0.65; Never used hormone therapy 0.06; Physical activity at 20–29 0.33; Smoking ever 0.35

Knee OA

RR (95.0% CI)

Age (years) 1.4 (1.1–1.8); Mean BMI (kg/m2) over 11 years 1.2 (1.1–1.3); Never used hormone therapy 2.9 (0.8–11.6); Physical activity at 20–29 Trend; Smoking ever 0.9 (0.8–1.0)

P Age (years) 0.02; Mean BMI (kg/m2) over 11 years 0.004; Never used hormone therapy 0.12; Physical activity at 20–29 0.03; Smoking ever 0.05

Significant trends: Increasing age, BMI and history of more frequent physical activity in younger years were risk factors for radiological knee OA. Never having used hormone therapy was a risk factor for radiological hand and knee OA

Limitations:

1. Only 57% of the initial participants had complete data
2. Did not have the power to detect very weak risk factors for OA
3. Self-reported exposures
4. No data on incident osteoarthritis

Source of funding: Shepherd Foundation

Authors: Tabak C, Smit HA, Räsänen L, Fidanza F, Menotti A, Nissinen A… Kromhout D

Year: 2001

Citation: Epidemiology 12(2): 239-45

Country of study: Finland, Italy, Netherlands

Aim of study: Used to assess association between alcohol consumption and 20-year COPD mortality

Study design: Longitudinal

Quality score: (++, + or -): -

Source population

Samples of men ages 40-59 years recruited in 1960 from seven countries and with vital status information during 30 years of follow-up

Study (eligible and selected) population
Analysis restricted to Finnish, Italian, Dutch cohorts comprising **2,953** men **Follow-up:** Approximately 20 years from 1965-70 to 1990 **Exclusion:** - **Attrition:** 1,729 men died over 20 years of follow-up
Exposures at midlife
Alcohol consumption in 1965-1970 estimated using cross-check dietary history method Participants categorised into: none, <=1 drink per week (occasional), >1 per week and <=3 per day (light), >3 and <=9 per day, and >9 per day (with 1 drink = 10 grams alcohol)
Outcomes at 55 years or over
Chronic obstructive pulmonary disease (COPD) mortality assessed between 1970 and 1990 using clinical records, family doctors, specialists, relatives, other sources
Analysis
Analysis strategy: Cox proportional hazards model used to assess association between baseline alcohol consumption and 20-year COPD mortality **Confounders:** Age, BMI, energy intake, cigarette smoking, and country
Results, limitations, source of funding
• 73 men died from COPD during follow-up • U-shaped relation between alcohol use and COPD mortality **Limitations:** None reported **Source of funding:** None reported

Authors: Tsugane S, Sasazuki S, Kobayashi M, Sasaki S **Year:** 2004 **Citation:** British Journal of Cancer 90(1): 128–134 **Country of study:** Japan **Aim of study:** To examine if salt-preserved foods and salt increase the risk of stomach cancer **Study design:** Prospective study **Quality score: (++, + or -):** +
Source population
Number of people: 54,498 **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 18,684 men, 20,381 women **Characteristics:**

Men

1 (low) Age (years) 48.7; Current smokers (%) 49; Daily alcohol drinkers (%) 25; Fruit and vegetables Fruit 2.3, Green vegetables 3.2, Yellow vegetables 2.4, Other vegetables 3

2 Age (years) 49; Current smokers (%) 51; Daily alcohol drinkers (%) 34; Fruit and vegetables Fruit 2.9, Green vegetables 3.4, Yellow vegetables 2.6, Other vegetables 3.5

3 age (years) 49.4; Current smokers (%) 54; Daily alcohol drinkers (%) 42; Fruit and vegetables Fruit 3.1, Green vegetables 3.6, Yellow vegetables 2.7, Other vegetables 3.9

4 Age (years) 49.9; Current smokers (%) 56; Daily alcohol drinkers (%) 46; Fruit and vegetables Fruit 3.4, Green vegetables 3.6, Yellow vegetables 2.8, Other vegetables 4.1

5 Age (years) 50.1; Current smokers (%) 56; Daily alcohol drinkers (%) 47; Fruit and vegetables Fruit 3.5, Green vegetables 4, Yellow vegetables 2.9, Other vegetables 4.4

Women

1 (low) Age (years) 48.9; Current smokers (%) 8.2; Daily alcohol drinkers (%) 2.1; Fruit and vegetables Fruit 3.2, Green vegetables 3.6, Yellow vegetables 3.1, Other vegetables 3.5

2 Age (years) 49.3; Current smokers (%) 6.5; Daily alcohol drinkers (%) 2.7; Fruit and vegetables Fruit 4, Green vegetables 3.9, Yellow vegetables 3.3, Other vegetables 4.1

3 Age (years) 49.7; Current smokers (%) 4.7; Daily alcohol drinkers (%) 1.8; Fruit and vegetables Fruit 4.3, Green vegetables 4, Yellow vegetables 3.4, Other vegetables 4.4

4 Age (years) 50; Current smokers (%) 3.6; Daily alcohol drinkers (%) 2; Fruit and vegetables Fruit 4.5, Green vegetables 4.1, Yellow vegetables 3.5, Other vegetables 4.6

5 age (years) 50; Current smokers (%) 4.2; Daily alcohol drinkers (%) 2.2; Fruit and vegetables Fruit 4.5, Green vegetables 4.2, Yellow vegetables 3.5, Other vegetables 4.7

Location:

Cohort I: Ninohe in Iwate Prefecture, Yokote in Akita Prefecture, Saku in Nagano Prefecture, Ishikawa in Okinawa Prefecture and Katsushika in the Tokyo Metropolitan area

Cohort II: Mito in Ibaraki Prefecture, Kashiwazaki in Niigata Prefecture, Chuohigashi in Kochi Prefecture, Kamigoto in Nagasaki Prefecture, Miyako in Okinawa Prefecture and Suita in Osaka Prefecture

Recruitment strategy: Population registries maintained by the local city, town or village office

Length of follow-up: Various

Response rate and loss to follow-up: 34 persons were lost to follow-up within the study period

Eligible population: Inhabitants in the study areas, aged 40–59 years old in Cohort I and 40–69 years in Cohort II at the beginning of the each study

Excluded populations: Self-reported serious illness at baseline as well as non-Japanese subjects; subjects who had already moved away at the baseline and subjects who reported extreme total energy intake

Exposures at midlife

Relevant exposures: Diet

Time: 1990

Measurement of exposure: Self-report questionnaire

Outcomes at 55 years or over

Outcomes: Gastric cancer

Outcome measurement: Death certificates, diagnosed cases of cancer were reported by hospitals, cases of gastric cancer were extracted from the cancer registry

Time: 2001

Analysis

Analysis strategy: Cox proportional-hazards model

Confounders: Age in 1990, cigarette smoking, and fruit and vegetable intake and PHC area

Results, limitations, source of funding

Number: 486

Effect estimates:

Relative risks (RR) of incident gastric cancer by quintiles of salt intake at baseline

Men

1 Reference

2 0.89 – 2.09

3 0.88 – 2.07

4 1.01 – 2.34

5 0.98 –2.29

P for trend 0.08

Women

1 Reference

2 0.41 – 1.37

3 0.45 – 1.48

4 0.25 – 0.95

5 0.61 –1.94

P for trend 0.85

Significant trends: Restriction of salt and salted food intake is a practical strategy to prevent gastric cancer in areas with high risk

Limitations:

1. Limited food items on scale
2. Precise estimation of salt intake may be implausible

Source of funding: Grants-in-aid for cancer research and for the second term comprehensive 10-year strategy for cancer control from the Ministry of Health, Labor and Welfare of Japan

Authors: Tuomilehto J, Hu G, Bidel S, Lindstrom J, Jousilahti P

Year: 2004

Citation: JAMA 291(10): 1213-1219

Country of study: Finland

Aim of study: Determine the relationship between coffee consumption and the incidence of type 2 DM

Study design: Prospective study

Quality score: (++, + or -): ++

Source population

Number of people: 16,670 **Demographics:** Not reported
Study (eligible and selected) population
Number of people: 7,655 **Characteristics:** **Daily Coffee Consumption** Men **2** Age, mean (SD), y 49.1 (8.4); Body mass index, mean (SD) 26.6 (3.7); Education, mean (SD), y 9.9 (4.2); Physical activity, No. (%) Light occupational 573 (46); Low leisure time 342 (27); Tea 847 (68); Alcohol 757 (61); Current smoker, No. (%) 211 (17); Obesity, No. (%) 214 (17) **>10** Age, mean (SD), y 46.3 (7.9); Body mass index, mean (SD) 27.3 (4.1); Education, mean (SD), y 8.4 (3.3); Physical activity, No. (%) Light occupational 279 (32); Low leisure time 311 (36); Tea 91 (11); Alcohol 482 (56); Current smoker, No. (%) 481 (56); Obesity, No. (%) 189 (22) Women **2** Age, mean (SD), y 49.3 (8.8); Body mass index, mean (SD) 26.4 (4.9); Education, mean (SD), y 10.0 (4.0); Physical activity, No. (%) Light occupational 726 (52); Low leisure time 466 (34); Tea 920 (66); Alcohol 572 (41); Current smoker, No. (%)/ 93 (7); Obesity, No. (%) 278 (20) **>10** Age, mean (SD), y 45.6 (7.6); Body mass index, mean (SD) 27.5 (5.0); Education, mean (SD), y 8.6 (3.5); Physical activity, No. (%) Light occupational 128 (34); Low leisure time 164 (43); Tea 48 (13); Alcohol 145 (38); Current smoker, No. (%) 147 (39); obesity, No. (%) 82 (22) **Location:** North Karelia, Kuopio, and Turku-Loimaa, Finland **Recruitment strategy:** Random sample was stratified by sex and 4 equally large 10-year age groups **Length of follow-up:** Mean 12 years **Response rate and loss to follow-up:** 74% to 88% **Eligible population:** Finnish men and women **Excluded populations:** Participants diagnosed with coronary heart disease or stroke (n=590), participants with known DM at baseline (n=435), and participants with incomplete data on any variables required for this analysis (n=1016).
Exposures at midlife
Relevant exposures: Diet **Time:** 1982, 1987, and 1992 **Measurement of exposure:** Self-administered questionnaire
Outcomes at 55 years or over
Outcomes: Type 2 diabetes **Outcome measurement:** National Hospital Discharge Register and the Drug Register of the National Social Insurance Institution **Time:** December 31 1998, or until death
Analysis
Analysis strategy: Cox proportional hazards regression model **Confounders:** Age, study year, body mass index, systolic blood pressure, education, occupational

physical activity, walking or cycling to or from work, leisure time physical activity, cigarette smoking, alcohol and tea consumption
Results, limitations, source of funding
Number: 381 **Effect estimates:** <u>Men</u> **<2** 1.00 **3-4** 0.73 (0.47-1.13) **5-6** 0.70 (0.45-1.05) **7-9** 0.67 (0.40-1.12) **>10** 0.45 (0.25-0.81) **P for Trend** .12 <u>Women</u> **<2** 1.00 **3-4** 0.71 (0.48-1.05) **5-6** 0.39 (0.25-0.60) **7-9** 0.39 (0.20-0.74) **>10** 0.21 (0.06-0.69) **P for Trend** <.001 <u>Combined</u> **<2** 1.00 **3-4** 0.76 (0.57-1.01) **5-6** 0.54 (0.40-0.73) **7-9** 0.55 (0.37-0.81) **>10** 0.39 (0.24-0.64) **P for Trend** <.001 **Significant trends:** Coffee drinking has a graded inverse association with the risk of type 2 DM **Limitations:** 1. Glucose tolerance test was not performed in the baseline and follow up surveys 2. Self-report for data on coffee intake **3.** Residual confounding due to measurement error **Source of funding:** 46885, 53585, 204274, and 205657 from the Academy of Finland and the National Public Health Institute, Helsinki, Finland.

Authors: Tyas SL, White LR, Petrovitch H, Webster Ross G, Foley DJ, Heimovitz HK, Launer LJ **Year:** 2003 **Citation:** Neurobiology of Aging 24(4): 589-96 **Country of study:** USA, Hawaii **Aim of study:** Study the association between mid-life smoking and late-life dementia **Study design:** Follow-up study **Quality score: (++, + or -):** +

Source population

Number of people: 8006

Demographics: Not reported

Study (eligible and selected) population

Number of people: 3,734

Characteristics:

Mid-life smoking status (mean (S.E.)

Never Age (years) 78.3 (0.13); Education (years) 10.9 (0.09); Apolipoprotein (%) 17.9; Alcohol intake (oz. per month) 7.0 (0.43)

Former Age (years) 77.7 (0.15); Education (years) 10.3 (0.10); Apolipoprotein (%) 19.5; Alcohol intake (oz. per month) 13.7 (0.68)

Current Age (years) 76.8 (0.14); Education (years) 10.2 (0.10); Apolipoprotein (%) 18.4; Alcohol intake (oz. per month) 18.0 (0.89)

Location: Honolulu, USA, Hawaii

Recruitment strategy: Not reported

Length of follow-up: 25-31 years

Response rate and loss to follow-up: Not reported

Eligible population: Participants in the Honolulu Heart Program

Excluded populations: Fifty-six of men who were known to be smokers but could not be classified as current or former smokers

Exposures at midlife

Relevant exposures: Smoking

Time: 1965–1971

Measurement of exposure: Self-report questionnaires, asked if smoked (never/former/current)

Outcomes at 55 years or over

Outcomes: Alzheimer disease

Outcome measurement: 100-point Cognitive Abilities Screening Instrument and the IQCODE. Dementia was diagnosed according to DSM-III-R criteria; probable and possible AD according to the NINCDS-ADRDA.

Time: 1991–1996

Analysis

Analysis strategy: Multiple logistic regression model

Confounders: Age, education, presence of an apolipoprotein E-E4 allele, alcohol intake, systolic blood pressure categories, diastolic blood pressure categories, use of antihypertensive medication, ankle-brachial index, history of cerebrovascular accident and forced expiratory volume in 1s adjusted for height

Results, limitations, source of funding

Number: AD (n = 3050) AD ± CVD (n = 3102) VaD (n = 3024)

Effect estimates:

AD Never 1.0; Former 0.93 (0.58–1.50); Current 1.17 (0.69–1.98)

AD ± CVD Never 1.0; Former 0.88 (0.58–1.33); Current 1.31 (0.85–2.01)

VaD Never 1.0; Former 0.82 (0.43–1.52); Current 1.14 (0.60–2.13)

All dementia Never 1.0; Former 0.80 (0.58–1.10); Current 1.11 (0.79–1.55)

Significant trends: Amount smoked is associated with an increasing risk of AD and Alzheimer-type neuropathology. Very heavy smoking was not associated with AD

Limitations:

Author: Restriction to Japanese-American men

Reviewer:

1. Self-report exposures;
2. Residual confounding
3. Survival bias

Source of funding: National Institutes of Health through National Institute on Aging contract no. N01-AG-4-2149; National Heart, Lung, and Blood Institute contract no. N01-HC-O5102; and NIH grants 1-PO1-AGO5119 and 5-P50-AGO5144

Authors: Valtonen M, Laaksonen DE, Laukkanen J, Tolmunen T, Rauramaa R, Viinamäki H… Kauhanen J

Year: 2010

Citation: European Journal of Cardiovascular Prevention and Rehabilitation 17(5): 524-9

Country of study: Finland

Aim of study: Investigated the association of leisure-time physical activity with the development of hopelessness during the follow-up

Study design: Population-based cohort study

Quality score: (++, + or -): +

Source population

Number of people: 2682

Demographics: Not reported

Study (eligible and selected) population

Number of people: 509

Characteristics:

According to hopelessness

< 4points Age (years) 50.3 (6.6); Body mass index (kg/m2) 26.5 (3.2); Waist girth (cm) 89.0 (9.1); Alcohol consumption (g/week) 66 (8, 89); Smoker (%) 25.7; Adult socioeconomic status 7.0 (4.3)

> 4points Age (years) 51.7 (7.1); Body mass index (kg/m2) 26.4 (3.2); Waist girth (cm) 90.0 (9.2); Alcohol consumption (g/week) 68 (5, 104); Smoker (%) 38.2; Adult socioeconomic status 8.5 (4.1)

Location: Kuopio, Finland

Recruitment strategy: Not reported

Exposures at midlife

Relevant exposures: Leisure-time physical activity

Time: 1984 and 1989

Measurement of exposure: Kuopio Ischemic Heart Disease Risk Factor Study 12-month LTPA Questionnaire

Outcomes at 55 years or over

Outcomes: Hopelessness

Outcome measurement: Psychological questionnaire

Time: 1995-2000

Analysis

Analysis strategy: Logistic regression analysis

Confounders: Age category, smoking, alcohol consumption, cardiovascular disease and adulthood socioeconomic status, body mass index, elevated depressive symptoms, leisure-time physical activity; metabolic equivalent; maximal oxygen uptake

Results, limitations, source of funding

Number: Not reported

Effect estimates

Total LTPA (min/week)

< 270 min/week 1

270–486 min/week 0.90 (0.47–1.73)

> 486 min/week 0.89 (0.47–1.68)

P for linear trend 0.126

Low-intensity LTPA (< 4.5 METs, min/week**)**

< 111 min/week 1

111–270 min/week 0.90 (0.44–1.84)

> 271 min/week 1.65 (0.85–3.19)

P for linear trend 0.108

Moderate-to-vigorous LTPA (Z 4.5 METs, min/week)

< 60 min/week 1

61–150 min/week 0.80 (0.40–1.60)

> 150 min/week 0.60 (0.32–1.13)

P for linear trend 0.112

Vigorous LTPA (Z 7.5 METs, min/week)

< 10 min/week 1

10–59 min/week 0.83 (0.44–1.56)

> 60 min/week 0.57 (0.28–1.14)

P for linear trend 0.126

Significant trends: Moderate-to-vigorous physical activity seems to prevent development of hopelessness in middle-aged men

Limitations:

Author:

1. Hopelessness scale not been compared with other hopelessness scales;
2. Includes only middle-aged white men

Reviewer:

1. Self-report for data on PA
2. Residual confounding due to measurement error

Source of funding: Academy of Finland (grants 118551, 41471, 1041086 and 2041022), the Ministry of Finland (grants 167/722/96, 157/722/97, 156/722/98), and the National Heart, Lung and Blood Institute of the USA (grant HL44199).

Authors: Villegas R, Yang G, Gao YT, Cai H, Li H, Zheng W, Shu XO

Year: 2010

Citation: International Journal of Epidemiology 39(3): 889-99

Country of study: China

Aim of study: To examine how dietary patterns are associated with type 2 diabetes in middle-aged women

Study design: Population-based prospective study

Quality score: (++, + or -): ++

Source population

Number of people: 81,170

Demographics: Not reported

Study (eligible and selected) population

Number of people: 64,191

Characteristics:

Cluster 1 Age (years, mean ± SE) 52.5 ± 0.05; Education (%) None 13.6, Elementary school 12.8, Up to high school 63.6, College 9.9; Income level (%) <10 000 18.5, 10 000–19 999 40.9, 20 000–29 999 26.4, >30 000 14.2; Occupation (%) Professional 15.0, Clerical 11.8, Manual 21.9, Housewife/retired 51.2; Smoking (%) 2.7; Alcohol consumption (%) 2.1; Exercise participation (%) 32.9

Cluster 2 Age (years, mean ± SE) 49.1 ± 0.05; Education (%) None 2.9, Elementary school 5.2, Up to high school 73.1, College 18.8; Income level (%) <10 000 11.0, 10 000–19 999 34.4, 20 000–29 999 31.7, >30 000 22.9; Occupation (%) Professional 26.4, Clerical 14.5, Manual 24.1, Housewife/retired 35.0; Smoking (%) 1.5; Alcohol consumption (%) 2.3; Exercise participation (%) 33.0

Cluster 3 Age (years, mean ± SE) 48.1 ± 0.17; Education (%) None 2.1, Elementary school 4.1, Up to high school 76.5, College 17.4; Income level (%) <10 000 13.9, 10 000–19 999 33.2, 20 000–29 999 31.4, >30 000 21.4; Occupation (%) Professional 23.6, Clerical 15.1, Manual 26.8, Housewife/retired 35.0; Smoking (%) 2.2; Alcohol consumption (%) 4.6; Exercise participation (%) 32.4

Location: Shanghai, China

Recruitment strategy: Not reported

Length of follow-up: 6.9 years

Response rate and loss to follow-up:

Between 2000 and 2002 99.8%

Between 2002 and 2004 98.7%

Between 2004 and 2006 94.9%

Eligible population: Middle-aged women

Excluded populations: <40 years or 470 years at the time of interview, participants that had extreme values for total energy intake

Exposures at midlife

Relevant exposures: Diet

Time: 1996 to 2000

Measurement of exposure: In-person interview using a food-frequency questionnaire

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: Follow-up survey

Reported diagnosis of T2D and met at least one of the criteria as recommended by the American Diabetes Association

Time: 1996 to 2000

Analysis
Analysis strategy: Cox regression model **Confounders:** Age, kcal/day, physical activity, alcohol consumption, smoking, education level, income level, occupation and hypertension, waist-to-hip ratio and BMI.
Results, limitations, source of funding
Number: Not reported **Effect estimates:** **Associations between dietary clusters and the incidence of T2D stratified by age group** RR 95% CI All Cluster 1 1.00; Cluster 2 0.78 (0.71–0.8); Cluster 3 1.05 (0.81–1.3) Age < 50 years Cluster 1 1.00; Cluster 2 0.77 (0.66–0.9); Cluster 3 0.98 (0.66–1.4) Age > 50 years Cluster 1 1.00; Cluster 2 0.83 (0.73–0.9); Cluster 3 1.19 (0.86–1.6) **Significant trends:** A dietary pattern low in staple foods and high in dairy milk, which was associated with lower risk of T2D **Limitations:** 1. Self-reports of T2D 2. Residual confounding **Source of funding:** R01 CA070867 from the National Cancer Institute and R01 HL079123 from the National Heart, Lung and Blood Institute

Authors: Villegas R, Xiang YB, Elasy T, Li HL, Yang G, Cai H… Shu XO **Year:** 2011 **Citation:** American Journal of Clinical Nutrition 94(2): 543-51 **Country of study:** China **Aim of study:** Examine associations between fish, shellfish, and long-chain n-3 fatty acids and the risk of T2D **Study design:** Prospective population-based cohort study **Quality score: (++, + or -):** ++
Source population
Number of people: Not reported **Demographics:** Not reported
Study (eligible and selected) population
Number of people: SWHS 74,942 women SMHS 61,500 men **Characteristics:**

Shanghai Women's Health Study

Q1 Age (y) 54 (46, 64); Energy intake (kcal/d) 1483.6 ± 323.4; BMI (kg/m2) 24.3 ± 3.6; Smoking (%) 4.1; Alcohol (%) 2.2; Exercise (%) 33.8; Education (%) None 22.3, Elementary 16.5, High school 53.4, College 7.8; Income level (%) I 24.0, II 41.5, III 23.0, IV 11.5; Occupation (%) Professional 11.2, Clerical 9.8, Manual labour 18.9, Housewife/retired 60.1

Q5 Age (y) 54 (46, 64); Energy intake (kcal/d) 1483.6 ± 323.4; BMI (kg/m2) 24.3 ± 3.6; Smoking (%) 4.1; Alcohol (%) 2.2; Exercise (%) 33.8; Education (%) None 22.3, Elementary 16.5, High school 53.4, College 7.8; Income level (%) I 24.0, II 41.5, III 23.0, IV 11.5; Occupation (%) Professional 11.2, Clerical 9.8, Manual labour 18.9, Housewife/retired 60.1

Shanghai Men's Health Study

Q1 Age (y) 54 (48, 65); Energy intake (kcal/d) 1777 ± 394.7; BMI (kg/m2) 23.4 ± 3.1; Smoking (%) 60.2; Alcohol (%) 25.0; Exercise (%) 32.6; Education (%) None 11.3, Elementary 38.1, High school 32.3, College 18.2; Income level (%) I 16.4, II 46.9, III 30.2, IV 6.3; Occupation (%) Professional 22.6, Clerical 20.5, Manual labour 56.9, Housewife/retired N/A

Q5 Age (y) 49 (45, 56); Energy intake (kcal/d) 2121 ± 453.6; BMI (kg/m2) 23.7 ± 2.9; Smoking (%) 64.9; Alcohol (%) 37.4; Exercise (%) 32.8; Education (%) None 2.5, Elementary 28.9, High school 41.4, College 27.2; Income level (%) I 12.2, II 36.5, III 37.3, IV 13.6; Occupation (%) Professional 27.3, Clerical 23.8, Manual labour 48.9, Housewife/retired N/A

Location: Shanghai, China

Recruitment strategy: Two samples; the Shanghai Women's Health Study and the Shanghai Men's Health Study

Length of follow-up:

8.9 y for the SWHS

4.1 y for the SMHS

Response rate and loss to follow-up:

92% for women

75% for men

Eligible population:

SWHS women aged 40–70y

SMHS men aged 40–74y

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Diet

Time:

SWHS 1996 to 2000

SMHS 2002 to 2006

Measurement of exposure: In-person interview using a food-frequency questionnaire

Outcomes at 55 years or over

Outcomes: Type 2 diabetes

Outcome measurement: Follow-up survey.

Reported diagnosis of T2D and met at least one of the criteria as recommended by the American Diabetes Association

Time:

SWHS 1996 to 2000 SMHS 2002 to 2006
Analysis
Analysis strategy: Cox regression model **Confounders:** Age, energy intake (kcal/d), waist-to-hip ratio, BMI, smoking, alcohol consumption, physical activity, income level, educational level, occupation, family history of diabetes, hypertension, and dietary pattern
Results, limitations, source of funding
Number: SWHS 3037 of whom 3034 had valid dietary data SMHS 903, valid dietary data available for 900 **Effect estimates:** RR (95% CI) **Shanghai Women's Health Study** **Combined fish and shellfish** Q1 1.00; Q2 0.93 (0.83, 1.03); Q3 0.80 (0.71, 0.89); Q4 0.83 (0.74, 0.94); Q5 0.86 (0.76, 0.98) **Fish** Q1 1.00; Q2 0.96 (0.86, 1.06); Q3 0.84 (0.75, 0.94); Q4 0.80 (0.71, 0.90); Q5 0.89 (0.78, 1.01) **Saltwater fish** Q1 1.00; Q2 1.00 (0.90, 1.12); Q3 0. 89 (0.79, 1.00); Q4 0.95 (0.85, 1.06); Q5 0.84 (0.74, 0.95) **Freshwater fish** Q1 1.00; Q2 0.96 (0.86, 1.07); Q3 0.82 (0.73, 0.92); Q4 0.89 (0.80, 1.00); Q5 0.87 (0.77, 0.98) **Shellfish** Q1 1.00; Q2 0.91 (0.82, 1.01); Q3 0.79 (0.71, 0.89); Q4 0.80 (0.71, 0.91); Q5 0.86 (0.76, 0.99) **Long-chain n-3 fatty acids** Q1 1.00; Q2 0.90 (0.80, 1.00); Q3 0.84 (0.75, 0.94); Q4 0.87 (0.77, 0.98); Q5 0.84 (0.74, 0.95) **P for trend** Combined fish and shellfish 0.004 Fish 0.003 Saltwater fish 0.01 Freshwater fish 0.01 Shellfish 0.006 Long-chain n-3 fatty acids 0.005 **Shanghai Men's Health Study** **Combined fish and shellfish** Q1 1.00; Q2 0.93 (0.76, 1.14); Q3 0.80 (0.64, 0.99); Q4 0.88 (0.70, 1.09); Q5 0.92 (0.73, 1.16) **Fish** Q1 1.00; Q2 0.92 (0.75, 1.13); Q3 0.80 (0.65, 1.00); Q4 0.89 (0.72, 1.11); Q5 0.94 (0.74, 1.17) **Saltwater fish** Q1 1.00; Q2 0.72 (0.58, 0.91); Q3 1.13 (0.92, 1.37); Q4 0.87 (0.71, 1.07); Q5 0.87 (0.69, 1.09) **Freshwater fish** Q1 1.00; Q2 0.86 (0.70, 1.07); Q3 0.81 (0.65, 1.00); Q4 0.95 (0.77, 1.17); Q5 0.88 (0.70, 1.09) **Shellfish** Q1 1.00; Q2 0.93 (0.76, 1.12); Q3 0.70 (0.56, 0.86); Q4 0.66 (0.53, 0.82); Q5 0.82 (0.65, 1.02)

Long-chain n-3 fatty acids Q1 1.00; Q2 0.95 (0.77, 1.17); Q3 0.86 (0.69, 1.07); Q4 0.96 (0.77, 1.19); Q5 0.89 (0.70, 1.12)

P for trend

Combined fish and shellfish 0.36

Fish 0.50

Saltwater fish 0.56

Freshwater fish 0.49

Shellfish 0.003

Long-chain n-3 fatty acids 0.40

Significant trends: An inverse association between fish and shellfish intake and T2D in women was found

Reported limitations:

Author: Self-reports of T2D

Reviewer:

1. Self-report for data on diet
2. Residual confounding due to measurement error

Source of funding: US Public Health Service grants from the National Cancer Institute (R01 CA070867 and R01 CA082729)

Authors: Virta JJ, Heikkilä K, Perola M, Koskenvuo M, Räihä I, Rinne JO, Kaprio J

Year: 2010

Citation: European Journal of Epidemiology 28(5): 405-16

Country of study: Finland

Aim of study: Monitor the effects of midlife alcohol consumption and drinking patterns on cognitive impairment risks in late life

Study design: Prospective follow-up study

Quality score: (++, + or -): +

Source population

Number of people: 3,310

Demographics: Not reported

Study (eligible and selected) population

Number of people: 1,486

Characteristics:

Men 753 (50.67 %), Women 733 (49.33 %); Age distribution (F = 40.35, p < 0.01) < 70 years 333 (22.41 %), 70–74 years 662 (44.55 %), 75–79 years 239 (16.08 %), > 79 years 252 (16.96 %); Education (F = 72.61, p < 0.01) 0–6y 733 (49.33 %), 7–12y 583 (39.23 %), 13–16y 135 (9.08 %), other 35 (2.36 %)

Location: Finland

Recruitment strategy: Not reported

Length of follow-up: 22.8 years (SD 2.1 years)

Response rate and loss to follow-up:

1975 was 89%

1981 was 84%

Eligible population: Same-sexed twin pairs born in Finland before 1937 with both co-twins alive in 1967

Excluded populations: No baseline questionnaire data for 384 subjects; 543 subjects who had not filled the questionnaires adequately regarding alcohol consumption; 375 were not interviewed at all or not fully; three subjects had missing education information; one interviewed subject had answered all questions regarding alcohol consumption in 1981 but not in 1975; one outlier reported a daily alcohol intake of 219 grams; subjects with mild impairment in cognitive function

Exposures at midlife

Relevant exposures: Alcohol consumption and smoking

Time: 1975

Measurement of exposure: Self-report

Outcomes at 55 years or over

Outcomes: Cognitive impairment risks

Outcome measurement: The TELE. A self-report telephone interview

Time: 1981

Analysis

Analysis strategy: Logistic regression analysis

Confounders: Age, gender, and education

Results, limitations, source of funding

Number: Not reported

Effect estimates:

Alcohol consumption in 1981

OR (95% CI)

Abstainer 1.51 (1.04–2.18)

Light drinker 1.00

Moderate drinker 0.87 (0.58–1.32)

Heavy drinker 2.03 (1.17–3.54)

Binge drinking in 1976 and 1981

Neither 1976 nor 1981 1.00

Only 1976 or 1981 1.87 (1.04–3.38)

Both 1976 and 1981 1.98 (1.05–3.72)

Number of pass-outs in 1981

0 1.00

1–2 0.94 (0.50–1.78)

> 2 4.10 (1.54–10.94)

Significant trends: Both abstainers and heavy drinkers were found to have an increased risk of cognitive impairment in comparison to light drinkers. Light to moderate alcohol use is associated with a lower risk of cognitive impairment

Limitations:

Author: None reported

Reviewer:

1. Self-report for data on exposures
2. Residual confounding due to measurement error

Source of funding: Academy of Finland (project #205954), the Sigrid Juselius Foundation and Clinical grants of Turku University Hospital

Authors: Virtaa JJ, Järvenpää T, Heikkilä K, Perola M, Koskenvuo M, Räihä … Kaprio J

Year: 2010

Citation: Journal of Alzheimers Disease 22(3): 939-48

Country of study: Finland

Aim of study: To assess the influence of alcohol intake on cognitive impairment

Study design: Longitudinal

Quality score: (++, + or -): ++

Source population

3,310 individuals (same-sexed twin pairs) born in Finland before 1937 with both co-twins alive in 1967 contacted

Baseline questionnaires administered in 1975 and 1981 (response rates: 89% and 84%, resp.)

Study (eligible and selected) population

Analysis restricted to **1,486** Finnish participants comprised of same-sexed monozygotic or dizygotic twins

Mean age in 1981: 51.7 years

Follow-up: 1975-81 to 1999-07 (mean follow-up: 22.8 years)

Exclusion:

1. Lack of data (n=534)
2. Those who died (n=21)
3. Participants with incomplete interview data or missing information (n=378)
4. Insufficient data captured at both interviews (n=1)
5. Daily alcohol intake outlier (n=1)
6. Those with mild cognitive impairment at baseline

Attrition: Inadequate self-reported alcohol data mostly for women with lower levels of education

Exposures at midlife

Self-reported total weekly (for beer, wine) or monthly (for spirits) alcohol intake

1 drink=12 g ethanol

Participants categorized as abstainers, light drinkers (alcohol intake > 0 and <=3 drinks /week), moderate drinkers (> 3 and <= 7 drinks for women, > 3 and <= 14 drinks /week for men), and heavy drinkers (> 7 drinks for women, > 14 for men)

Number of pass-outs and at least monthly binge drinking assessed at baseline (1975-81)

Outcomes at 55 years or over
Cognitive function assessed using TELE, a self-report telephone interview Monozygotic and dizygotic twins ages 65 years and older interviewed in 1999-01 and 2003-07
Analysis
Analysis strategy: Logistic regression used to assess the influence of alcohol intake on cognitive impairment **Confounders:** Gender, age, educational level
Results, limitations, source of funding
• The odds for cognitive impairment were higher among abstainers and heavy drinkers compared to light drinkers (OR=1.51, [1.04, 2.18]; and 2.03, [1.17, 3.54], respectively) • The odds for cognitive impairment were higher among binge drinkers compared to non-binge drinkers (odds ratios ranged from OR=1.87, [1.04, 3.38] to OR=1.98, [1.05, 3.72]) • The odds for cognitive impairment were higher among those who passed out more than 2 times due to excess drinking compared to those who did not report pass-outs (OR=4.10, [1.54, 10.94]) • Among APOE 4 carriers: abstainers and heavy drinkers had higher odds for cognitive impairment compared to light drinkers (OR=1.96, [1.12, 3.41], OR=4.08, [1.85, 9.00], respectively) **Limitations:** 1. Social desirability bias associated with self-reported alcohol intake 2. Telephone interview to assess cognitive function is less specific and sensitive than clinical evaluation **Source of funding:** The Academy of Finland, the Sigrid Juselius Foundation and Clinical grants of Turku University Hospital (EVO)

Authors: Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y, Isogawa A… Tsugane S; JPHC Study Group **Year:** 2005 **Citation:** Diabetic Medicine 22(3): 323-331 **Country of study:** Japan **Aim of study:** To assess the influence of alcohol consumption and other risk factors on self-reported diabetes among middle-aged Japanese people **Study design:** Longitudinal **Quality score: (++, + or -):** +
Source population
Japanese residents of 14 administrative districts supervised by 4 public health centres 43,149 residents ages 40-59 years living in Ninohe, Karumai, Yokote, Omonogawa, Minami-Saku County, Gushikawa, Onna completed the baseline questionnaire in 1990 (response rates: 76% for men and 82% for women) 32,126 participants completed 5- and 10-year follow-up questionnaires
Study (eligible and selected) population
Analysis restricted to **28,893** eligible participants with complete data and who responded to the baseline, 5- and 10-year follow-up questionnaires (response rates: 70.4% for men and 78.2% for

women)

Follow-up: 10 years

Exclusion: Participants with the following characteristics at baseline:

1. Diabetes (n=1120)
2. Cardiovascular disease (n=470)
3. Chronic liver disease (n=311)
4. Kidney disease (n=546)
5. Cancer (n=689)
6. Missing exposure data (n=298)

Attrition: No significant differences in terms of BMI and lifestyle characteristics between those who responded to both follow-up questionnaires and those who did not

Exposures at midlife

Smoking habits, alcohol intake, and physical activity assessed through self-administered questionnaires

Smoking
Smokers classified as 'never smoked', 'former smokers', 'current smokers'

>'current smokers' further sub-divided into: smoked 1-19 or >=20 cigarettes/day

Alcohol use

Alcohol intake measured using data on type, frequency per week, and daily quantity consumed

Total daily alcohol intake was calculated, using the alcohol content of the following beverages in calculations: 23g ethanol per 180ml of sake, 36g ethanol per 180 ml of sochu or awamori, 10g ethanol per 30ml of whisky/brandy, 6g ethanol per 60ml of wine, 23g ethanol per 633ml of beer

Participants classified as 'non-drinkers and infrequent occasional drinkers' (consuming alcohol on 3 or fewer days per month) or 'drinkers' who were further subdivided by tertiles of daily ethanol consumption

Questionnaire measured alcohol use with high degree of validity

Physical activity

Physical activity assessed through questions on leisure time sports activities

If respondents participated in sports at least once a week, they were categorized as 'active'; otherwise, they were considered 'inactive'

Outcomes at 55 years or over

Men who reported diagnosis of incident type 2 diabetes at 5- and/or 10-year follow-up questionnaires

To determine the validity of self-reported diabetes diagnoses:

>a sample of medical records was reviewed, and diabetes diagnosis confirmed for 82%-94% of participants

>results from blood samples of volunteering participants were compared to self-reported diabetes diagnoses; sensitivity and specificity of study questionnaire for diabetic hyperglycemia were 46% and 98%, respectively

Analysis

Analysis strategy: Multiple logistic regression used to assess contributions of smoking, alcohol use, and physical activity on type 2 diabetes incidence over 10-year follow-up period

Confounders: Age, BMI (also assessed as effect modifier), family history of diabetes, hypertension

Effect modification: Sex, BMI

Results, limitations, source of funding

703 and 480 incident cases of diabetes among men and women, respectively, during 10-year follow-up period

Men

- The odds of developing diabetes over 10 years were higher among those smoking >=20 cigarettes/day and past smokers compared to never-smokers (OR=1.37, [1.11, 1.69]; OR=1.35, [1.08, 1.69], respectively)
- The odds of developing diabetes were higher among men drinking between 23-46g ethanol/day than 'non-drinkers and infrequent occasional drinkers' (OR=1.26, [1.02-1.56])

Women

- The odds of developing diabetes over 10 years were higher among those smoking >=20 cigarettes/day and past smokers compared to never-smokers (OR=2.94, [1.57, 5.50]; OR=2.77, [1.67, 4.61], respectively)

Stratification by BMI among males:

- Compared to 'non-drinkers and infrequent occasional male drinkers', the odds of developing diabetes over 10 years were higher among males consuming 23-46g/day and over 46g/day of ethanol (OR=1.91, [1.05, 3.46]; OR=2.89, [1.63, 5.11], respectively)

Limitations:

1. Self-reported information leading to possible under-estimation of OR
2. Possible follow-up bias between diabetic and non-diabetic categories (e.g. excess mortality among diabetic patients affecting response rate)

Source of funding: Grant-in-aid for Cancer Research and for the Second Term Comprehensive Ten-Year
Strategy for Cancer Control, and Health Sciences Research grants

Authors: Walda IC, Tabak C, Smit HA, Räsänen L, Fidanza F, Menotti A… Kromhout D

Year: 2002

Citation: European Journal of Clinical Nutrition 56(7): 638-643.

Country of study: Finland, Italy and The Netherlands

Aim of study: To investigate the relation of baseline antioxidant, fruit, vegetable and fish intake with chronic obstructive pulmonary disease mortality

Study design: Prospective study

Quality score: (++, + or -): +

Source population

Number of people: 2953

Demographics: Not reported

Study (eligible and selected) population

Number of people: 2917

Characteristics:

Finland Age in y (mean (s.d.) 59.1 (5.5), BMI in kg=m2 (mean (s.d.) 24.7 (3.8), Cigarette smoking Pack years (mean (s.d.) 21.2 (17.2), Current smoker (%) 50.4, Former smoker (%) 29.7, Never smoker (%) 19.8

Italy Age in y (mean (s.d.) 59.3 (4.9); BMI in kg=m2 (mean (s.d.) 26.0 (3.9); Cigarette smoking Pack years (mean (s.d.) 13.7 (13.9), Current smoker (%) 50.8, Former smoker (%) 19.5, Never smoker (%) 29.7 **The Netherlands** Age in y (mean (s.d.) 59.6 (5.4); BMI in kg=m2 (mean (s.d.) 25.1 (2.7); Cigarette smoking Pack years (mean (s.d.); 20.2 (15.2), Current smoker (%) 52.0, Former smoker (%) 40.3, Never smoker (%) 7.7 **Location:** Ilomantsi, Poytya and Mellila, Finland. Crevalcore and Montegiorgio, Italy. Zutphen, The Netherlands. **Recruitment strategy:** Not reported **Length of follow-up:** 20 years **Response rate and loss to follow-up:** Not reported **Eligible population:** Men aged 50-69 y at baseline **Excluded populations:** Not reported
Exposures at midlife
Relevant exposures: Diet **Time:** 1958 to 1965 **Measurement of exposure:** Dietary survey
Outcomes at 55 years or over
Outcomes: Chronic obstructive pulmonary disease mortality **Outcome measurement:** Clinical records, from family doctors, specialists and relatives and from other useful sources collected by local investigators **Time:** 1978-1985
Analysis
Analysis strategy: Cox Proportional Hazards Model **Confounders:** Country, age and smoking, BMI, energy intake, alcohol consumption
Results, limitations, source of funding
Number: 73 **Effect estimates:** Fruit intake (per 100 g) 0.86 (0.69 – 1.07) Vitamin E intake (per 5 mg), 0.93 (0.65 – 1.33) **Significant trends:** A protective effect of fruit and possibly vitamin E intake against COPD **Limitations:** Author: 1. Confidence intervals were wide 2. Validity and reproducibility of diet 3. Misclassification of intake 4. Data on food consumption from 1970 Reviewer: 1. Self-report for data on exposures 2. Residual confounding due to measurement error

Source of funding: Not reported

Authors: Wang L, Manson JE, Buring JE, Lee IM, Sesso HD

Year: 2008

Citation: Hypertension 51(4): 1073-9

Country of study: US

Aim of study: To determine the association between dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

39,876 US female health professionals ages 45 years and older and free of cardiovascular disease and cancer (except non-melanoma skin cancer) were randomized into the Women's Health Study in 1992-95 (baseline)

39,310 completed semi-quantitative food frequency questionnaire (SFFQ)

Study (eligible and selected) population

28,886 women

Mean age of 53.8 years

Follow-up: 10 years

Exclusion: Women with:

1. Insufficient completion of the SFFQ
2. Implausible total energy intake
3. Missing data on exposure
4. Pre-randomization cardiovascular disease or cancer
5. Baseline hypertension

Censoring: Women who developed cardiovascular disease over study period censored on date of cardiovascular disease diagnosis

Attrition: -

Exposures at midlife

Annual follow-up SFFQ used to assess portion size of each food item that participants consumed over the previous year with responses ranging from 'never or less than once per month' to '6+ per day'

Average daily intake calculated based on intake frequency and portion size of item

Total dairy product intake summed dairy items (e.g., low-fat dairy items include skim or low-fat milk, sherbet, yogurt, and cottage/ricotta cheese, high-fat dairy items include whole milk, cream, sour cream, ice cream, cream cheese, and other cheese)

Nutrient intake was calculated based on intake frequency of item as well as the nutrient content of the specified portion size

Pearson correlation coefficients between SFFQ responses and dietary records ranged from 0.25-0.79

Outcomes at 55 years or over

Self-reported incident hypertension defined as meeting one of the following: new physician diagnosis of BP; newly-initiated BP treatment; self-reported systolic BP >=140 mmHg; self-reported diastolic BP >=90 mmHg

Time of event was also captured

High validity of self-reported BP

Analysis

Analysis strategy: Cox regression model used to estimate the hazard ratio (presented as the relative risk of developing incident hypertension across quintiles of dairy intake

Confounders: Age, race, total energy intake, randomised treatment, smoking, alcohol use, exercise, postmenopausal, multivitamin use, BMI, history of diabetes and hypercholesterolemia, intake of fruit and vegetable, whole grain, red meat.

When dietary calcium and vitamin D were assessed: same confounders were included in the adjusted model as above, with the exception of: intake of fruit and vegetable, whole grain, red meat; also, additional confounders included in adjusted model were dietary sodium, fibre, saturated fats, and cholesterol

Results, limitations, source of funding

- 8,710 cases of incident hypertension identified during 10 years of follow-up
- The risk of hypertension was smaller across increasing quintiles of low-fat dairy products and total dairy products (trend test p-values: 0.001 and 0.0003)
- Trend test p-value was significant (p=0.002) for risk of hypertension across quintiles of intake of skim milk, although no clear direction of trend was evident (same observation applies to hypertension risk and quintiles of intake of dietary vitamin D, trend test p-value=0.02)
- Risk for hypertension appears to decrease with increasing intake of dietary calcium (p<0.0001)

Limitations:

1. Exposure was measured at a single point in time (subject to random error leading to underestimation of true association)
2. Self-reported outcome data
3. Residual confounding
4. Limited generalizability as cohort comprises predominantly white health professional women

Source of funding: National Institutes of Health, Bethesda, Md.

Authors: Wang L, Lee IM, Zhang SM, Blumberg JB, Buring JE, Sesso HD

Year: 2009

Citation: American Journal of Clinical Nutrition 89(3): 905-12

Country of study: USA

Aim of study: To assess the association between baseline flavonoid intake and the risk of total and site-specific cancers

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

39,876 female health professionals free of cardiovascular disease and cancer (except non-melanoma skin cancer) were assigned into the Women's Health Study, a randomized double-blind, placebo-controlled trial

39,876 women completed a validated semi-quantitative food-frequency questionnaire (SFFQ), which has been shown to have reasonable validity and reproducibility

Study (eligible and selected) population
38,408 women **Sociodemographics:** Predominantly white female health professionals **Follow-up:** Person-years of observation were calculated from time of randomization to cancer diagnosis, death, last day of follow-up, or 16 March 2007, whichever came first Average of 11.5 years of follow-up **Exclusion:** i) Insufficient completion of SFFQ (n=21) ii) Women with implausible daily energy intake [n=829] iii) Women with cardiovascular disease or cancer diagnosed before randomization but reported after randomization [n=59 **Attrition:** -
Exposures at midlife
At baseline, participants were asked how often they had consumed specified unit of each food item listed in questionnaire, with responses ranging from ‘never or less than once per month’ to ‘6+ per day’ Average daily intake of each food item was calculated by multiplying intake frequency by portion size of items Nutrient intake was calculated by multiplying unit intake frequency by nutrient content of portion size Total flavonoids were analysed and these included 3 flavonols (quercetin, kaempferol, myricetin) and 2 flavones (apigenin and luteolin); major sources of flavonoids analysed included apples, broccoli, onions, tofu, and tea
Outcomes at 55 years or over
Confirmed cancer cases, except non-melanoma skin cancer Every six months and then annually thereafter, data on newly-diagnosed cancer was collected through questionnaires Deaths ascertained through family member reports, postal authorities, National Death index; cancer was identified through pathology or cytology reports, or rarely, through clinical and radiologic or laboratory marker evidence
Analysis
Analysis strategy: Cox regression was used to assess the association between 1) intake of total and individual flavonoids, or the 2) intake of flavonoid-rich foods and incidence of total invasive cancer as well as site-specific cancers **Confounders:** Age, race, total energy intake, randomized treatment assignment, BMI, smoking, alcohol use, physical activity, postmenopausal status, hormone replacement therapy use, multivitamin use, family history of cancer in a parent or sibling, and intake of fruit and vegetables, fibre, folate, and saturated fat
Results, limitations, source of funding
• 3234 cancer cases identified during average of 11.5 years of follow-up • Incidence of total invasive cancer did not differ significantly across quintiles of total and individual quantified flavonoid intakes

- Lack of an association between total quantified flavonoid intake and incidence of common site-specific cancers (e.g. breast cancer, colorectal cancer, lung cancer, endometrial cancer, ovarian cancer); tests for linear trends in incidence of site-specific cancers across quintiles for each individual flavonoid were also non-significant
- No association between total and individual flavonoid intake and rare site-specific cancers (e.g. stomach, pancreatic, bladder, brain, thyroid, cervical cancer, lymphoma/leukemia)
- Similar lack of an association between intake of flavonoid-rich foods and total cancer, as well as site-specific common and rare cancers

Limitations:

1. Possible incomplete assessment of flavonoid intake due to missing information on certain flavonoid-containing food items
2. Quantities of flavonoids in food may differ by species variety, growth condition, maturation, preparation, and food-processing methods; therefore, these factors can contribute to random errors in intake assessment and bias results towards null
3. Random error of self-report (cumulative intake and dietary changes during follow-up not captured – can lead to underestimation of associations)
4. Lack of associations with cancer may have been due to small number of cases
5. Associations with cancer may have been present for different flavonoid intake amounts

Source of funding: None reported

Authors: Wang L, Lee IM, Manson JE, Buring JE, Sesso HD

Year: 2010

Citation: Archives of Internal Medicine 8;170(5): 453-61

Country of study: USA

Aim of study: To assess the association between alcohol consumption and risk of becoming overweight or obese in middle-aged and older women

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

39,876 US female health professionals ages 38-89 years and free of cardiovascular disease and cancer (except non-melanoma skin cancer) were randomised into the Women's Health Study in 1992-95 (baseline)

Study (eligible and selected) population

Of 19,563 women with a baseline BMI of 18.5-25 kg/m2, analysis was restricted to **19,220** women meeting inclusion criteria

Sociodemographics: Predominantly white female health professionals

Follow-up: Average 12.9 years of follow-up

Exclusion: Women with:

i) Missing data on baseline exposure [n=5]
ii) No updated outcome information during study period [n=128]
iii) Baseline diabetes [n=194]
iv) Pre-randomization cardiovascular disease or cancer [n=17]

Attrition: -

Exposures at midlife

Self-reported alcohol intake assessed using baseline, validated, semiquantitative food frequency questionnaire (SFFQ) that measured frequency of alcohol consumption over the past year with responses ranging from ‘never or less than once per month’ to ‘6+ per day’ Alcohol intake also took alcohol content of beverages into account, assuming ethanol of 13.2g for 360 ml beer, 10.8 g for 12. ml red or white wine, and 15.1 g for 45 ml liquor Total alcohol intake categorized as: 0, >0- <5, 5- <15, 15- <30, >= 30g/day Correlation coefficient comparing self-reported alcohol intake in questionnaire with diet records ranged from 0.81-0.90 SFFQ has demonstrated reasonable validity and reproducibility
Outcomes at 55 years or over
Incident cases of overweight or obesity assessed at 2-, 3-, 5-, 6-, and 9-year follow-up questionnaires for 19,220 women (16,322 of these women continued to have their weight updated at 11-, 12-, and 13-year follow-up time points) BMI was calculated using self-reported weight at follow-up and height at baseline, and categorized as: normal (18.5 to <25 kg/m2); overweight (25 to 30 kg/m2); obese (>=30 kg/m2) Cases of ‘overweight or obesity’ comprised women with a normal BMI at baseline and a BMI >=25 kg/m2 at follow-up Cases of ‘obesity’ comprised women with a normal BMI at baseline and a BMI>=30 kg/m2 at follow-up Time of event and censoring For cases, time of event was estimated from last-reported normal BMI to first reported BMI >=25 kg/m2 For non-cases, time of censoring was the latest date of reported normal BMI Women who developed diabetes during study period censored on date of diabetes diagnosis High correlation between self-reported weight and clinic-measured weight (r=0.97)
Analysis
Analysis strategy: Cox regression model used to estimate the hazard ratio (presented as the relative risk of becoming a) overweight or obese and b) obese across categories of total alcohol intake) **Confounders:** Race, baseline BMI, randomised treatment (vitamin E, aspirin, B-carotene, placebo), total non-alcohol energy intake, physical activity, smoking, post-menopausal status, post-menopausal hormone use, multivitamin use, history of hypercholesterolemia, hypertension, intake of fruit and vegetables, whole grains, refined grains, red meats and poultry, low-fat dairy products, high-fat dairy products, energy-adjusted total fat, carbohydrates, fibre
Results, limitations, source of funding
• Of 19,220 women with normal baseline BMI, 7,942 (41.3%) become ‘overweight or obese’ over 12.9 years of follow-up, and 732 (3.8%) became obese during this time • Increasing levels of alcohol consumed contributed to decreasing incidence of overweight or obesity (BMI >=25); this trend was observed for ‘all alcohol’, beer, red wine, white wine (trend test p-values: <0.0001, 0.04, < 0.0001, and <0.0001, respectively) • For example, the risk of overweight or obesity was smallest among those consuming 15-<30 g/day of ‘total alcohol’ compared to non-drinkers (RR=0.70, [0.62, 0.79]) • Increasing levels of alcohol consumed contributed to decreasing incidence of obesity (BMI >=30); this trend was observed for ‘all alcohol’, beer, red wine, white wine, liquor (trend test p-values: <0.0001, 0.02, 0.004, 0.0003, 0.005) • For example, the risk of obesity was smallest among those consuming >=30 g/day of ‘total alcohol’ compared to non-drinkers (RR=0.29, [0.15, 0.54])

- Similar inverse association between total alcohol intake and risk of becoming overweight or obese was observed for women in different age strata (<50, 50-<60, >=60), smoking strata, physical activity groups, and baseline BMI groups

Limitations:

1. Self-reported weight resulting in non-differential misclassification
2. Social desirability bias with respect to alcohol intake (under-report), and lack of information on change in alcohol drinking patterns over time
3. Residual confounding
4. Limited generalizability as participants were predominantly white female health professionals

Source of funding: National Institutes of Health, Bethesda, MD

Authors: Wang L, Manson JE, Gaziano JM, Buring JE, Sesso HD

Year: 2012

Citation: American Journal of Hypertension 25(2): 180-189

Country of study: USA

Aim of study: To determine the association between intake of total, subgroup, and individual items of fruits and vegetables and the risk of hypertension

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

39,876 US female health professionals ages 39-89 years, and free from cardiovascular disease and cancer (except non-melanoma skin cancer) were included in the Women's Health Study, a randomized, double-blind, placebo-controlled trial, with follow-up questionnaires every 6 months for the first year and annually thereafter

Study (eligible and selected) population

Analysis restricted to **28,082** out of 39,310 women who completed semi-quantitative food frequency questionnaire (FFQ)

Sociodemographics: Predominantly white female health professionals

Follow-up: Average follow-up of 12.9 years. Follow-up from randomization at baseline to the date of incident hypertension (outcome), the last day in the study, or Feb. 2007, whichever came first

Exclusion: Women with:

i) Hypertension (systolic BP>=140 mmHg or diastolic BP >=90 mmHg or history of anti-hypertensive treatment) at baseline (n=10,751)
ii) (Self-reported) implausible total daily energy intake [n=829]
iii) Pre-randomization cardiovascular disease or cancer [n=41]
iv) Missing FFQ items [n=21]
v) Incomplete outcome information [n=109]

Censoring: Women who developed cardiovascular disease over study period and whose treatment may influence BP

Attrition: -

Exposures at midlife

Self-reported fruit and vegetable consumption was assessed using validated FFQ that included 28 vegetable items and 16 fruit items

Participants were asked how often they had consumed a unit of each food item over the past year with responses ranging from ‘never or less than once per month’ to ‘6+ times per day’

Average daily intake of individual fruit and vegetable items was summed to create measures of a) total fruit, b) total vegetable, and c) total fruit and vegetable intake

Vegetables were also categorized into: green leafy vegetables; cruciferous vegetables; and dark and yellow vegetable

Pearson correlation coefficients comparing FFQ responses with dietary records ranged from 0.50-0.84

Outcomes at 55 years or over

Self-reported incident hypertension defined as meeting one of the following: physician diagnosis of BP; newly-initiated BP treatment; self-reported systolic BP >=140 mmHg; self-reported diastolic BP >=90 mmHg

Time of event was self-reported (correlation coefficient comparing self-reported with measured BP among health professionals: 0.60-0.72)

High validity of self-reported BP

Analysis

Analysis strategy: Cox models were used to assess influence of hypertension across levels of fruit and vegetable intake. Stratification by age, BMI, smoking status, baseline systolic/diastolic BP

Confounders: Age, race, total energy intake, randomised treatment (vitamin E, aspirin, B-carotene, placebo), smoking, alcohol use, exercise, postmenopausal status, postmenopausal hormone use, multivitamin supplement use, history of diabetes or hypercholesterolemia, intake of whole grains, red meats, low-fat dairy product, and nuts; if fruit intake was assessed, model was also adjusted for vegetable intake, and vice versa

Results, limitations, source of funding

- During 12.9 years of follow-up, 13,633 women developed incident hypertension
- There was a significant inverse association between baseline intake of apples, oranges, and raisins, and incidence of hypertension (trend test p-values: 0.03, 0.01, 0.0004);
- Women consuming 1 serving/week and 2-4 servings/week of strawberries had a slight increased risk for hypertension compared to women never or rarely consuming strawberries (trend test p-value: 0.04)
- Compared to women in the lowest category of intake (<0.2 servings/day) of dark-yellow vegetables, the risk of hypertension was lowest among women in the fourth (0.6-<1.0 servings/day) and highest (>=1.0 servings/day) categories of intake (HR=0.93, [0.87, 0.99]; HR=0.88, [0.82, 0.95], respectively)
- Trend tests between intake of cruciferous vegetables, dark-yellow vegetables, legumes, onions, and incident hypertension were significant (p<0.05); however, no clear direction was evident for the trend
- The risk of hypertension was lower among women consuming 0.6-<1.0 servings/day and >=1.0 servings/day of dark-yellow vegetables compared to women in the lowest intake category of <0.2 servings/day (HR=0.93, [0.87, 0.99]; HR=0.88, [0.82, 0.95], respectively)

<u>Stratification by BP:</u> There was a significant interaction of baseline BP with fruit intake:

- >Among women with baseline systolic/diastolic BP <120/80 mmHg, the risk of hypertension decreased with increasing total fruit intake (trend test p-value=0.003); no trend observed for BP >=120/80 mmHg

Limitations:

1. Fruit and vegetable intake measured at one point in time (baseline), thus introducing possible measurement error and non-differential misclassification

2. Self-reported outcome data again leading to misclassification
3. Residual confounding by unmeasured or imprecisely measured hypertension risk factors
4. Limited study generalizability due to homogeneity of cohort in terms of race, education, and SES

Source of funding: National Institutes of Health, Bethesda, MD, along with an investigator-initiated grant from the California Strawberry Commission, Watsonville, CA

Authors: Wannamethee SG, Shaper AG, Walker M

Year: 2001

Citation: British Journal of Cancer 85(9): 1311-1316

Country of study: England

Aim of study: To assess physical activity and risk of cancer in middle-aged men

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

Prospective study of 7735 men ages 40-59 years selected from registers of general practices in 24 towns in England, Wales and Scotland; initially examined in 1978-80

Study (eligible and selected) population

7630 men with available data

Follow-up: Follow-up of 18.8 years achieved for 99% of cohort

Exclusion: Excluded men who were diagnosed with cancer prior to or in the same year as screening [n=42]

Attrition: -

Exposures at midlife

Physical activity assessment: regular walking or cycling (weekday journeys including travel to and from work), recreational activity (gardening, pleasure walking, do-it-yourself jobs) and sporting (running, golf, swimming, tennis, sailing, digging)

Total physical activity score calculated for each participant based on frequency and type (intensity) of activity
>categories used: inactive and occasional; light; moderate; moderately vigorous; vigorous

Outcomes at 55 years or over

Cancer cases up to Dec. 1997 ascertained from death certificates, cancer registry, postal questionnaires mailed to surviving members in 1992, 1996, 1998

Analysis

Analysis strategy: Cox proportional hazards model used to assess effects of physical activity on risk of cancer

Confounders: Age, BMI, alcohol consumption, smoking, social class

Results, limitations, source of funding

- 969 cases out of 7588 men

- Men who engaged in vigorous physical activity had a significantly reduced risk of total cancers compared to those who did not or engaged in occasional activity (RR=0.65, [0.44, 0.88])
- The greater the physical activity level, the lower the risk for total cancers (sig. trend, p<0.0001)
- Moderate-vigorous exercise was associated with a significantly reduced risk of combined upper digestive tract cancer (oral, esophagus, stomach cancer) (OR=0.37 [0.16, 0.86])
- Vigorous exercise was associated with a significantly increased risk of bladder cancer [OR=2.06, (1.08, 3.95)]

Limitations: Residual confounding, i.e. diet

Source of funding: Department of Health, University College Medical School, London

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Authors: Wannamethee SG, Shaper AG

Year: 2002

Citation: Heart 87(1): 32-36

Country of study: UK

Aim of study: Examine effects of taking up regular drinking by middle aged non-drinkers and occasional drinkers on major coronary heart disease events and total mortality

Study design: Prospective cohort study

Quality score: (++, + or -): +

Source population

Number of people: 7,735 men

Demographics: Not reported

Study (eligible and selected) population

Number of people: 7,157 men

Characteristics:

TT (292). Mean age (years) 51.1: Never smoked 43.2: Current smoker (Q5) 28.1: Active (Q1) 38.3
Ex (299). Mean age (years) 51.2: Never smoked 16.1: Current smoker (Q5) 40.8: Active (Q1) 29.6
Stable occ (1150). Mean age (years) 49.7: Never smoked 30.9: Current smoker (Q5) 29.9: Active (Q1) 41.3
New occ (782). Mean age (years) 50.1: Never smoked 25.1: Current smoker (Q5) 33.7: Active (Q1) 38.0
New reg (305). Mean age (years) 49.4: Never smoked 24.5: Current smoker (Q5) 30.1: Active (Q1) 44.0
Reg (3675). Mean age (years) 49.6: Never smoked 22.8: Current smoker (Q5) 32.6: Active (Q1) 41.3

Location: England, Wales, and Scotland

Recruitment strategy: Men aged 40–59 years selected from the age–sex registers of general practices in each of 24 towns in England, Wales, and Scotland

Length of follow-up: 16.8 years (CI) 15.5 to 18.0 years

Response rate and loss to follow-up: 78% and 99%

Eligible population: Men in Britain

Excluded populations: Women

Exposures at midlife

Relevant exposures: Smoking, drinking, physical activity

Time: 1978–1980

Measurement of exposure: Never smoked, ex-smokers at both Q1 and Q5, ex-smokers at Q5 only, and two groups of current cigarette smokers at Q5 (1–19 and > 20/day).

A physical activity score was derived on the basis of frequency and type of activity: inactive, occasional, light, moderate, moderately vigorous, and vigorous.

Eight drinking categories: non-drinkers; occasional drinkers: < 2 units a month; light drinkers: weekend, three to six drinks a day; weekdays, one to two drinks a day; 1–15 units/week; moderate drinkers: weekend, more than six drinks a day; weekdays, three to six drinks a day; 15–42 units/week; heavy drinkers: more than six drinks a day; > 42 units/week.

In men without diagnosed coronary heart disease alcohol categories were classified into six groups: Teetotallers; Ex-drinkers; stable occasional; new occasional; new regular drinker and Stable regular drinkers

Outcomes at 55 years or over

Outcomes: Risk of mortality and major coronary heart disease events

Outcome measurement: All deaths and all major coronary heart disease events occurring in the period were recorded

A major coronary heart disease event includes non-fatal myocardial infarction, fatal myocardial infarction, and sudden cardiac death classified as caused by coronary heart disease

Information on non-fatal myocardial infarction was obtained from reports provided by general practitioners, supplemented by regular two yearly reviews of the general practice records and by self-reported questionnaires

Time: Up to December 2000

Analysis

Analysis strategy: Cox proportional hazards model. Adjustments for risk factors were based on risk factors measured at Q1 and Q5. In the adjustment, age and body mass index were fitted as continuous variables, and physical activity (six levels), smoking (five levels), social class (seven levels), employment status (yes/no), self-rated health and recall of stroke (yes/no), and diabetes (yes/no) were fitted as categorical variables

Confounders: Relative risk adjusted for age, social class, smoking, BMI, physical activity, employment status, pre-existing stroke, diabetes, regular drug treatment, and self-assessed health status. Adjustment for physical activity is based on physical activity data at screening.

Results, limitations, source of funding

Number: 654 men

Effect estimates:

Diagnosed coronary heart disease by alcohol group

TT (43) 95% CI

CHD mortality
Cases 17
Rate/1000 p-y 34.0
Adjusted RR 1.71 (0.92 to 3.15)

CVD mortality
Cases 21
Rate/1000 p-y 42.0
Adjusted RR 1.62 (0.93 to 2.82)

Total mortality
Cases 28
Rate/1000 p-y 56.0
Adjusted RR 1.31 (0.82 to 2.10)

Ex (59) 95% CI

CHD mortality
Cases 22
Rate/1000 p-y 37.1
Adjusted RR 1.56 (0.89 to 2.73)

CVD mortality
Cases 26
Rate/1000 p-y 43.8
Adjusted RR 1.49 (0.89 to 2.49)

Total mortality
Cases 39
Rate/1000 p-y 65.7
Adjusted RR 1.46 (0.96 to 2.22)

Stable occ (112)

CHD mortality
Cases 31
Rate/1000 p-y 22.8
Adjusted RR 1.00

CVD mortality
Cases 38
Rate/1000 p-y 27.9
Adjusted RR 1.00

Total mortality
Cases 57
Rate/1000 p-y 41.9
Adjusted RR 1.00

New occ (87)
CHD mortality
Cases 27
Rate/1000 p-y 26.0
Adjusted RR 95% CI 1.05 (0.62 to 1.79)

CVD mortality
Cases 33
Rate/1000 p-y 31.8
Adjusted RR 1.07 (0.66 to 1.74)

Total mortality
Cases 46
Rate/1000 p-y 44.3
Adjusted RR 1.00 (0.67 to 1.51)

New reg (37)
CHD mortality
Cases 12
Rate/1000 p-y 29.6
Adjusted RR 95% CI 1.19 (0.60 to 2.34)

CVD mortality
Cases 16
Rate/1000 p-y 39.4
Adjusted RR 1.30 (0.72 to 2.37)

Total mortality
Cases 23
Rate/1000 p-y 56.7
Adjusted RR 1.23 (0.75 to 2.04)

Reg (316)
CHD mortality
Cases 106
Rate/1000 p-y 28.3
Adjusted RR 95% CI 1.33 (0.88 to 2.00)

CVD mortality
Cases 129
Rate/1000 p-y 34.4
Adjusted RR 1.33 (0.92 to 1.93)

Total mortality
Cases 182
Rate/1000 p-y 48.6
Adjusted RR 1.25 (0.92 to 1.69)

Significant trends: Among men with a diagnosis of CHD the teetotallers and ex-drinkers had an increased adjusted risk of mortality from CHD and CVD compared with stable occasional drinkers. new regular drinkers showed no benefit for CHD mortality, and some increase (non-significant) in CVD and total mortality was observed compared with stable occasional drinkers

Limitations: No limitations reported by the author

Source of funding: Not reported

Authors: Wannamethee SG, Shaper AG

Year: 2003

Citation: American Journal of Clinical Nutrition 77(5): 1312-1317

Country of study: UK

Aim of study: To assess the influence of alcohol consumption patterns on body weight and weight gain

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

7,735 men ages 40-59 years selected from registers of general practices of 24 towns in England, Wales and Scotland were examined from Jan. 1978 to July 1980 as part of the British Regional Heart Study

Response rate: 78%

At baseline, questionnaires were administered to participants, physical measurements were made and blood samples drawn

7,275 of the surviving participants completed a postal questionnaire in 1983-85 to assess changes in health behaviours and other risk factors

Study (eligible and selected) population

7,608 men

Follow-up: 5 years

Exclusion: Men with diagnosed diabetes at baseline (n=118)

Attrition: -

Exposures at midlife

Baseline

Frequency, quantity and type of alcohol measured at baseline and after 5 years, with the following categories used to classify participants: non-drinkers; occasional drinkers (<1 unit/week); light-moderate (1-20 units/week), including weekend drinkers of 1-2 or 3-6 units/day and daily drinkers of 1-2 units/day; heavy (21-42 units/week), including weekend drinkers of >6 units/day and daily drinkers of 3-6 units/day; very heavy (>42 units/week), comprising daily drinkers of >6 units/day

1 unit of alcohol is approx. 10 g alcohol

Exposure was validated using biochemical and hematologic measurements

After 5 years

Participants were asked about past and current drinking habits, and same drinking categories used as those at baseline

Men classified into stable or changed groups on the basis of intake reported at baseline and after 5 years:

Stable groups: Stable non-occasional (non-drinkers or occasional drinkers at baseline who remained non-drinkers or occasional drinkers after 5 years); stable light-moderate (light-moderate drinkers at both waves); stable heavy (heavy or very heavy drinkers at both waves)

Changed groups: Light-moderate to none-occasional (light-moderate drinkers at baseline who reported being non-drinkers or occasional drinkers after 5 years; none-occasional to light-moderate (non-drinkers or occasional drinkers at baseline who reported light-moderate drinking after 5 years); ex-heavy (heavy or very heavy drinkers at baseline who reported being non-drinkers, occasional drinkers, or light-moderate drinkers at after 5 years); new heavy (none-occasional and light-moderate drinkers at baseline who reported heavy or very heavy drinking after 5 years).

Outcomes at 55 years or over

BMI was measured at baseline and 5 years later using height and weight measurements (kg/m2)

High BMI: >=28 or upper quintile of BMI distribution of men at baseline

Percentage change in body weight since baseline screening calculated:

Weight loss was defined as a loss of >=4% of body weight, weight gain as a gain of >=4% of body weight, while stable weight was weight gained or lost that was <4% of body weight

The following weight change categories were used: weight loss; stable (weight); gain of 4-10%; gain of >10% of body weight

Analysis

Analysis strategy: Logistic regression was used to assess the influence of alcohol consumption patterns on body weight and weight gain

Confounders: Age, social class, physical activity, cigarette smoking, initial BMI

Results, limitations, source of funding

- The proportion of men with high BMI increased significantly with higher levels of alcohol intake at baseline
- At baseline: stable heavy and ex-heavy drinkers had the highest proportion of men with BMI>=28 (20.8% and 23.5%, respectively)
- 5 years after baseline: stable (continuing) heavy drinkers and new heavy drinkers had the highest

proportion of men with BMI >=28 (25.7% and 27.2%, respectively)

- The odds of weight gain >=4% over 5 years were greater for stable heavy drinkers compared to stable none-occasional drinkers (OR=1.29 [1.10, 1.51])
- The odds of weight gain >=4% over 5 years were greater for new heavy drinkers compared to the stable none-occasional group (OR=1.45, [1.09, 1.92])

Stratification by smoking:

- Among non-smokers, the odds of weight gain >=4% were greater for stable heavy drinkers compared to stable none-occasional drinkers (OR=1.75, [1.19, 2.56])
- Among non-smokers, the odds of weight gain >=4% were greater for ex-heavy drinkers compared to stable none-occasional drinkers (OR=1.55, [1.07, 2.25])

Limitations: Findings cannot be generalised to women

Source of funding: None reported

Authors: Waring ME, Eaton CB, Lasater TM, Lapane KL

Year: 2010

Citation: American Journal of Epidemiology 171(5): 550-556

Country of study: USA

Aim of study: Incident diabetes in relation to weight patterns during middle age

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

5,209 men and women ages 28-62 years, living in Framingham, Massachusetts, and without clinically apparent cardiovascular disease were enrolled in Framingham Heart Study in 1948-52

Biennial study visits involved an interview, a clinical examination, and laboratory tests

Study (eligible and selected) population

1,476 participants

Follow-up: From age 50 years to the first examination with diagnosis of incident diabetes or the last examination attended

Exclusion:

Of 5,079 who provided informed consent, the following were excluded:

i) Enrolled in the FHS cohort after 40 years of age [n=3,071]
ii) Did not attend FHS examinations after age 50 [n=218]
iii) Those missing BMI measurements at several study waves [n=213]

Of 1,577 study participants, individuals excluded were those:

i) Who were consistently underweight [n=20]
ii) With diabetes before 50 years [n=23]
iii) With missing data on covariates [n=58]

Attrition: -

Exposures at midlife

Weight patterns during middle age (40-50 years) were assessed using principal component analysis

BMI from age 40 to 50 years was calculated and guided by standard BMI cut-offs (BMI<25, BMI 25-29.9, BMI>=30), participants were categorized as being normal weight, overweight, or obese

Weight change was also measured and categorized as: weight loss, stable weight, and weight gain

Weight cycling was also assessed

Outcomes at 55 years or over

Type 2 diabetes was ascertained through assessment of non-fasting plasma glucose level and/or reported treatment with insulin or medication for diabetes

Analysis

Analysis strategy: Cox proportional hazards regression was used to analyse the influence of weight patterns on incident diabetes

Confounders: Gender, education, family history of diabetes, weight status at age 25 years, physical activity, smoking, alcohol use, hormone use, weight change, weight cycling

Results, limitations, source of funding

- 217 cases of type 2 diabetes diagnosed over 35,359 person-years of follow-up
- Diagnosis made at median age of 67.8 years
- Adults who were overweight during middle age had 2.9 times the rate of diabetes incidence (HR=2.9, [2.0, 4.1]) as those who were normal weight during middle age
- Adults who were obese had 7.7 times the rate of diabetes (HR=7.7, [4.9, 12.1]) as those who were normal weight

Limitations:

1. Fasting glucose measurements not available; study definition of diabetes may have been less sensitive than American Diabetes Association criteria
2. Potential misclassification of diabetes diagnosis date (unlikely to explain results)
3. Residual confounding due to measurement error and unmeasured variables (potential misclassification of smoking, alcohol, and hormone use at time of diagnosis; recall bias in recalled weight; information lacking on current or previous pregnancies/history of gestational diabetes)
4. Biannual measurements limited ability to detect changes occurring more frequently than every two years

Source of funding: None reported

Authors: Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K

Year: 2005

Citation: Neurology 64(2): 277-281

Country of study: USA

Aim of study: Evaluate if midlife cardiovascular risk factors are associated with risk of late-life dementia

Study design: Retrospective cohort study

Quality score: (++, + or -): +

Source population

Number of people: 11,368

Demographics: Not reported

Study (eligible and selected) population

Number of people: 8,845

Characteristics:

Diagnosis of dementia

No Age at MHC exam, y 41.97 (1.42); Age in 1994, y 68.37 (2.64); Age at end of follow-up, y 76.59 (3.34); Female 4,341 (53.4); Male 3,783 (46.6); Race White 5,952 (73.6), Black 1,285 (15.9), Asian 511 (6.3), Other 360 (4.4); Education Grade school 1,093 (13.5), High school 2,766 (34.1), Trade school 529 (6.5), College 3,606 (44.4), Unknown 130 (1.6); Marital status Married 6,646 (81.8), Never married 412 (5.1), Divorced/widowed/separated 754 (9.3), Unknown 312 (3.8)

Yes Age at MHC exam, y 42.25 (1.39); Age in 1994, y 69.32 (2.43); Age at end of follow-up, y 74.86 (3.41); Female 410 (56.9), Male 311 (43.1); Race White 499 (69.2), Black 165 (22.9), Asian 31 (4.3), Other 26 (3.6); Education Grade school 132 (18.3), High school 240 (33.3), Trade school 45 (6.2), College 291 (40.4), Unknown 13 (1.8); Marital status Married 543 (75.3), Never married 35 (4.9), Divorced/widowed/separated 95 (13.2), Unknown 48 (6.7)

Location: San Francisco, Oakland. USA

Recruitment strategy: Members of the Kaiser Permanente Medical Care Program

Length of follow-up: 30 years

Response rate and loss to follow-up: Not reported

Eligible population: Participants ages 40 to 44 who were still members of the health plan in 1994

Excluded populations: Nine participants with missing data for sex were excluded, 1,700 with missing smoking information were excluded, and 814 with missing cholesterol information were excluded

Exposures at midlife

Relevant exposures: Diet and smoking

Time: 1964 to 1973

Measurement of exposure: Interview

Outcomes at 55 years or over

Outcomes: Dementia

Outcome measurement: Medical records

Time: January 1994 to April 2003

Analysis

Analysis strategy: Cox proportional hazards model

Confounders: Age at mid-life exam, age at start of case ascertainment, race, education, and sex

Results, limitations, source of funding

Number: 721

Effect estimates:

HR (95% CI)

Hypertension 1.24 (1.04–1.48)

Diabetes 1.46 (1.19–1.79)

High cholesterol 1.42 (1.22–1.66)

Smoking 1.26 (1.08–1.47)

Cardiovascular composite score

1 1.27 (1.02–1.58)

2 1.69 (1.34–2.12)

3 2.31 (1.71–3.11)

4 2.37 (1.10–5.10)

Significant trends: Presence of multiple cardiovascular risk factors at midlife substantially increases risk of late-life dementia in a dose dependent manner

Limitations:

Author:

1. Did not have the ability to determine subtypes of dementia
2. Self-report of physician diagnoses, medication use, and smoking

Reviewer

1. Self-report for data on exposures
2. Residual confounding due to measurement error

Source of funding: The National Institutes of Health (1K12AR47659)

Authors: Wiles NJ, Haase AM, Gallacher J, Lawlor DA, Lewis G

Year: 2007

Citation: American Journal of Epidemiology 165(8): 946-54

Country of study: Wales

Aim of study: To determine the association between leisure-time and occupational physical activity on common mental disorder among middle-aged men

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

2,512 men ages 45-59 years living in Caerphilly, South Wales took part in 1979-83 cohort study

Study (eligible and selected) population

2,398 men who participated in 1979-83 survey (phase I) and who had moved into the study area were re-contacted and invited to participate in 1984-88

Follow-up: Participants surveyed in 1984-88 (phase II – study baseline) followed-up until 1989-93 (phase III) and, again, until 1993-97 (phase IV)

Study population of men participating in phases II-III: n=1,158

Study population of men participating in phases II-IV: n=1,016

Sociodemographics: 53% of men employed at phase II, mean age of 57 years, 87.5% were married, two thirds were from lower social classes

Exclusion: Participants with prevalent common mental disorder in phase II and non-cases taking antidepressants excluded

Attrition: Of the 1,703 men who formed the total longitudinal analysis, 442 and 606 participants had missing outcome data in phases III and IV (possible loss to follow-up), respectively

Exposures at midlife

Phase II (baseline) leisure-time physical activity assessed using Minnesota Leisure Time Physical Activity questionnaire measuring type, frequency, and duration of activities in the last 12 months

>Total energy expenditure on activities calculated and divided into low, medium, and high categories; percentage of heavy-intensity physical activity divided into none, low, and high

Physical activity at current work or in last job held assessed using self-administered questionnaire (modified from the Health Insurance Plan questionnaire) focusing on time spent walking, sitting, and lifting/carrying, with scores ranging from 1 (least active) to 4 (most active)

Outcomes at 55 years or over

Common mental disorders, comprising anxiety and depression, measured at phases II and IV using validated psychiatric disorders screening questionnaire. Incident cases based on either:

a) Meeting predefined cut-off score on screening questionnaire and report of antidepressant use in phase II or IV
b) Report of antidepressant/ anxiolytic use in phase II or IV

Analysis

Analysis strategy: Logistic regression used to assess association between leisure-time or occupational physical activity and common mental disorder during phases II-III and phases II-IV, separately

Confounders for 5-year follow-up analysis (phase II-III): Age, social class, marital status, employment status, smoking habits, alcohol consumption, social support, BMI, phase II common mental disorders score, phase II HDL cholesterol level, change in triglyceride level between phase II and phase III, phase II job demand variables

Confounders for 10-year follow-up analysis (phase II-IV): Age, social class, marital status, employment status, smoking habits, alcohol consumption, social support, BMI, phase II common mental disorder score, phase II HDL cholesterol level, change in triglyceride level between phase II and phase IV, and phase II job demand variables

Results, limitations, source of funding

5-year follow-up:

- The odds of a common mental disorder at phase III were lower among those with low and high percentage of leisure time spent in heavy-intensity activity at phase II (OR=0.61, [0.40, 0.93], and OR=0.54, [0.35, 0.83], respectively)

10-year follow-up:

- The odds of a common mental disorder at phase IV were higher among those with increasing job class activity at phase II (significant results ranging from OR=1.85, [1.06, 3.23] to OR=2.41, [1.48, 3.92])

Limitations:

1. Possible exposure and outcome (non-differential) misclassification. E.g. measuring physical activity at one point in time may cause misclassification; also, measuring disease at 2 time points may have missed relapsing cases that occurred between these two time point
2. Residual confounding: should have included other measures of SES status, e.g. housing tenure
3. Participants who were physically active in their leisure time may lead healthier lifestyles (thus; other unmeasured variables may account for observed association)
4. Cannot generalize results to women

Source of funding: Medical Research Council (MRC)

Authors: Willcox BJ, He Q, Chen R, Yano K, Masaki KH, Grove JS… Curb JD

Year: 2006

Citation: JAMA 296(19): 2343-2350

Country of study: USA

Aim of study: To test whether midlife biological, lifestyle, and sociodemographic risk factors are associated with overall survival and exceptional survival

Study design: Prospective cohort study

Quality score: (++, + or -): ++

Source population

Number of people: 8,006

Demographics: Japanese American middle-aged men (mean age, 54 [range, 45-68] years)

Study (eligible and selected) population

Number of people: 5,820

Characteristics:

Exceptional. Age at baseline, y 55.5 (5.2): Height, cm 163.2 (5.4): Weight, kg 61.8 (7.8): BMI in youth 21.8 (1.9): Ever smoker, No. (%) 364 (56.4): Smoking, pack-years 14.0 (19.6): High alcohol consumption (3 drinks/d), No. (%) 42 (6.8) 76: Alcohol consumption, oz/mo 10.3 (16.3): Physical activity index 32.8 (4.3)

Usual, Diseased. Age at baseline, y 55.0 (5.6): Height, cm 162.9 (5.6): Weight, kg 63.1 (8.0): BMI in youth 22.0 (2.0): Ever smoker, No. (%) 469 (62.4): Smoking, pack-years 18.8 (22.4): High alcohol consumption (3 drinks/d), No. (%) 76 (10.3): Alcohol consumption, oz/mo 12.0 (20.9): Physical activity index 32.6 (4.1)

Usual, Disabled: Age at baseline, y 51.7 (3.4): Height, cm 162.6 (5.6): Weight, kg 63.3 (8.8): BMI in youth 22.1 (2.1): Ever smoker, No. (%) 663 (62.8): Smoking, pack-years 19.4 (22.0): High alcohol consumption (3 drinks/d), No. (%) 123 (11.4): Alcohol consumption, oz/mo 12.6 (24.8): Physical activity index 33.4 (4.8)

Nonsurvival: Age at baseline, y 54.1 (5.5): Height, cm 163.0 (5.7): Weight, kg 63.3 (9.8): BMI in youth 22.3 (2.3): Ever smoker, No. (%) 2561 (76.1): Smoking, pack-years 28.1 (25.5): High alcohol consumption (3 drinks/d), No. (%) 592 (17.6): Alcohol consumption, oz/mo 16.7 (26.9): Physical activity index 32.9 (4.5)

Location: Island of Oahu

Recruitment strategy: Not reported

Length of follow-up: Up to 40 years (1965-2005)

Response rate and loss to follow-up: Not reported

Eligible population: Island inhabitants

Excluded populations: Not reported

Exposures at midlife

Relevant exposures: Smoking status, alcohol consumption, and physical activity

Time: Not reported

Measurement of exposure: High alcohol intake was dichotomized as 3 or more drinks/d (based on an increased risk of mortality in the HHP/HAAS cohort) or less than 3 drinks/d.

Smoking was dichotomized as ever or never.

Outcomes at 55 years or over
Outcomes: Overall survival and exceptional survival **Outcome measurement:** 1 of 4 phenotypes: a) Non-survivors — men who died before a specified age (75, 80, 85, or 90 years) b) So-called "usual survivors but disabled"—men who survived until the specified age but with physical or cognitive disability and with or without a major chronic disease; c) Usual survivors with major chronic diseases but no disability d) Exceptional survivors **Time:** Not reported
Analysis
Analysis strategy: Continuous variables were dichotomized as high or low based on conventional cut-off points or median values. Odds ratios for mortality vs survival (for each specified age) and, among survivors, for having at least 1 morbid condition vs being free of these conditions were estimated using logistic regression models. Backward stepwise logistic regression was used to select a subset of variables in the final model (including variables significant at the .10 level). **Confounders:** Age-Adjusted
Results, limitations, source of funding
Number: 5, 820 **Effect estimates:** **Age-Adjusted ORs of Selected Risk Factors for Death (Nonsurvival) or Unhealthy Survival (Usual Survival) at Age 85** <u>Nonsurvival vs Survival</u> *OR (95% CI) P Value* Ever smoker 2.05 (1.83-2.29) .001 High alcohol consumption (3 drinks/d) 1.97 (1.68-2.31) .001 <u>Usual Survival vs Exceptional Survival</u> *OR (95% CI) P Value* Ever smoker 1.27 (1.06-1.53) .01 High alcohol consumption (3 drinks/d) 1.84 (1.29-2.62) .001 **Stepwise Logistic Regression Model of Risk of Death (Nonsurvival) or Unhealthy Survival (Usual Survival) at Age 85 Years** <u>Nonsurvival† vs Survival</u> *OR (95% CI) P Value* Lifestyle Ever smoker 1.94 (1.72-2.18) .001 High alcohol consumption (3 drinks/d) 1.58 (1.34-1.88) .001 <u>Usual Survival‡ vs Exceptional Survival§</u> *OR (95% CI) P Value* Lifestyle Ever smoker 1.23 (1.01-1.50) .04 High alcohol consumption (3 drinks/d)

1.61 (1.11-2.34) .01

Significant trends: Never smoking is associated with overall survival but has only a borderline association with exceptional survival.

Limitations:

Authors:

1. Study population consists of ethnic Japanese men which limits generalizability (applicability to women)
2. Cohort effects
3. Excluded men with chronic diseases at baseline

Reviewers: Do not report findings for physical activity

Source of funding: This study was supported by contract N01-HC-05102 from the National Heart, Lung, and Blood Institute, contract N01-AG-4-2149 and grants 5 U01 AG019349-05, R01 AG027060-01 (Hawaii Lifespan Study), and K08 AG22788-02 from the National Institute on Aging, and grant 2004-0463 from the Hawaii Community Foundation

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Authors: Xu Q, Anderson D, Courtney M

Year: 2010

Citation: Health Care for Women International 31(12): 1082-1096

Country of study: Australia

Aim of study: To determine the influence of lifestyle factors on mental outcomes

Study design: Longitudinal

Quality score: (++, + or -): -

Source population

10,923 women from South East Queensland, Australia recruited from rural and urban areas

Study (eligible and selected) population

886/1,500 women ages 45-60 years were recruited and participated in 2001 survey and of these participants, 564 agreed to participate again in 2006

Analysis restricted to **564** women

2006 response rate: 37.6%

Follow-up: Non-response for 2006 survey due to:

i) Migration out of study area [n=2]
ii) Death [n=3]
iii) Non-participation [n=28]
iv) Address change [n=104]
v) Loss to follow-up [n=13]
vi) Other reasons for non-response [n=172]

Sociodemographics: Mean age of women was 55 years

78.1% (n=438) of women were married or in relationships; 83.1% (n=466) were born in Australia; 28.4% (n=159) were college-educated; 40.8% (n=219) did not have paid employment; 41.8% (n=236) had family annual income less <= $40,000

Exclusion: -

Attrition: 322/886 women dropped out between 2001 and 2006.

Women lost to follow-up were slightly younger than those who remained (54.36 vs. 54.95 years, p=0.003)

Exposures at midlife

Physical activity measure assessed frequency of participation in exercise each week using the following response options:

>None
>1-2 times/week
>3-4 times/week
>5-6 times/week

Alcohol use was measured using the following options:

>Never
>Drank in past
>Occasionally
>Regularly

Smoking status was categorised as:

>Never smoker
>Past smoker
>Current smoker

Caffeine consumption was dichotomized (yes/no)

Outcomes at 55 years or over

General mental well-being, and psychological symptoms including depression and anxiety were measured using SF-36 and the self-reported Greene Climacteric Scale (GCS) questionnaire, respectively

Test-retest reliability of the GCS is 0.87

Analysis

Analysis strategy: Logistic regression was used to determine the influence of lifestyle factors on mental outcomes

Confounders: BMI, sociodemographics, menopausal status, mental health status in 2001

Results, limitations, source of funding

- Women who exercise 5-6 times per week scored 1 point lower on the anxiety scale (p=0.013), 1 point lower on the depression scale (p=0.001), 2 points lower on the psychological scale (p=0.002), and 9 points higher on the mental well-being scale (p=0.001) compared to women who did not exercise
- Women who smoked had a 6.725 point lower score in mental well-being than non-smokers (p=0.006)
- Women who consumed caffeinated drinks regularly had a lower mental well-being by 5 points compared to those who did not drink caffeinated beverages
- Past alcohol drinkers reported lower anxiety scores compared to non-drinkers (p=0.040)

Limitations:

1. Physical activity measurement did not include intensity and duration
2. Alcohol measurement may be imprecise; potentially useful to assess volume of alcohol consumption

Source of funding: None reported

Authors: Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K

Year: 2001

Citation: Archives of Internal Medicine 161(14): 1703-8

Country of study: USA

Aim of study: To determine whether physical activity is associated with the risk of developing cognitive decline

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

9,704 predominantly white community-dwelling women 65 years of older recruited from Baltimore, Minneapolis, the Monongahela Valley near Pittsburgh, and Portland in the United States and examined in 1986-88 (baseline)

Participants examined at baseline visit also underwent biennial clinic visits and completed annual questionnaires

Study (eligible and selected) population

Analysis restricted to **5,925** participants with cognitive test measurements at baseline and follow-up 6 and 8 years later

Follow-up: Mean of 7.5 years of follow-up

Sociodemographics: The mean age of women across quartiles of expended energy was 70.2-71.7 years, and the mean number of years of education across energy quartiles were 12.3-13.4 years

Exclusion:

i) Black women
ii) Women unable to walk without assistance or who had bilateral hip replacements
iii) Women with baseline cognitive impairment [n=950], with missing baseline cognitive scores [n=53] with baseline physical limitations [n=939], with missing information on physical limitations [n=10], and women who did not complete the baseline physical activity assessments [n=51]
iv) Women who died [n=596], were unavailable for follow-up [n=238], did not have follow-up cognitive measurements [n=942]

Attrition: Women without cognitive follow-up measurements had lower baseline scores on cognitive testing and were less physically active compared to participants (p<0.001)

Exposures at midlife

Self-reported baseline physical activity was assessed using:

a) Interview questions on walking and stair climbing, and
b) A reliable scale measuring the frequency and duration of participation per week during the past year in 33 different physical activities (used to calculate kilocalories expended per week)

Outcomes at 55 years or over

Cognitive assessment using MMSE performed at baseline, and follow-up 6 and 8 years later

Analysis

Analysis strategy: logistic regression was used to assess the influence of physical activity (blocks walked per week or total kilocalories expended per week) on cognitive function in all women, as well as in sub-groups of women ages <=70 or >70 years; women with educational level <12 or >=12 years; and among those with or without of co-morbidities

Confounders: Baseline age, educational level, health status, functional limitation, depression score, stroke, diabetes, hypertension, myocardial infarction, smoking, oestrogen use

Results, limitations, source of funding

- 1178 (20%) participants developed cognitive decline over 7.5 years of follow-up
- Analysis of blocks walked per week (n=5,921):
  >the odds of cognitive declined were lowest among the two highest physical activity quartiles compared to the lowest activity quartile (OR=0.63 [0.52, 0.77]; OR=0.66 [0.54, 0.82])
- Analysis of total kilocalories expended per week (n=5,925):
  > the odds of cognitive decline were lowest among the two highest physical activity quartiles compared to the lowest activity quartile (OR=0.78 [0.64, 0.96]; OR=0.74 [0.60, 0.90])
- The odds of cognitive decline were low among those in the highest physical activity quartile regardless of age, comorbidities, education, (same findings observed when physical activity was assessed as blocks walked per week or kilocalories expended per week)

Limitations:

1. Self-reported data (recall bias)
2. Clinical assessment for dementia not performed, therefore cannot determine cause of cognitive decline
3. Sample was not racially diverse

Source of funding: Public Health Service, Bethesda, Md.

Authors: Yu S, Yarnell JW, Sweetnam PM, Murray L; Caerphilly study

Year: 2003

Citation: Heart 89(5): 502-6

Country of study: Wales

Aim of study: To assess the influence of leisure or job physical activity on all-cause, CHD, or CVD mortality

Study design: Longitudinal

Quality score: (++, + or -): +

Source population

2,512 men ages 45-59 years were recruited in 1979-1983 from Caerphilly and its surrounding villages

Study (eligible and selected) population

Analysis restricted to **1975** men, including those re-examined in 1984-88 and men who had moved into the study area

Follow-up: Mean follow-up of 10.5 years

Follow-up from date of examination in 1984-88 to date of death or Sept. 25, 1997

Exclusion:

i) Men with symptomatic evidence of CHD, history of myocardial infarction, grade 1 or grade 2 angina, probable ischemia [n=393]
ii) Men who died within two years of study inception [n=30]
iii) Deaths from congenital anomalies or injury and poisoning were censored for analyses of all-cause mortality (n=7)
iv) Men with missing data on variables related to the job physical activity questionnaire (n=23)

Attrition: -

Exposures at midlife
Physical activity was assessed using self-administered questionnaires: Leisure physical activity Validated baseline Minnesota Leisure Time Physical Activity questionnaire administered in 1984-1988 to assess type and duration of leisure activities during the previous 12 months and to estimate energy expenditure (expressed as an activity index [AI] in kcal/day) >4 AI scores characterized each person, one for each class of intensity activity and their sum total AI Job physical activity Job physical activity questionnaire (slightly modified Health Insurance Plan questionnaire) used to assess physical activity at work, or at last job with categories ranging from low to high occupational physical activity
Outcomes at 55 years or over
Mortality from all causes, CVD, and cancer were ascertained using the National Health Service Central Registry
Analysis
Analysis strategy: Cox proportional hazards regression was used to assess the influence of leisure or job physical activity on all-cause, CHD, or CVD mortality **Confounders (for analysis of total activity during leisure):** Age, diastolic blood pressure, BMI, smoking status, social class (manual), family history of CHD among first degree relatives before age 55, history of diabetes mellitus in the past 5 years, job physical activity class **Confounders (for analysis of heavy intensity activity during leisure):** Confounders listed above, combined light and moderate intensity activity
Results, limitations, source of funding
252 total deaths over 10 years, with 111 deaths being caused by CVD, 82 by CHD, and 98 by cancer Analysis of total activity during leisure: • The greater the kcal/day consumed through total activity during leisure, the smaller the risk of CHD death (trend p-value=0.039) • People expending 395.5-2747.2 kcal/day had a lower risk of CHD death than those expending 0.0-161.6 kcal/day (HR=0.55, [0.31, 0.98]) Analysis of heavy intensity activity during leisure: • The greater the energy expenditure of heavy intensity activity during leisure at baseline, the smaller the risk of all-cause death, CVD death, and CHD death during follow-up (trend p-values: 0.006, 0.001, and 0.009, respectively) • People expending 23.9-2142.9 kcal/day had a lower risk of all-cause death, CVD death, and CHD death than those expending 0.0-0.6 kcal/day (HR=0.61, [0.43, 0.86]; HR=0.38, [0.21, 0.67]; HR=0.36, [0.18, 0.73], respectively) **Limitations:** 1. Lack of information on changes of physical activity over time can cause misclassification 2. Men with low levels of leisure-time physical activity at baseline may have already been sick; thus, the illness may have been the cause rather than the result of lack of physical activity 3. Self-reported data resulting in potential misclassification **Source of funding:** British Heart Foundation and the Medical Research Council

APPENDIX C – Quality summary of cohort studies

Key to headings – Section 1: Population; 1.1 source population; 1.2 eligible population; 1.3 selected participants or areas. Section 2: Methods of Selection; 2.1 comparison group; explanatory variables; 2.3 contamination; 2.4 confounding factors; 2.5 setting applicability to the UK. Section 3: Outcomes; 3.1 reliable outcome measures; 3.2 outcome measurement; 3.3 important outcomes assessed; 3.4 follow-up time in exposure;. NA: not applicable; NR: not reported.

	Population							Method of selection of exposure (or comparison) group							Outcomes							
Author (Year)	**1**	**1.2**	**1.2b**	**1.3.**	**1.3b**	**1.3c**	**1.3d**	**2.1**	**2.2**	**2.3**	**2.3b**	**2.4a**	**2.4b**	**2.5**	**3.1**	**3.1b**	**3.1c**	**3.2**	**3.3**	**3.3b**	**3.4**	**3.4b**
Agahi (2013)	-	-	-	-	-	-	-	+	+	NA	NA	-	-	+	-	NR	NR	+	NA	NA	NA	NA
Agrigoroarei 2011	+	++	+	++	+	+	++	+	++	NA	NA	+	-	-	+	NR	NR	-	NA	NA	NA	NA
Akbaraly (2013)	+	+	-	+	+	-	+	-	++	NA	NA	-	-	++	++	NR	+	++	NA	NA	++	++
Alonso (2009)	-	-	-	-	++	-	+	+	++	NA	NA	+	+	-	++	NR	NR	++	NA	NA	++	++
Andel (2008)	-	+	-	+	+	-	-	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	-
Anttila (2004)	-	-	-	-	++	+	-	+	+	NA	NA	+	+	-	++	NR	NR	+	NA	NA	++	++
Ascherio (2001)	+	++	-	-	+	-	+	+	+	NA	NA	-	-	-	++	NR	NR	++	NA	NA	NA	NA
Baba (2006)	-	-	-	-	++	NR	++	++	++	NA	NA	-	+	-	++	NR	NR	++	NA	NA	++	++
Beulens (2007)	+	+	NR	+	++	++	++	++	++	NA	NA	++	++	+	++	NR	NR	+	NA	NA	++	++
Beulens (2008)	-	-	-	-	NR	+	+	++	++	NA	NA	+	+	-	-	NR	++	+	NA	NA	++	++
Bielak (2012)	+	++	+	++	++	+	++	++	++	NA	NA	+	+	-	+	+	+	+	+	NA	NA	-
Blanco-Cedres 2002	+	++	+	+	+	+	+	-	NR	NA	NA	-	-	-	++	+	-	+	NA	NA	NA	++
Boudik (2004)	-	-	-	+	-	NR	-	NR	-	NA	NA	-	-	-	++	+	-	-	NA	NA	NA	NA
Britton (2008)	-	+	-	+	++	+	++	NR	NR	NA	NA	-	-	++	+	+	-	++	NA	NA	NA	NA
Carlson (2008)	+	++	+	+	++	+	++	NR	++	NA	NA	++	++	-	+	NR	++	+	NA	NA	NA	NA
Chang (2010)	-	-	-	-	NR	-	-	NR	NR	NA	NA	-	-	-	++	++	NR	++	NA	NA	NA	NA
Chang (2013)	-	-	-	-	+	+	+	NR	NR	NA	NA	-	-	-	++	+	-	++	NA	NA	++	NA

	Population							Method of selection of exposure (or comparison) group							Outcomes							
Author (Year)	**1**	**1.2**	**1.2b**	**1.3.**	**1.3b**	**1.3c**	**1.3d**	**2.1**	**2.2**	**2.3**	**2.3b**	**2.4a**	**2.4b**	**2.5**	**3.1**	**3.1b**	**3.1c**	**3.2**	**3.3**	**3.3b**	**3.4**	**3.4b**
Christensen (2006)	-	-	-	-	++	NR	NR	-	++	NA	NA	-	-	+	-	NR	NR	+	NA	NA	NA	NA
Debette (2011)	.	++	-	++	+	-	++	+	+	NA	NA	+	-	-	+	NR	NR	-	NA	NA	NA	-
Dudas (2007)	-	++	+	++	++	++	++	+	+	NA	NA	+	-	+	-	-	-	++	++	NA	NA	-
Ekelund (2005)	-	++	+	-	-	+	-	+	++	NA	NA	+	+	++	++	+	+	+	+	NA	+	++
Elwood (2013)	+	+	+	++	++	+	++	NR	++	NA	NA	++	++	++	++	+	++	++	+	NA	NA	NA
Emberson (2005)	-	++	+	+	++	-	-	-	+	NA	NA	-	-	++	-	-	-	-	+	NA	NA	++
Englund (2011)	-	-	-	-	-	-	+	-	+	NA	NA	-	-	+	-	-	-	-	+	NA	NA	-
Englund (2013)	-	-	-	-	-	-	+	-	+	NA	NA	-	-	+	-	-	-	-	+	NA	NA	-
Eskelinen (2008)	-	+	-	-	+	-	-	-	+	NA	NA	+	+	+	-	+	+	+	+	NA	NA	-
Eskelinen (2009)	+	+	-	-	++	+	-	NR	+	NA	NA	-	-	-	++	+	-	+	NA	NA	NA	NA
Field (2009)	-	+	+	-	+	+	+	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	++
Fogelholm (2000)	-	+	-	+	-	+	+	+	+	NA	NA	-	-	++	-	NR	NR	+	NA	NA	+	+
Friedland (2001)	-	+	+	+	+	-	+	+	+	NA	NA	-	-	-	++	++	++	+	+	NA	NA	-
Gerber (2012)	++	+	+	+	+	+	++	++	++	NA	NA	++	++	+	++	++	++	++	++	NA	NA	NA
Guallar-Castillon (2012)	+	+	+	-	+	+	-	-	+	NA	NA	+	+	-	++	++	+	++	+	NA	+	+
Haaponen-Niemi (2000)	-	++	++	+	++	+	+	+	+	NA	NA	+	+	-	++	++	+	++	+	NA	+	+
Halperin (2008)	-	-	-	-	-	+	-	-	+	-	-	+	+	-	+	-	-	+	+	-	+	+
Hamer (2013)	-	++	+	++	++	+	++	+	++	NA	NA	++	++	++	-	-	+	+	+	NA	+	-
Happonen (2004)	-	-	-	-	-	-	-	-	+	NA	NA	+	+	+	++	+	+	++	+	NA	+	+

	Population							Method of selection of exposure (or comparison) group							Outcomes							
Author (Year)	**1**	**1.2**	**1.2b**	**1.3.**	**1.3b**	**1.3c**	**1.3d**	**2.1**	**2.2**	**2.3**	**2.3b**	**2.4a**	**2.4b**	**2.5**	**3.1**	**3.1b**	**3.1c**	**3.2**	**3.3**	**3.3b**	**3.4**	**3.4b**
Hara (2002)	-	-	-	-	-	+	-	-	+	NA	NA	+	+	-	-	+	+	++	+	NA	+	++
Harmsen (2006)	-	+	-	-	+	+	-	+	+	NA	NA	-	-	++	+	-	+	++	+	NA	+	++
He (2004)	+	+	NR	-	NR	-	+	+	++	NA	NA	-	-	-	-	NR	NR	+	NA	NA	++	+
Hodge (2013)	-	+	++	+	+	+	+	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	-
Holmberg (2006)	-	-	NR	-	+	+	-	++	-	NA	NA	+	+	+	++	NR	NR	++	NA	NA	-	-
Holme (2007)	+	+	+	+	-	-	+	-	++	NA	NA	-	-	++	++	++	NR	++	NA	NA	++	++
Holtermann (2009)	-	-	NR	-	++	+	+	+	++	NA	NA	-	-	+	++	NR	NR	+	NA	NA	++	NA
Holtzman (2004)	+	+	-	+	++	+	+	+	++	NA	NA	++	++	-	+	NR	NR	+	NA	NA	NA	NA
Hu (2003)	-	-	-	-	+	+	+	+	+	NA	NA	+	+	-	-	+	-	+	+	NA	NA	++
Hu (2004)	-	+	+	+	+	+	+	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	++
Hu (2005)	-	+	-	+	+	+	+	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	++
Hu (2007) Mov Disord	-	-	-	-	+	+	+	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	++
Hughes (2010)	-	-	-	-	-	-	+	+	+	NA	NA	++	+	-	+	+	+	+	+	NA	NA	-
Humphries (2001)	-	-	-	-	+	+	+	-	+	NA	NA	+	+	++	++	+	++	+	+	NA	+	+
Inoue (2004)	+	+	+	+	++	+	+	+	+	NA	NA	+	+	-	-	-	-	+	+	NA	+	+
Iso (2004)	-	-	+	+	++	+	+	+	+	NA	NA	+	+	-	-	-	-	+	+	NA	+	+
Jakobsen (2009)	-	+	+	-	-	+	+	+	++	NA	NA	++	+	-	+	+	+	+	+	NA	NA	++
Janzon (2004)	-	-	-	-	+	-	-	-	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	+
Johnsen (2006)	-	-	+	-	-	-	-	-	+	NA	NA	+	-	-	+	+	+	+	+	NA	NA	+
Kareholt (2011)	-	-	-	+	+	+	-	+	+	NA	NA	+	+	-	+	-	++	-	-	NA	NA	+
Kato (2009)	+	-	+	-	+	+	-	+	+	NA	NA	+	+	-	+	+	-	-	+	NA	-	-
Kesse-Guyot (2012)	-	-	-	-	-	-	-	-	+	+	+	+	+	-	+	-	+	-	+	-	+	+
Khalili (2002)	+	-	-	-	+	+	-	-	+	NA	NA	-	-	-	+	+	+	+	+	NA	NA	++

	Population							Method of selection of exposure (or comparison) group							Outcomes							
Author (Year)	**1**	**1.2**	**1.2b**	**1.3.**	**1.3b**	**1.3c**	**1.3d**	**2.1**	**2.2**	**2.3**	**2.3b**	**2.4a**	**2.4b**	**2.5**	**3.1**	**3.1b**	**3.1c**	**3.2**	**3.3**	**3.3b**	**3.4**	**3.4b**
Kesse-Guyot (2012)	-	-	-	-	-	-	-	-	+	+	+	+	+	-	+	-	+	-	+	-	+	+
Khalili (2002)	+	-	-	-	+	+	-	-	+	NA	NA	-	-	-	+	+	+	+	+	NA	NA	++
Kimm (2011)	-	+	+	-	++	+	+	+	+	NA	NA	-	-	-	+	-	-	+	+	NA	+	+
King (2007)	-	+	+	+	-	-	-	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	-
Knopman (2001)	+	++	+	++	-	+	++	+	+	NA	NA	+	+	-	++	+	+	+	NA	NA	++	+
Lahti (2010)	-	+	+	+	+	+	+	++	+	NA	NA	-	+	-	-	+	+	-	+	NA	NA	-
Laitala (2009)	+	++	+	+	++	++	++	++	++	NA	NA	++	++	++	++	++	NR	+	NA	NA	++	+
Laitinen (2006)	-	+	-	-	++	+	+	+	+	NA	NA	-	+	-	++	+	NR	++	NA	NA	NA	NA
Lajous (2013)	+	-	+	+	NR	+	++	++	++	NA	NA	++	++	-	++	+	+	+	NA	NA	++	+
Lang (2007)	+	+	+	+	+	+	+	+	+	NA	NA	-	-	-	+	+	NR	+	NA	NA	+	+
Langlois (2001)	+	-	+	-	++	-	+	+	++	NA	NA	+	+	-	+	++	NR	++	NA	NA	++	++
Laurin (2004)	+	-	+	-	++	+	++	++	+	NA	NA	+	+	-	++	++	NR	+	NA	NA	++	++
Lehto (2013)	-	-	-	-	-	-	-	+	+	NA	NA	+	+	-	+	+	+	-	-	NA	NA	-
Lesodottir 2007	+	++	+	+	-	+	+	+	++	NA	NA	+	+	+	++	+	+	+	NA	NA	NA	+
Levitan (2007)	-	+		-	-	+	+	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	-
Levitan (2009)	-	+		-	-	+	+	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	++
Levitan (2010)	-	+	+	-	-	+	+	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	++
Lim (2013)	+	-	+	+	++	+	+	+	+	NA	NA	+	+	-	+	+	+	+	NA	NA	++	++
Lin (2003)	++	++	++	+	-	+	+	+	+	NA	NA	+	+	-	+	+	+	+	++	NA	NA	++
Liu (2003)	+	+	+	+	-	+	++	++	++	NA	NA	+	+	-	-	NR	++	+	NA	NA	++	+

	Population							Method of selection of exposure (or comparison) group							Outcomes							
Author (Year)	**1**	**1.2**	**1.2b**	**1.3.**	**1.3b**	**1.3c**	**1.3d**	**2.1**	**2.2**	**2.3**	**2.3b**	**2.4a**	**2.4b**	**2.5**	**3.1**	**3.1b**	**3.1c**	**3.2**	**3.3**	**3.3b**	**3.4**	**3.4b**
Liu (2004)	+	++	++	++	++	+	++	++	+	NA	NA	+	-	-	++	+	+	++	NA	NA	+	++
Malmberg (2006)	+	+	+	-	++	+	-	-	+	NA	NA	+	+	-	-	-	-	-	-	NA	NA	+
Mannami (2004)	+	-	+	-	-	+	+	+	+	NA	NA	+	+	-	+	++	+	+	+	NA	NA	++
Masaki (2003)	-	+	-	+	-	+	+	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	++
Meisinger (2007)	-	+	+	+	+	+	+	+	+	NA	NA	-	-	-	++	+	+	+	+	NA	NA	++
Menotti (2000)	+	-	+	-	+	+	-	-	+	NA	NA	+	+	-	+	+	+	++	+	NA	NA	-
Menotti (2006)	+	-	-	-	+	+	-	-	++	NA	NA	++	++	-	+	+	+	++	+	NA	NA	-
Menotti (2012)	-	-	-	-	+	+	+	+	+	NA	NA	+	+	+	+	NR	NR	-	NA	NA	+	+
Meyer (2011)	-	-	-	-	+	+	+	+	+	NA	NA	+	+	+	+	NR	NR	-	NA	NA	+	+
Miura (2004)	+	-	+	-	-	+	-	++	++	NA	NA	+	+	++	++	+	++	+	NA	NA	++	++
Moayyeri (2009)	-	+	+	+	+	+	-	+	+	NA	NA	+	+	-	++	++	++	+	+	NA	NA	-
Morgan (2012)	-	+	+	+	++	+	+	+	+	NA	NA	+	+	++	+	+	+	+	+	NA	NA	+
Mursu (2008)	-	-	-	-	++	+	-	-	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	++
Nafziger (2007)	+	-	-	-	+	+	+	-	-	-	-	+	+	-	++	+	+	++	+	NA	NA	-
Nakamura (2009)	+	+	+	++	+	+	+	+	+	NA	NA	-	-	-	+	+	+	++	+	-	+	-
Nakayama (2000)	+	-	+	-	+	-	+	-	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	-
Noborisaka (2013)	-	+	+	-	+	+	-	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	-
Nokes (2012)	+	++	+	+	+	+	+	+	++	NA	NA	+	+	+	++	+	++	++	+	NA	NA	NA
Nooyens (2008)	-	+	+	+	+	+	+	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	-
Nooyens (2011)	-	+	-	+	+	+	-	+	+	NA	NA	+	+	-	+	+	++	-	+	NA	NA	-

	Population							Method of selection of exposure (or comparison) group							Outcomes							
Author (Year)	**1**	**1.2**	**1.2b**	**1.3.**	**1.3b**	**1.3c**	**1.3d**	**2.1**	**2.2**	**2.3**	**2.3b**	**2.4a**	**2.4b**	**2.5**	**3.1**	**3.1b**	**3.1c**	**3.2**	**3.3**	**3.3b**	**3.4**	**3.4b**
Osler (2003)	+	+	+	+	+	+	++	++	+	NA	NA	+	+	++	++	+	NR	+	NA	NA	+	++
Ostbye (2002)	-	-	+	-	NR	+	+	+	+	NA	NA	+	+	-	-	NR	NR	+	NA	NA	++	+
Ostenson (2012)	-	-	++	-	+	+	+	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	+
Otani (2003)	+	-	+	+	-	+	-	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	++
Patel (2006)	-	+	+	+	++	+	-	+	+	NA	NA	+	+	-	++	+	+	+	+	NA	NA	+
Patja (2005)	++	-	+	+	+	-	-	+	+	NA	NA	++	++	+	++	++	++	++	+	NA	NA	NA
Pelkonen (2000)	-	-	+	-	++	+	+	+	+	NA	NA	-	-	-	++	++	++	++	+	NA	NA	+
Pitsavos (2004)	-	-	++	-	++	+	+	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	++
Preis (2010)	-	-	-	-	-	-	+	+	+	NA	NA	++	++	-	++	++	++	++	+	NA	NA	++
Qiao (2000)	-	-	+	-	-	-	+	-	+	NA	NA	-	-	-	++	++	++	++	+	NA	NA	++
Qiu (2003)	-	+	+	+	++	+	+	++	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	++
Raikkonen (2001)	-	+	+	-	-	+	+	+	+	NA	NA	+	+	-	+	+	+	+	+	NA	NA	-
Rantakomi (2009)	+	+	+	+	-	+	+	+	+	NA	NA	+	+	-	++	++	++	++	+	NA	NA	-
Ravona-Springer (2013)	-	+	+	+	+	+	+	+	+	NA	NA	+	+	+	NA	NA	-	+	+	+	NA	NA
Riserus (2007)	+	+	+	+	++	+	++	+	++	NA	NA	+	+	NA	NA	++	+	+	+	NA	NA	++
Ross (2000)	-	-	+	-	-	-	-	+	+	NA	NA	+	+	+	NA	NA	++	+	+	+	NA	NA
Rovio (2005)	-	+	+	+	+	+	++	++	+	NA	NA	+	+	+	NA	NA	-	+	+	+	NA	NA
Rovio (2007)	-	+	+	+	+	+	++	++	+	NA	NA	+	+	+	NA	NA	-	+	+	+	NA	NA
Ruder (2011)	+	++	++	++	++	++	++	++	++	NA	NA	+	++	NA	NA	NA	NA	+	++	NA	NA	NA
Rusanen (2011)	-	+	+	+	+		+	+	++	NA	NA	+	+	+	NA	NA	-	+	+	+	NA	NA

	Population							Method of selection of exposure (or comparison) group							Outcomes							
Author (Year)	**1**	**1.2**	**1.2b**	**1.3.**	**1.3b**	**1.3c**	**1.3d**	**2.1**	**2.2**	**2.3**	**2.3b**	**2.4a**	**2.4b**	**2.5**	**3.1**	**3.1b**	**3.1c**	**3.2**	**3.3**	**3.3b**	**3.4**	**3.4b**
Ruusunen (2010)	-	-	+	-	-	-	++	+	+	NA	NA	+	+	+	NA	NA	-	+	+	+	NA	NA
Sabia (2008)	+	++	+	++	+	+	+	+	++	NA	NA	+	+	NA	NA	++	+	+	+	NA	NA	++
Sabia (2009)	+	++	+	++	-	+	+	+	++	NA	NA	+	+	NA	NA	++	+	+	+	NA	NA	++
Sabia (2011)	++	++	+	++	-	+	++	+	+	NA	NA	+	+	NA	NA	++	+	+	+	NA	NA	++
Sairenchi (2004)	+	+	+	+	-	+	++	++	-	NA	NA	+	++	NA	NA	++	++	+	++	NA	NA	++
Samieri (2013)	-	+	+	-	-	+	+	+	+	NA	NA	+	+	+	NA	NA	-	+	+	+	NA	NA
Satoh (2006)	+	-	+	-	-	-	+	+	+	NA	NA	++	++	+	NA	NA	-	++	++	+	NA	NA
Seccareccia (2003)	+	+	+	+	++	+	+	+	+	NA	NA	++	++	+	NA	NA	-	++	++	+	NA	NA
Shaper (2003)	++	++	++	++	+	+	++	+	+	NA	NA	+	+	+	NA	NA	++	+	+	+	NA	NA
Sobue (2002)	++	+	+	-	+	+	++	+	+	NA	NA	++	++	+	NA	NA	++	++	++	+	NA	NA
Song (2004)	-	-	+	-	++	-	+	+	+	-	-	+	+	+	-	-	++	+	+	+	-	-
Song (2006)	-	-	+	-	++	-	+	+	+	-	+	+	+	-	-	+	++	+	+	-	-	+
Stevens (2009)	-	++	++	++	++	+	++	+	+	NA	NA	++	++	+	NA	NA	++	++	++	+	NA	NA
Strand (2013)	-	-	+	++	++	+	++	+	+	NA	NA	+	++	+	NA	NA	++	+	++	+	NA	NA
Strandberg (2008)	-	+	-	+	++	+	-	+	+	NA	NA	+	++	+	NA	NA	++	+	++	+	NA	NA
Strandhagen (2000)	-	++	++	++	+	+	+	+	+	NA	NA	+	++	+	NA	NA	-	+	++	+	NA	NA
Sun (2010)	-	-	+	-	++	+	-	+	++	NA	NA	++	++	+	NA	NA	-	++	++	+	NA	NA
Sun (2011)	+	+	+	-	++	+	+	+	++	NA	NA	++	++	NA	NA	++	+	++	++	NA	NA	++
Szoeke (2006)	-	+	+	++	+	+	+	+	+	NA	NA	++	++	+	NA	NA	-	++	++	+	NA	NA
Tabak (2001)	-	-	+	-	NR	+	-	+	+	NA	NA	+	+	NA	NA	+	++	+	+	NA	NA	+
Tsugane (2004)	-	+	+	-	-	-	+	+	+	NA	NA	+	+	+	NA	NA	++	+	+	+	NA	NA

	Population							Method of selection of exposure (or comparison) group							Outcomes							
Author (Year)	**1**	**1.2**	**1.2b**	**1.3.**	**1.3b**	**1.3c**	**1.3d**	**2.1**	**2.2**	**2.3**	**2.3b**	**2.4a**	**2.4b**	**2.5**	**3.1**	**3.1b**	**3.1c**	**3.2**	**3.3**	**3.3b**	**3.4**	**3.4b**
Tuomilehto (2004)	-	-	-	-	+	-	+	+	+	NA	NA	+	+	+	NA	NA	++	+	+	+	NA	NA
Tyas (2003)	-	+	++	+	+	+	+	+	+	NA	NA	+	+	+	NA	NA	-	+	+	+	NA	NA
Valtonen (2002)	+	+	+	-	+	+	+	+	+	NA	NA	+	+	+	+	+	-	+	+	NA	NA	NA
Villegas (2010)	++	++	++	++	++	++	++	++	+	NA	NA	+	+	+	NA	NA	++	+	+	+	NA	NA
Villegas (2011)	++	++	++	++	++	++	++	++	+	NA	NA	+	+	+	NA	NA	++	+	+	+	NA	NA
Virta (2010)	+	+	++	+	++	++	+	++	++	NA	NA	+	+	+	++	++	++	++	NA	NA	NA	++
Waki (2005)	+	-	+	-	+	+	++	+	-	NA	NA	+	-	NA	NA	NA	NA	+	-	NA	NA	NA
Walda (2002)	+	-	++	-	++	+	+	+	+	NA	NA	+	+	+	NA	NA		+	+	+	NA	NA
Wang (2008)	-	-	-	-	+	+	+	+	++	NA	NA	+	+	NA	NA	NA	NA	+	+	NA	NA	NA
Wang (2009)	+	NR	NR	NR	NR	NR	+	NR	++	NA	NA	++	++	++	++	++	++	++	+	NA	NA	NA
Wang (2012)	+	NR	NR	NR	NR	NR	+	NR	++	NA	NA	++	++	++	+	+	+	+	+	NA	+	+
Wannamethee (2001a) Br.J. Canc.	++	++	+	++	++	+	++	+	++	NA	NA	+	+	++	++	++	++	++	+	+	NA	NA
Wannamethee (2001b) Diab. Care	++	++	+	++	++	+	++	+	++	NA	NA	+	+	++	++	++	++	++	+	+	NA	NA
Wannamethee (2002)	-	+	+	+	++	+	+	+	+	NA	NA	-	+	+	NA	NA	++	-	+	+	NA	NA
Wannamethee (2003)	-	+	-	-	+	-	-	+	-	NA	NA	NR	+	NA	NA	NA	NA	NR	+	NA	NA	NA
Waring (2010)	++	++	++	++	-	+	+	++	++	NA	NA	++	++	+	NA	NA	++	++	++	+	NA	NA
	Population							**Method of selection of exposure (or comparison) group**							**Outcomes**							

Author (Year)	1	1.2	1.2b	1.3.	1.3b	1.3c	1.3d	2.1	2.2	2.3	2.3b	2.4a	2.4b	2.5	3.1	3.1b	3.1c	3.2	3.3	3.3b	3.4	3.4b
Whitmer (2005)	-	-	+	-	-	-	-	-	+	NA	NA	+	+	+	NA	NA	+	+	+	+	NA	NA
Willcox (2006)	++	++	+	+	NR	+	++	NR	++	NA	NA	+	+	++	++	++	+	++	+	NA	NA	++
Wiles (2007)	+	+	+	++	++	+	++	+	++	NA	NA	++	++	++	+	++	++	++	++	NA	NA	NA
Xu (2010)	+	+	-	-	-	-	-	NR	+	NA	NA	-	-	-	+	+	NR	+	NA	NA	NA	NA
Yaffe (2001)	+	-	-	+	+	-	+	++	+	NA	NA	-	-	-	+	NR	NR	+	NA	NA	NA	NA
Yu (2003)	-	-	+	-	+	-	++	++	+	NA	NA	-	-	++	-	NR	NR	++	NA	NA	NA	NA

Key to headings – Section 3.5 follow-up time meaningful; 4: Analyses; 4.1 powered to; 4.2 multiple explanatory variables; 4.3 analytical methods; 4.4 precision. Section 5: summary; 5.1 internally validity; 5.2 externally validity. NA: not applicable; NR: not reported.

			Analyses							Summary			
Author (Year)	**3.5**	**3.5b**	**4.1**	**4.1b**	**4.2**	**4.3**	**4.4**	**4.4b**	**4.4c**	**5.1**	**5.1b**	**5.2**	**Ranking**
Agahi (2013)	NA	-	NR	NR	+	-	++	+	++	-	+	+	-
Agrigoroarei (2011)	NA	NA	NR	NR	+	+	++	++	++	+	+	+	+
Akbaraly (2013)	NA	++	NR	NR	+	-	++	++	++	-	+	+	+
Alonso (2009)	NA	NR	NR	NR	+	++	++	++	++	++	+	+	+
Andel (2008)	++	+	-	+	+	+	+	+	+	+	+	+	+
Anttila (2004)	++	+	NR	NR	-	+	++	-	+	+	+	-	+
Ascherio (2001)	++	++	NR	NR	++	+	++	+	++	+	+	+	++
Baba (2006)	NA	++	NR	NR	++	+	++	+	++	+	+	+	+
Beulens (2007)	++	NR	NR	NR	++	++	++	++	++	++	++	-	++
Beulens (2008)	++	NR	NR	NR	++	++	++	++	++	+	++	-	+
Bielak (2012)	+	+	-	+	+	+	++	++	+	+	+	+	+
Blanco-Cedres (2002)	NA	NR	NR	NR	-	+	++	++	++	-	++	+	+
Boudik (2004)	++	NR	NR	NR	-	-	++	++	++	-	+	-	-
Britton (2008)	++	NA	NR	NR	-	-	++	++	++	-	+	-	+
Carlson (2008)	NA	NA	NR	NR	++	++	++	++	++	++	++	+	++
Chang (2010)	++	+	NR	NR	-	-	++	++	NR	-	+	-	-
Chang (2013)	NA	NA	NR	NR	-	-	++	++	++	-	+	-	-

			Analyses							Summary			
Author (Year)	**3.5**	**3.5b**	**4.1**	**4.1b**	**4.2**	**4.3**	**4.4**	**4.4b**	**4.4c**	**5.1**	**5.1b**	**5.2**	**Ranking**
Christensen (2006)	++	NA	NR	NR	-	-	++	-	+	-	-	-	-
Debette (2011)	++	++	-	+	+	-	++	++	++	+	-	+	+
Dudas (2007)	++	++	-	++	+	-	++	++	++	-	+	++	++
Ekelund (2005)	+	+	-	+	+	++	+	+	+	+	+	+	+
Elwood (2013)	++	++	NR	NR	++	++	+	++	+	+	++	++	++
Emberson (2005)	++	++	-	++	+	-	++	++	+	+	+	++	++
Englund (2011)	+	++	-	-	+	+	+	+	-	-	-	+	-
Englund (2013)	+	+	-	-	+	+	+	+	-	-	-	+	+
Eskelinen (2008)	++	++	-	++	++	+	+	+	++	-	-	+	+
Eskelinen (2009)	NA	NA	NR	NR	+	+	++	++	++	+	+	-	+
Field (2009)	++	+	-	+	+	++	+	+	+	+	+	+	+
Fogelholm (2000)	NA	+	NR	NR	+	+	++	+	+	+	+	+	+
Friedland (2001)	-	+	-	+	-	-	+	+	+	+	+	+	+
Gerber (2012)	++	++	NR	NR	++	++	++	+	NR	++	++	++	++
Guallar-Castillon (2012)	+	+	-	++	+	+	+	++	+	+	+	++	+
Haaponen-Niemi (2000)	+	+	-	++	+	+	++	++	+	+	+	+	+
Halperin (2008)	++	++	-	+	+	+	++	++	++	++	+	+	+
Hamer (2013)	++	+	-	+	+	+	+	+	+	++	+	+	++
Happonen (2004)	+	+	-	+	+	+	+	+	+	+	+	+	+
Hara (2002)	++	+	-	+	+	+	+	+	+	-	+	+	+

			Analyses							Summary			
Author (Year)	**3.5**	**3.5b**	**4.1**	**4.1b**	**4.2**	**4.3**	**4.4**	**4.4b**	**4.4c**	**5.1**	**5.1b**	**5.2**	**Ranking**
Harmsen (2006)	++	++	-	+	+	+	+	-	+	+	+	+	+
He (2004)	NA	NR	NR	NR	++	+	++	++	++	+	+	+	+
Hodge (2013)	+	+	-	+	+	-	++	++	+	+	+	+	
Holmberg (2006)	+	NR	NR	NR	++	+	++	+	++	+	+	+	+
Holme (2007)	++	NR	NR	NR	+	-	++	++	++	-	+	+	+
Holtermann (2009)	++	++	NR	NR	++	+	++	++	++	+	+	-	+
Holtzman (2004)	++	++	NR	NR	++	++	++	+	++	++	++	-	++
Hu (2003)	+	+	-	+	+	+	+	+	+	+	+	+	+
Hu (2004)	+	+	-	+	+	+	+	++	+	+	+	+	+
Hu (2005)	+	+	-	+	+	+	++	++	+	+	+	+	+
Hu (2007) Mov Disord	+	+	-	++	+	+	+	++	+	+	+	+	+
Hughes (2010)	++	+	-	+	++	+	++	++	+	+	+	+	+
Humphries (2001)	+	+	-	+	+	+	++	-	+	+	+	+	+
Inoue (2004)	++	++	-	++	+	++	+	++	++	+	+	+	+
Iso (2004)	++	++	-	++	+	++	+	++	++	+	+	+	+
Jakobsen (2009)	++	++	-	++	++	++	++	+	++	+	+	+	
Janzon (2004)	+	+	-	+	+	+	+	+	+	+	+	+	+
Johnsen (2006)	+	+	-	+	++	-	+	+	+	+	+	+	-
Kareholt (2011)	++	+	-	+	+	+	+	-	+	+	+	+	+
Kato (2009)	+	+	-	+	+	+	+	+	+	+	+	+	+
Kesse-Guyot (2012)	+	+	-	+	+	+	+	+	+	+	+	+	-

			Analyses							Summary			
Author (Year)	**3.5**	**3.5b**	**4.1**	**4.1b**	**4.2**	**4.3**	**4.4**	**4.4b**	**4.4c**	**5.1**	**5.1b**	**5.2**	**Ranking**
Khalili (2002)	++	+	-	+	+	+	++	++	+	+	+	+	+
Kimm (2011)	++	+	-	+	+	+	+	+	+	+	+	+	+
King (2007)	+	+	-	+	+	-	+	++	+	+	+	+	+
Knopman (2001)	+	+	NR	NR	+	+	++	+	+	+	+	+	+
Lahti (2010)	+	-	-	+	-	-	+	+	+	+	+	+	+
Laitala (2009)	++	+	NR	NR	++	+	++	+	+	+	+	+	++
Laitinen (2006)	NA	NA	NR	NR	++	+	++	++	++	+	++	+	++
Lajous (2013)	++	++	NR	NR	++	++	++	++	++	++	++	++	++
Lang (2007)	NA	NA	NR	NR	++	+	++	++	++	+	+	+	+
Langlois (2001)	++	++	NR	NR	+	++	++	+	++	+	+	+	+
Laurin (2004)	++	++	NR	NR	++	+	++	++	+	+	+	+	+
Lehto (2013)	++	++	-	+	+	+	+	+	+	+	+	+	+
Lesodottir (2007)	+	+	+	-	+	+	++	+	-	+	-	+	+
Levitan (2007)	+	+	-	++	+	+	+	+	+	+	+	+	+
Levitan (2009)	+	+	-	++	++	+	+	+	+	+	+	+	+
Levitan (2010)	+	+	-	++	++	+	+	+	+	+	+	+	+
Lim (2013)	+	+	NR	NR	+	++	++	++	++	+	+	+	-
Lin (2003)	+	+	-	++	+	+	++	++	++	+	+	+	++
Liu (2003)	NA	NR	NR	NR	++	+	++	++	++	+	+	+	+
Liu (2004)	++	+	NR	NR	+	+	++	+	++	+	+	+	+
Malmberg (2006)	++	++	-	+	+	+	+	+	+	+	+	+	+
Mannami (2004)	+	+	-	++	+	+	+	+	+	+	+	+	+
Masaki (2003)	+	+	-	+	+	+	+	+	+	+	+	+	+

			Analyses							Summary			
Author (Year)	**3.5**	**3.5b**	**4.1**	**4.1b**	**4.2**	**4.3**	**4.4**	**4.4b**	**4.4c**	**5.1**	**5.1b**	**5.2**	**Ranking**
Meisinger (2007)	++	+	-	-	-	-	+	+	+	+	+	+	+
Menotti (2000)	++	++	-	+	+	+	+	+	+	+	+	+	+
Menotti (2006)	++	++	-	+	++	+	+	+	+	+	+	+	+
Menotti (2012)	NA	NA	NR	NR	++	+	++	++	+	+	+	-	-
Meyer (2011)	NA	NA	NR	NR	++	+	++	++	+	+	+	-	-
Miura (2004)	++	+	NR	NR	+	+	++	++	+	+	+	+	+
Moayyeri (2009)	+	+	-	+	+	+	++	+	+	+	+	+	+
Morgan (2012)	++	++	-	+	+	+	+	+	+	+	+	+	+
Mursu (2008)	+	+	-	+	+	+	+	+	+	+	+	+	+
Nafziger (2007)	++	++	-	+	-	-	+	+	+	-	-	+	-
Nakamura (2009)	+	+	-	+	+	+	+	+	+	+	+	+	+
Nakayama (2000)	++	++	-	+	+	-	+	+	+	+	-	-	+
Noborisaka (2013)	++	++	-	+	+	+	++	++	+	+	+	+	+
Nokes (2012)	+	+	++	++	+	++	++	+	+	++	++	+	++
Nooyens (2008)	+	+	-	+	+	+	+	+	+	+	+	+	+
Nooyens (2011)	+	+	-	+	+	+	+	+	+	+	+	+	+
Osler (2003)	+	+	NR	NR	+	+	++	++	++	+	+	+	+
Ostbye (2002)	++	+	NR	NR	+	+	++	++	++	+	+	+	-
Ostenson (2012)	++	++	-	+	+	+	+	++	+	+	+	+	+
Otani (2003)	+	++	-	+	+	+	++	++	+	+	+	+	+
Patel (2006)	+	+	-	+	++	+	+	+	+	+	+	+	+

			Analyses							Summary			
Author (Year)	**3.5**	**3.5b**	**4.1**	**4.1b**	**4.2**	**4.3**	**4.4**	**4.4b**	**4.4c**	**5.1**	**5.1b**	**5.2**	**Ranking**
Patja (2005)	++	+	NA	NA	++	NA	++	+	+	+	+	+	+
Pelkonen (2000)	++	++	-	+	-	+	++	++	+	+	+	+	++
Pitsavos (2004)	++	++	-	++	++	+	++	++	+	+	+	+	++
Preis (2010)	++	++	-	+	++	++	++	++	++	+	+	+	++
Qiao (2000)	++	++	-	+	-	+	+	+	+	+	+	+	+
Qiu (2003)	+	++	-	+	+	+	++	++	+	+	+	+	+
Raikkonen (2001)	+	+	-	+	+	+	+	+	+	+	+	+	+
Rantakomi (2009)	+	+	-	+	+	-	+	+	+	+	+	+	+
Ravona-Springer (2013)	++	++	-	+	+	-	+	+	+	+	+	+	+
Riserus (2007)	++	-	NR	NR	+	+	++	+	+	+	+	+	+
Ross (2000)	++	+	-	+	-	+	+	+	+	+	+	+	+
Rovio (2005)	++	+	-	+	+	+	+	+	+	+	+	+	+
Rovio (2007)	++	+	-	+	+	+	+	+	+	+	+	+	+
Ruder (2011)	NA	NA	NR	NR	++	++	++	++	++	++	++	++	++
Rusanen (2011)	+	+	-	+	+	-	+	+	+	+	+	+	+
Ruusunen (2010)	++	+	-	+	+	+	+	+	+	+	+	+	+
Sabia (2008)	++	+	NR	NR	+	+	++	++	++	+	+	+	+
Sabia (2009)	++	-	NR	NR	+	+	++	+	++	+	+	+	+
Sabia (2011)	+	+	NR	NR	+	+	++	-	+	+	+	++	+
Sairenchi (2004)	+	-	NR	NR	+	+	++	++	++	+	+	+	+

			Analyses							Summary			
Author (Year)	**3.5**	**3.5b**	**4.1**	**4.1b**	**4.2**	**4.3**	**4.4**	**4.4b**	**4.4c**	**5.1**	**5.1b**	**5.2**	**Ranking**
Samieri (2013)	++	++	-	++	+	-	++	++	++	+	+	+	++
Satoh (2006)	+	+	-	+	+	-	+	++	+	+	+	+	+
Seccareccia (2003)	++	+	-	++	+	-	+	+	+	+	+	+	+
Shaper (2003)	++	+	-	++	+	+	+	+	+	+	+	+	++
Sobue (2002)	+	+	-	++	-	-	+	+	+	+	+	+	++
Song (2004)	+	+	-	++	-	-	++	++	++	-	-	+	++
Song (2006)	+	+	-	++	+	+	++	++	++	+	+	+	++
Stevens (2009)	+	+	-	++	-	-	+	++	++	-	+	++	++
Strand (2013)	++	++	-	++	+	+	++	++	+	+	+	+	++
Strandberg (2008)	++	++	-	+	-	+	+	+	+	+	+	+	+
Strandhagen (2000)	++	+	-	++	-	-	++	++	+	+	+	+	
Sun (2010)	+	+	-	+	++	+	+	+	+	+	+	+	++
Sun (2011)	++	+	NR	NR	++	+	++	++	++	+	+	+	++
Szoeke (2006)	+	+	-	+	+	+	+	+	+	+	+	+	+
Tabak (2001)	++	+	NR	NR	+	+	++	-	+	+	+	+	-
Tsugane (2004)	+	-	-	++	-	+	++	++	++	+	+	+	++
Tuomilehto (2004)	+	++	-	+	-	+	++	++	+	+	+	+	+
Tyas (2003)	++	+	-	+	+	+	+	++	+	+	+	+	+
Valtonen (2010)	++	++	NR	+	+	+	++	+	+	+	+	+	+
Villegas (2010)	+	++	-	++	+	+	++	++	++	++	+	++	++
Villegas (2011)	+	++	-	++	+	+	++	++	++	+	+	++	++

			Analyses							Summary			
Author (Year)	**3.5**	**3.5b**	**4.1**	**4.1b**	**4.2**	**4.3**	**4.4**	**4.4b**	**4.4c**	**5.1**	**5.1b**	**5.2**	**Ranking**
Virta (2010)	++	++	NR	NR	++	++	++	+	NR	++	++	+	++
Waki (2005)	NA	NA	NR	NR	++	+	++	++	+	-	+	+	+
Walda (2002)	++	+	-	+	+	-	++	++	++	+	+	+	+
Wang (2008)	NA	NA	NR	NR	++	+	++	++	++	+	+	+	+
Wang (2009)	+	+	NR	NR	+	+	++	++	++	++	+	+	+
Wang (2012)	+	+	NR	NR	+	+	++	++	++	++	+	+	+
Wannamethee (2001a) Br.J. Canc	++	++	+	+	+	+	++	+	+	+	+	+	+
Wannamethee (2001b) Diab. Care	++	++	+	+	+	+	++	+	+	+	+	+	+
Wannamethee (2002)	++	++	-	++	+	++	+	+	++	++	+	+	+
Wannamethee (2003)	NA	NA	NR	NR	++	-	++	++	++	-	+	-	+
Waring (2010)	++	++	-	+	+	+	++	++	+	+	+	+	++
Whitmer (2005)	+	+	-	+	+	+	+	+	+	+	+	+	+
Willcox (2006)	++	++	NR	NR	++	++	++	+	+	NA	++	+	++
Wiles (2007)	+	+	NR	NR	++	++	++	+	+	++	++	++	++
Xu (2010)	++	-	NR	NR	+	-	++	NR	+	-	+	-	-
Yaffe (2001)	NA	NA	NR	NR	+	+	++	++	++	-	+	-	+
Yu (2003)	NA	NA	NR	NR	+	-	++	++	+	-	+	-	+

APPENDIX D – Review Team

D.1 Expertise

Professor Carol Brayne – Professor Carol Brayne is Professor of Public Health Medicine in Department of Public Health and Primary Care in the University of Cambridge, Director of the Cambridge Institute of Public Health, and Lead of the Old Age theme in CLAHRC CP[1] and the NIHR School of Public Health Research (SPHR) Ageing Well Programme. Professor Brayne is a medically qualified epidemiologist and public health academic. Since the mid-1980s her main research area has been longitudinal studies of older people following changes over time in cognition, dementia natural history and associated features with a public health perspective. She is lead principal investigator in the group of MRC Cognitive function and Ageing Study (CFAS), which has informed and will continue to inform national policy and scientific understanding of dementia in whole populations. Her group's relevant achievements include the definitive systematic reviews of: the diagnosis of mild cognitive impairment; the effect of stroke on incident dementia; and the effect of statins on the prevention of vascular dementia. Ongoing work includes Alzheimer's Society-funded systematic reviews of early non-pharmacological intervention for dementia and population screening for dementia; NIHR Cochrane programme of reviews of diagnostic test accuracy for dementia, and work on diabetes and dementia with the Alzheimer's Society Vascular Dementia Systematic Review group.

Dr Louise Lafortune – Dr Lafortune is a Senior Research Associate for the Public Health and the Dementia, Frailty and End of Life theme in CLAHRC East of England, and the scientific coordinator of the NIHR SPHR Ageing Well Programme, which aims are to strengthen the evidence base for cost-effective and equitable public health interventions for older populations. Louise is specialised in Public Health and Ageing, and has nine years of industry experience in clinical trial, health economics and outcomes research. She has been involved in several projects aimed at improving care for frail older people (e.g. helped developed the joint strategic needs assessment (JSNA) for older people; support the ongoing development of integrated care for older people). In particular, she leads a programme of systematic reviews on population screening for dementia; co-lead the NIHR Cochrane programme of diagnostic test accuracy reviews for dementia; a review of systematic reviews looking at non-pharmacological interventions for behavioural problems, and a wide scope review of the literature looking at outcomes and quality of non-pharmacological interventions in early dementia. Her research interests encompass the development, evaluation and implementation of interventions and service delivery models aimed at improving care for

[1] CLAHRC CP: Collaboratives for Leadership in Applied Heatlh Research and Care for Cambridgeshire and Peterborough.

individuals with complex health and social care needs, namely frail older people. Concerned with the practical application of research findings for patient benefits, her responsibilities include knowledge synthesis, public health analysis and evaluation of changes in services configuration and delivery resulting from the use of research.

Dr Sarah Kelly – Dr Kelly is an experienced systematic reviewer. Sarah was lead reviewer on a systematic review for the World Health Organisation Nutrition Guideline development group on the evidence for a relationship between sugar consumption and dental caries that was used to develop World Health Organisation (WHO) guideline recommendations. Dr Kelly was project coordinator and information specialist for a systematic review of the diet, nutrition and physical activity determinants of obesity for the World Cancer Research Fund (WCRF) that contributed to the major WCRF publication 'Diet, Nutrition and Physical Activity determinants of Cancer (2007)'. She is lead reviewer on two Cochrane systematic reviews relating to nutrition and coronary heart disease and has contributed to a number of other Cochrane reviews about childhood obesity. She was also a reviewer on 2 systematic reviews on tracking of lifestyle behaviours from childhood to adulthood. Sarah has recently completed working on the Dementia Priority Setting Partnership with the James Lind Alliance and the Alzheimer's Society. The project aimed to identify research priorities for dementia from a stakeholder survey including healthcare professionals, patients, carers, relatives of people with dementia that involved data management, formatting and checking of research questions against the existing evidence base for dementia and development of an evidence based research framework for dementia. Sarah has extensive experience in designing and drafting protocols, database searching and systematic search strategies, study selection and data-extraction, quality assessment, analyses and drafting of reviews.

Steven Martin – Mr Martin is an experienced Research Associate at the Cambridge Institute of Public Health (CIPH). During his time at the CIPH Steven has contributed to a number of research programmes around dementia and old age. In particular he has worked as the main systematic reviewer on a wide scoping systematic review looking at non-pharmacological interventions in early dementia and a qualitative review looking at attitudes and preferences with regards to screening for dementia. He is experienced at writing search strategies, undertaking data extraction, quality assessment and synthesis of qualitative, quantitative and mixed-methods research. Steven's interests include the design, interpretation and synthesis of epidemiological evidence, with a particular focus on methodology and translational research aimed at improving health outcomes for vulnerable communities in society.

Olivia Remes – Ms Remes is a PhD student at the University of Cambridge, co directed by Professor Brayne and Dr Louise Lafortune. Olivia has a strong background in epidemiology and her PhD project focuses on the epidemiology of anxiety in the older population and the impact of this mental health condition of patterns of service utilisation.

Isla Kuhn – Ms Khun is Reader Services Librarian at the University of Cambridge Clinical School supporting the review team. Isla is an experienced librarian and has work with the team on all their evidence synthesis projects across a range of topics, specially ageing well and dementia.

Dr Nadja Smailagic – Dr Smailagic is a full time systematic reviewer on a NIHR funded Cochrane Collaboration programme of fifteen diagnostic test accuracy reviews for dementia. Nadja has extensive experience in designing and drafting protocols, study selection and data-extraction, quality assessment, analyses and drafting of reviews. Nadja is a GP with a background in mental health. In her previous role, she was responsible for developing the research agenda for a Mental Health Services for Older People (MHSOP) at the Nottinghamshire Healthcare NHS Trust. That involved negotiation with the Clinical Effectiveness and Clinical Governance for MHSOP, which led to the development of the 'MHSOP Evidence into Practice Group'. Nadja also co-lead the Dementia 'Managed Innovation Network.

D.2 Role in the review process

Core Staff	Roles & responsibilities
Principal investigators • Louise Lafortune (LL) • Carol Brayne (CB)	• Scientific & clinical oversight of the project • Approval of reports before sending to NICE
Scientific coordinator / project management Louise Lafortune (LL)	• Direct contact for NICE • Project management • Technical support for development of protocols, searches, quality assessment tools, data extraction forms • No involvement in actual selection of studies, quality assessment and analysis • Support in drafting of report, final editing and approval • Main presenter at PHAC meetings (supported by SK)
First Systematic Reviewer • Sarah Kelly (SK)	• Drafting of protocols, search strategies, running searches (with support from Clinical School librarian), scanning titles, selecting full text, quality assessment, analysis and writing of draft reports

	• Support LL with presentation at PHAC
Second Systematic Reviewer • Steven Martin (SM)	• Support first reviewer with listed tasks
Forth Systematic Reviewer • Ms Olivia Remes	• Support first reviewer with listed task (namely for Alcohol papers)
Admin/Technical Support • Andy Cowan (AC)	• Ordering, printing, scanning, listing, sorting articles; preparing reference lists & bibliographies (using word, excel and Endnote mainly) • Keeping all project files in order (according to structure agreed with NICE & official processes etc.) • Chasing authors for information • Helping with formatting reports, tables, presentations, etc. (according to NICE manuals)
Extended team	
Nadja Smailagic	• Third reviewer (where/when necessary as arbitrator will resolve disagreements) (e.g. inclusion of studies, quality assessment, analysis) • Technical support (e.g. on quality assessment, data extraction, analysis)

D.3 Conflicts of interest

Dr Louise Lafortune, who co-led the project with Professor Brayne, is a topic expert on the new PHAC in relation to the topic of Disability, Dementia and Frailty**.**

The potential conflict of interest (CoI) is with drafting of new recommendations based on evidence that originates from the reviews her team has produced. She has no conflict regarding evidence from other sources, nor in commenting / advising on recommendations based on evidence from any source once they have been drafted. This potential CoI was handled as follows:

- For meetings - and parts of meetings - where we consider evidence that has not come from her team, she worked as a full PHAC member.
- In meetings (or the parts of meetings) where evidence reviews from her team are presented and discussed, she stepped back from the PHAC role and become a presenter / advisor to the committee. She discussed her team's reviews and advise the committee on how to interpret / use the evidence they contain, however she did not then take an active part in drafting new recommendations based on those reviews.

The other members of the team have no conflict of interest to declare.

APPENDIX E – Search strategies

E.1 Sample search strategy used to identify primary studies

Sample search: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Note: Searches terms were modified were necessary when searching other databases.

1 ((dement* or alzheimer* or disability* or disabled or diabet* or angina or stroke or copd or frail* or bronchiti* or melanoma* or carcinoma* or cancer* or neoplasm* or tumo?r* or blind* or deaf* of glaucoma*) adj3 (prevent* or control* or limit* or restric* or restrain* or obstruct* or inhibit* or imped* or delay* or constrain*)).ti,ab. (276946)

2 (lewy* adj2 bod* adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or imped* or delay* or constrain*)).ti,ab. (67)

3 ((coronary* or vascular* or cardiac or cardiovasc* or cardio vasc* or cerebrovasc* or heart*1 or myocardia*) adj3 (bypass* or graft* or disease* or event* or infarct* or re?vascular* or isch?emi* or peripheral* or complication* or disorder*) adj3 (prevent* or control* or limit* or restrict* or restrain* or imped* or obstruct* or inhibit* or delay* or constrain*)).ti,ab. (29741)

4 (((glucose adj3 (intoleran* or toleran*)) or (insulin adj3 resistan*)) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or imped* or delay* or constrain*)).ti,ab. (2630)

5 (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 (prevent* or control* or limit* or restrict* or restrain* or inhibit* or imped* or delay* or constrain*)).ti,ab. (1247)

6 (((visual adj3 impair*) or (vision* adj3 disorder*) or (macular adj3 degenerat*)) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or imped* or delay* or constrain*)).ti,ab. (436)

7 (hear* adj3 (impair* or difficult* or hard* or disorder*) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or imped* or delay* or constrain*)).ti,ab. (368)

8 ((cognition disorder* or cognitive impair*) adj3 (prevent* or control* or limit* or restrict* or restrain* or obstruct* or inhibit* or imped* or delay* or constrain*)).ti,ab. (950)

9 exp Dementia/pc (4213)

10 exp Wheelchairs/ (3567)

11 exp Cardiovascular Diseases/pc (156094)

12 exp Cardiovascular Deconditioning/ (244)

13 exp Cerebrovascular Disorders/pc (21793)

14 exp Diabetes Mellitus/pc (20043)

15 exp Pulmonary Disease, Chronic Obstructive/pc (596)

16 exp Lung Diseases, Obstructive/pc (6349)

17 exp Frail Elderly/ (6818)

18 Melanoma/pc (1547)

19 exp Blindness/pc (1957)

20 exp Vision Disorders/pc (3318)

21 exp Deaf-Blind Disorders/pc (3)

22 exp Hearing Disorders/pc (3446)

23 exp Glaucoma/pc (887)

24 exp Lung Neoplasms/pc (4337)

25 exp Skin Neoplasms/pc (4524)

26 exp Colorectal Neoplasms/pc (9228)

27 exp Colonic Neoplasms/pc (3678)

28 exp Intestinal Neoplasms/pc (9545)

29 exp Rectal Neoplasms/pc (754)

30 exp Stomach Neoplasms/pc (1463)

31 exp Mouth Neoplasms/pc (1249)

32 exp macular degeneration/pc (783)

33 exp cognition disorders/pc (2314)

34 ((ageing or aging) adj3 (well or success* or positive* or active* or healthy or unhealthy or unsuccess*)).ti,ab. (6519)

35 (compress* adj3 morbid*).ti,ab. (181)

36 or/1-35 (503786)

37 exp *Middle Aged/ (847)

38 (middle adj age*).ti. (9779)

39 (baby adj2 boomer*).ti. (221)

40 (midlife or "mid life" or "midlives" or "mid lives").ti. (1675)

41 or/37-40 (12244)

42 Epidemiologic studies/ (6282)

43 exp case control studies/ (668222)

44 exp cohort studies/ (1374003)

45 Case control.tw. (80438)

46 (cohort adj (study or studies)).tw. (90189)

47 Cohort analy*.tw. (3823)

48 (Follow up adj (study or studies)).tw. (38213)

49 (observational adj (study or studies)).tw. (46124)

50 Longitudinal.tw. (146429)

51 Retrospective.tw. (276650)

52 Cross sectional.tw. (175165)

53 Cross-sectional studies/ (181453)

54 or/42-53 (1929289)

55 exp Regression Analysis/ (308240)

56 ((multivariat* or regress* or varia* or bivariat*) adj3 analys*).tw. (337057)

57 exp multivariate analysis/ (86933)

58 or/54-57 (2266895)

59 letter/ (835895)

60 editorial/ (353835)

61 comment/ (583940)

62 animal/ (5513032)

63 human/ (13712336)

64 62 not (62 and 63) (3974352)

65 59 or 60 or 61 or 64 (5249555)

66 dement*.ti,ab. (71853)

67 alzheimer*.ti,ab. (94300)

68 (lewy* adj2 bod*).ti,ab. (6183)

69 (disabilit* or disabled).ti,ab. (123911)

70 (wheelchair* or walking aid* or walker*1).ti,ab. (14208)

71 cardiovascular*.ti,ab. (284550)

72 (coronary* adj3 (bypass* or graft* or disease* or event*)).ti,ab. (147435)

73 cerebrovascular*.ti,ab. (38161)

74 cardio?vasc*.ti,ab. (285073)

75 (myocardial* adj3 (infarct* or re?vascular* or isch?emi*)).ti,ab. (174190)

76 (vascular* adj3 (peripheral* or disease* or complication*)).ti,ab. (56118)

77 (angina* or stroke*).ti,ab. (196749)

78 (heart* adj3 (disease* or attack* or bypass*)).ti,ab. (138679)

79 diabet*.ti,ab. (421288)

80 ((glucose adj3 (intoleran* or toleran*)) or (insulin adj3 resistan*)).ti,ab. (83550)

81 copd.ti,ab. (27312)

82 (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ti,ab. (61501)

83 (chronic* adj3 bronchiti*).ti,ab. (10432)

84 frail*.ti,ab. (9086)

85 (lung adj3 (cancer* or neoplasm* or tumo?r*)).ti,ab. (116128)

86 melanoma*.ti,ab. (82712)

87 ((bowel* or colorectal* or rect* or intestin* or colon*) adj3 (cancer* or neoplasm* or tum?or*)).ti,ab. (124255)

88 (stomach* adj3 (cancer* or neoplasm* or tum?or*)).ti,ab. (11225)

89 ((oral* or mouth*) adj3 (cancer* or neoplasm* or tum?or*)).ti,ab. (14878)

90 (blind* or (visual* adj3 impari*) or (vision* adj3 disorder*)).ti,ab. (220907)

91 (deaf* or (hear* adj3 (impair* or difficult* or hard* or disorder*))).ti,ab. (45625)

92 glaucoma*.ti,ab. (43418)

93 ((ageing or aging) adj3 (well or success* or positive* or active* or healthy or unhealthy or unsuccess*)).ti,ab. (6519)

94 maculopath*.ti,ab. (3012)

95 ((macul or retina* or choroid*) adj3 degener*).ti,ab. (7847)

96 (macula* adj2 lutea).ti,ab. (112)

97 (skin* adj3 (cancer or neoplasm* or tumo?r*)).ti,ab. (22468)

98 (cogniti* adj3 (disorder* or degenerat*)).ti,ab. (5517)

99 ((limit* or difficult*) adj3 (mobil* or walk* or ambulat*)).ti,ab. (5193)

100 osteoporo*.ti,ab. (52576)

101 osteopenia*.ti,ab. (7137)

102 (bone* adj3 (dens* or loss* or mass* or age* or defect* or mineral* or disease* or health*)).ti,ab. (104300)

103 ur?emi*.ti,ab. (25975)

104 ((kidney* or renal*) adj3 (transplant* or graft* or fail* or disease*)).ti,ab. (212407)

105 (hemodialysis or haemodialysis or dialysis or pre-dialysis or predialysis).ti,ab. (118000)

106 (CKD or CKF or CRD or CRF or ESKD or ESRD or ESKF or ESRF).ti,ab. (35716)

107 (obes* adj2 diabet*).ti,ab. (15199)

108 (mody or niddm).ti,ab. (7673)

109 (diabet* and (non insulin* depend$ or noninsulin* depend* or noninsulindepend* or non insulindepend*)).ti,ab. (11972)

110 ((typ* 2 or typ* II) adj diabet*).ti,ab. (79809)

111 ((ketoresist* or keto* resist* or nonketo* or non keto*) adj diabet*).ti,ab. (263)

112 ((adult* or matur* or late or slow or stabl*) adj diabet*).ti,ab. (1313)

113 ((plurimetabolic* or metabolic) adj syndrom*).ti,ab. (29347)

114 (insulin* defic* adj relativ*).ti,ab. (7)

115 hyperglyc?em*.ti,ab. (41987)

116 (compress* adj3 morbid*).ti,ab. (181)

117 exp dementia/ (122570)

118 exp Disabled Persons/ (46518)

119 exp Wheelchairs/ (3567)

120 exp Cardiovascular Deconditioning/ or exp Cardiovascular diseases/ (1885236)

121 exp Cerebrovascular Disorders/ (277649)

122 exp Diabetes Mellitus/ (320101)

123 exp Pulmonary Disease, Chronic Obstructive/ (24783)

124 exp Lung Diseases, Obstructive/ (167822)

125 exp Frail Elderly/ (6818)

126 exp Lung Neoplasms/ (179429)

127 exp Skin Neoplasms/ (97248)

128 exp melanoma/ (75062)

129 exp intestinal neoplasms/ or exp colorectal neoplasms/ or exp colonic neoplasms/ or exp rectal neoplasms/ (173781)

130 exp Stomach Neoplasms/ (74319)

131 exp Mouth Neoplasms/ (55023)

132 exp Blindness/ (20465)

133 exp Vision Disorders/ (58963)

134 exp Deaf-Blind Disorders/pc or exp hearing disorders/ or exp hearing impaired persons/ (70943)

135 exp glaucoma/ (42761)

136 exp macular degeneration/ (17379)

137 exp retinal degeneration/ (31530)

138 exp retinal neovascularization/ (2366)

139 exp choroidal neovascularization/ (4692)

140 exp macula lutea/ (10257)

141 exp cognition disorders/ (64141)

142 exp mobility limitation/ (2363)

143 exp "bone and bones"/ (484556)

144 exp bone density/ (41566)

145 exp osteoporosis/ (45428)

146 exp bone diseases, metabolic/ (63376)

147 exp uremia/ (22454)

148 exp renal insufficiency/ (124924)

149 exp kidney failure, chronic/ (78957)

150 exp renal dialysis/ (92574)

151 exp renal dialysis/ or exp dialysis/ (115058)

152 exp Diabetes mellitus, non insulin dependent/ (87707)

153 exp Insulin resistance/ (56125)

154 exp hyperglycemia/ (26892)

155 exp Diabetes Mellitus/ (320101)

156 or/66-155 (4784767)

157 exp health behavior/ (100801)

158 exp risk reduction behavior/ (7634)

159 exp Health promotion/ (55508)

160 exp primary prevention/ (115346)

161 exp preventive medicine/ (32449)

162 exp life style/ (65495)

163 exp food habits/ (21495)

164 exp food preferences/ (10186)

165 exp food preferences/ (10186)

166 exp vision tests/ (81401)

167 exp hearing tests/ (38265)

168 exp SMOKING/ (125355)

169 exp SMOKING CESSATION/ (21260)

170 exp "Tobacco Use Disorder"/ (8504)

171 exp "Tobacco Use Cessation"/ (21973)

172 exp Tobacco smoke pollution/ (10787)

173 exp ALCOHOL DRINKING/ (53408)

174 exp alcohol deterrents/ (4214)

175 exp drinking behavior/ (58899)

176 exp temperance/ (2647)

177 exp Loneliness/ (2183)

178 exp EXERCISE/ (115713)

179 exp Sports/ (114218)

180 exp exercise therapy/ (30462)

181 exp physical exertion/ (55019)

182 exp physical fitness/ (22555)

183 exp "Physical Education and Training"/ (13758)

184 exp exercise test/ (51288)

185 exp walking/ (20457)

186 exp running/ (13969)

187 exp jogging/ (702)

188 exp bicycling/ (7943)

189 exp swimming/ (19044)

190 exp dancing/ (1856)

191 exp gardening/ (475)

192 exp fitness centers/ (339)

193 exp sedentary lifestyle/ (2625)

194 (health* adj3 (behavior* or behaviour*)).ti,ab. (29899)

195 ((ageing or aging) adj3 (well or success* or positive* or active* or healthy)).ti,ab. (6481)

196 (food* adj3 choice*).ti,ab. (3151)

197 dieting.ti,ab. (2965)

198 (diet* adj3 (health* or balance* or fat* or salt* or sugar* or mediterranean or choice* or improv* or unhealthy or nutritious)).ti,ab. (60083)

199 ((fruit* or vegetable* or salt* or fat* or sugar*) adj3 (intake* or consum* or eat* or ate)).ti,ab. (33245)

200 (undernutrition or undernourish* or under-nutrition* or under-nourish*).ti,ab. (7463)

201 (multimicronutrient* or multi-micronutrient* or micronutrient* or micro-nutrient* or multinutrient* or multi-nutrient*).ti,ab. (8883)

202 ("five a day" or "5 a day").ti,ab. (179)

203 ("health check" or "check-up").ti,ab. (5509)

204 "health mot*".ti,ab. (285)

205 ((eye or eyesight or sight* or vision* or visual* or hearing) adj3 (test* or check* or screen*)).ti,ab. (20270)

206 (smok* or tobacco or cigar* or nicotine).ti,ab. (252522)

207 ((Alcohol* or Drunk* or Drink*) and (consum* or misuse or abus* or intoxicat* or harmful or excess* or binge or hazardous or heavy or temperan* or abstinen*)).ti,ab. (100162)

208 temperan*.ti,ab. (237)

209 teetotal*.ti,ab. (257)

210 (loneli* or lonely).ti,ab. (3656)

211 (socialis* or socializ*).ti,ab. (9480)

212 (social* adj3 (isolat* or network* or contact* or alien*)).ti,ab. (17204)

213 (sedentary or exercis* or sport*).ti,ab. (251538)

214 "physical condition*".ti,ab. (4515)

215 (balance* and (exercise* or retrain* or re-train* or reeducat* or re-educat*)).ti,ab. (6739)

216 inactiv*.ti,ab. (252817)

217 (walk* or run* or jog* or swim* or danc* or garden* or cycl* or bicycl* or bike* or recreation*).ti,ab. (1102662)

218 ("resistance trainiing" or "acquatic exercis*" or "wellness centre*" or "wellness center*").ti,ab. (154)

219 ("weight gain*" or "weight los*" or "overweight" or "over weight").ti,ab. (130192)

220 (obesity and "related behavio*").ti,ab. (510)

221 (overeat* or "over eat*").ti,ab. (1973)

222 (waist adj3 (circumference* or measur*)).ti,ab. (16292)

223 ((bmi or "body mass index") adj3 (gain* or loss* or lose* or lost or change*)).ti,ab. (4960)

224 (weight adj2 (cycling or reduc* or los* or maint* or decreas* or increas* or watch* or control*)).ti,ab. (106278)

225 "weight change*".ti,ab. (7524)

226 ((behavio?r or lifestyle or "life style") adj3 (change* or changing or modification or modify or modifying or therapy or therapies or program* or intervention* or counsel*)).ti,ab. (47776)

227 ((physical* or keep* or cardio* or aerobic or fitness) adj3 (fit* or activit* or train*)).ti,ab. (115603)

APPENDIX F – Search results

Table F1. Databases searches – Primary studies

Database name	Search date	# records retrieved	After de duplication
MEDLINE/in-process MEDLINE	12.12.13	1398	1182
EMBASE	12.12.13	1154	1091
PsychINFO	12.12.13	3906	3906
CINAHL	12.12.13	423	423
Web of knowledge	12.12.13	3440	3440
	Total	10321	10042

Table F2. Websites searched

Database name	Search date	# records retrieved
NHS Evidence Search	26-27.11.13	151
Public Health Observatories	27.11.13	12
Health Evidence Canada	27.11.13	39
Beth Johnson Foundation	27.11.13	14
British Library	27.11.13	60
Department of Health	27.11.13	19
E-Print Network	27.11.13	1
	Total	296

APPENDIX G – Excluded studies and reason for exclusion

G.1 Primary studies

Study	Reason excluded
Abramson JL, Vaccarino V. (2002) Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Archives of Internal Medicine 162(11): 1286-1292.	X-sect, outcome is inflammation
Agardh EE, Ahlbom A, Andersson T et al. (2007) Socio-economic position at three points in life in association with type 2 diabetes and impaired glucose tolerance in middle-aged Swedish men and women. International Journal of Epidemiology 36(1): 84-92.	X-sect
Akbaraly TN, Kivimaki M, Shipley MJ et al. (2010) Metabolic syndrome over 10 years and cognitive functioning in late midlife: the Whitehall II study. Diabetes Care 33(1): 84-89.	Not health behaviours (HB)
Akbaraly TN, Portet F, Fustinoni S et al. (2009) Leisure activities and the risk of dementia in the elderly. Results from the Three-City Study. Neurology 73(11): 854-861.	Not midlife, analyses in older people
Albanese E, Hardy R, Wills A et al. (2012) No association between gain in body mass index across the life course and midlife cognitive function and cognitive reserve--the 1946 British Birth Cohort study. Alzheimer's & Dementia 8(6): 470-482.	Obesity is exposure, outcome cog fn at age 53 (<55y)
Alfred T, Ben-Shlomo Y, Cooper R et al. (2013) Genetic variants influencing biomarkers of nutrition are not associated with cognitive capability in middle-aged and older adults. Journal of Nutrition 143(5): 606-612.	Exposure not HB
Almeida, OP, Hulse GK, Lawrence D. (2002) Smoking as a risk factor for Alzheimer's disease: contrasting evidence from a systematic review of case–control and cohort studies. Addiction 97: 15–28.	SR, not specifically midlife, look at again with SRs
Alter DA, Wijeysundera HC, Franklin B et al. (2012) Obesity, lifestyle risk-factors, and health service outcomes among healthy middle-aged adults in Canada. BMC Health Services Research 12: 238.	Exposure obesity, outcome HC costs
Anderson R, Anderson D, Hurst C. (2010) Modeling factors that influence exercise and dietary change among midlife Australian women: results from the Healthy Aging of Women Study. Maturitas 67(2): 151-158.	Not longitudinal, survey of midlife - review 1?
Anonymous. (2003) Summaries for patients. Overweight and obesity by middle age are associated with shortened lifespan.[Original report in Ann Intern Med. 2003 Jan 7;138(1):24-32; PMID: 12513041]. Annals of Internal Medicine 138(1): I44.	Summary of Peeters paper

Anonymous. (2013) Summaries for patients. The association between physical fitness and dementia.[Original report in Ann Intern Med. 2013 Feb 5;158(3):162-8; PMID: 23381040]. Annals of Internal Medicine 158(3): I-36.	Summary of DeFina 2013 paper
Ansari RM. (2009) Effect of physical activity and obesity on type 2 diabetes in a middle-aged population. Journal Of Environmental & Public Health 195285.	X-sect
Anstey KJ, Cherbuin N, Budge M et al. (2011) Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obesity Reviews 12(5): e426-437.	SR, BMI as exposure
Anttila T, Helkala EL, Kivipelto M et al. (2002) Midlife income, occupation, APOE status, and dementia: a population-based study. Neurology 59(6): 887-893.	Not HB
Arnlov J, Ingelsson E, Sundstrom J et al. (2010) Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation 121(2): 230-236.	Obesity as exposure
Arnlov J, Sundstrom J, Ingelsson E et al. (2011) Impact of BMI and the metabolic syndrome on the risk of diabetes in middle-aged men. Diabetes Care 34(1): 61-65.	Obesity as exposure
Arvanitakis Z, Wilson RS, Bienias JL et al. (2006) Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Archives of Neurology 61(5):661-6.	Diabetes is exposure
Asia Pacific Cohort Studies Collaboration. (2003) Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. International Journal of Epidemiology 32:563-72.	Not HB, cholesterol as exposure
Baker DW, Sudano JJ, Albert JM et al. (2001) Lack of health insurance and decline in overall health in late middle age. New England Journal of Medicine 345(15): 1106-1112.	Exposure is health insurance, outcome overall health, follow up 2 years
Barengo NC, Hu G, Lakka TA et al. (2004) Low physical activity as a predictor for total and cardiovascular disease mortality in middle-aged men and women in Finland. European Heart Journal 25(24): 2204-2211.	Not cohort study, sequential X-sect
Barnes D, Yaffe K. (2011) The projected impact of risk factor reduction on alzheimer's disease prevalence. Alzheimer's and Dementia 1): S511.	Not specifically midlife but important paper. Include as SR?
Barnes DE, Yaffe K, Byers AL et al. (2012) Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. Archives of General Psychiatry 69(5): 493-498.	Exposure is depression
Baron-Epel O, Azizi E. (2003) The association between counseling, sun protection, and early detection of skin cancer in middle-aged Israelis. Cancer Detection & Prevention 27(5): 338-344.	X-sect

Beeri MS, Goldbourt U. (2011) Late-life dementia predicts mortality beyond established midlife risk factors. American Journal of Geriatric Psychiatry 19(1): 79-87.	Exposure is dementia in late life, outcome is mortality
Behre CJ, Bergstrom G, Schmidt CB. (2011) Increasing leisure time physical activity is associated with less prevalence of the metabolic syndrome in healthy middle-aged men. Angiology 62(6): 509-512.	X-sect
Berentzen TL, Jakobsen MU, Halkjaer J et al. (2011) Changes in waist circumference and the incidence of diabetes in middle-aged men and women. PLoS ONE 6(8): e23104.	Exposure is waist circumference (same paper)
Berentzen TL, Jakobsen MU, Stegger JG et al. (2011) Changes in waist circumference and the incidence of acute myocardial infarction in middle-aged men and women. PLoS One 6(10): e26849.	Exposure is waist circumference
Bertrais S, Beyeme-Ondoua JP, Czernichow S et al. (2005) Sedentary behaviors, physical activity, and metabolic syndrome in middle-aged French subjects. Obesity Research 13(5): 936-944.	X-sect
Beydoun, MA, Wang YF. (2010) Pathways linking socioeconomic status to obesity through depression and lifestyle factors among young US adults. Journal of Affective Disorders 123(1-3): 52-63.	Not midlife - young adults
Biggs ML, Mukamal KJ, Luchsinger JA et al. (2010) Association between adiposity in midlife and older age and risk of diabetes in older adults. JAMA 303(24): 2504-2512.	Exposure is obesity, outcome diabetes
Bjorkelund C, Bondyr-Carlsson D, Lapidus L et al. (2005) Sleep disturbances in midlife unrelated to 32-year diabetes incidence: the prospective population study of women in Gothenburg. Diabetes Care 28(11): 2739-2744.	Sleep duration and problems as exposure
Bjornholt JV, Erikssen G, Liestol K et al. (2001) Prediction of Type 2 diabetes in healthy middle-aged men with special emphasis on glucose homeostasis. Results from 22.5 years' follow-up. Diabetic Medicine 18(4): 261-267.	Not HB
Bodegard J, Erikssen G, Bjornholt JV et al. (2004) Symptom-limited exercise testing, ST depressions and long-term coronary heart disease mortality in apparently healthy middle-aged men. European Journal of Cardiovascular Prevention & Rehabilitation 11(4): 320-327.	Exposure not HB
Boone-Heinonen J, Gordon-Larsen P, Kiefe CI et al. (2011) Fast food restaurants and food stores: longitudinal associations with diet in young to middle-aged adults: the CARDIA study. Archives of Internal Medicine 171(13): 1162-1170.	Not diagnosed health outcomes (diet quality)
Bowling A, Dieppe P. (2005) What is successful ageing and who should define it? BMJ 331 24-31.	SR of definitions of healthy ageing

Breeze E, Clarke R, Shipley MJ et al. (2006) Cause-specific mortality in old age in relation to body mass index in middle age and in old age: follow-up of the Whitehall cohort of male civil servants. International Journal of Epidemiology 35(1): 169-178.	Exposure is BMI, outcome is mortality
Briggs JE, McKeown PP, Crawford VL et al. (2006) Angiographically confirmed coronary heart disease and periodontal disease in middle-aged males. Journal of Periodontology 77(1): 95-102.	
Brown WJ, Mishra G, Lee C et al. (2000) Leisure time physical activity in Australian women: Relationship with well being and symptoms. Research Quarterly for Exercise and Sport 71(3): 206-216.	X-sect
Buckley J, Tucker G, Hugo G et al. (2013) The Australian baby boomer population--factors influencing changes to health-related quality of life over time. Journal of Aging & Health 25(1): 29-55.	Sedentary behaviour exposure but follow up is 4 years
Burazeri G, Kark JD. (2010) Prevalence and determinants of binge drinking in middle age in a transitional post-communist country: a population-based study in Tirana, Albania. Alcohol & Alcoholism 45(2): 180-187.	X-sect
Busetto L, Romanato G, Zambon S et al. (2009) The effects of weight changes after middle age on the rate of disability in an elderly population sample. Journal of the American Geriatrics Society 57(6): 1015-1021.	Exposure is weight loss/weight gain
Calton BA, Lacey JV Jr, Schatzkin A et al. (2006) Physical activity and the risk of colon cancer among women: A prospective cohort study (United States). International Journal of Cancer 15;119(2):385-91.	Mean age at baseline 61 y and >92% postmenopausal. But not specifically midlife, includes >65 years and not separated in analysis.
Carlsson S, Hammar N, Efendic S et al. (2000) Alcohol consumption, Type 2 diabetes mellitus and impaired glucose tolerance in middle-aged Swedish men. Diabetic Medicine 17(11): 776-781.	X-sect
Carroll D, Phillips AC, Ring C et al. (2005) Life events and hemodynamic stress reactivity in the middle-aged and elderly. Psychophysiology 42(3): 269-276.	X-sect
Carroll S, Cooke CB, Butterly RJ et al. (2001) Associations of leisure-time physical activity and obesity with atherogenic lipoprotein-lipid markers among non-smoking middle-aged men. Scandinavian Journal of Medicine & Science in Sports 11(1): 38-46.	X-sect
Carroll S, Cooke CB, Butterly RJ. (2000) Leisure time physical activity, cardiorespiratory fitness, and plasma fibrinogen concentrations in nonsmoking middle-aged men. Medicine & Science in Sports & Exercise 32(3): 620-626.	X-sect

Carroll S, Cooke CB, Butterly RJ. (2000) Metabolic clustering, physical activity and fitness in nonsmoking, middle-aged men. Medicine & Science in Sports & Exercise 32(12): 2079-2086.	X-sect
Caspers K, Arndt S, Yucuis R et al. (2010) Effects of alcohol- and cigarette-use disorders on global and specific measures of cognition in middle-age adults. Journal of Studies on Alcohol & Drugs 71(2): 192-200.	Outcomes midlife
Caspers KM, Yucuis R, McKirgan LM et al. (2009) Lifetime substance misuse and 5-year incidence rates of emergent health problems among middle-aged adults. Journal of Addictive Diseases 28(4): 320-331.	Outcomes midlife - X-sect?
Cassidy A, Mukamal KJ, Liu L et al. (2013) High anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. Circulation 127(2): 188-196.	Mean age at baseline is 25-42 (mean 36)
Castelo-Branco C, Blumel JE, Roncagliolo ME et al. (2003) Age, menopause and hormone replacement therapy influences on cardiovascular risk factors in a cohort of middle-aged Chilean women. Maturitas 45(3): 205-212.	Exposures measured include smoking and sedentary behaviour but no analysis of associations with DDF, just follow up of same measures 5 years later.
Ceria-Ulep CD, Grove J, Chen R et al. (2010) Physical aspects of healthy aging: assessments of three measures of balance for studies in middle-aged and older adults. Current Gerontology & Geriatrics Research 2010: 849761.	X-sect
Chen M, He M, Min X et al. (2013) Different physical activity subtypes and risk of metabolic syndrome in middle-aged and older Chinese people. PLoS One 8(1): e53258.	X-sect
Cheung YB, Machin D, Karlberg J et al. (2004) A longitudinal study of pediatric body mass index values predicted health in middle age. Journal of Clinical Epidemiology 57(12): 1316-1322.	Exposure in childhood, outcomes midlife
Chi D, Nakano M, Yamamoto K. (2003) Correlates of serum high-density lipoprotein cholesterol: a community-based study of middle-aged and older men and women in Japan. Asia-Pacific Journal of Public Health 15(1): 17-22.	X-sectional
Chiang CJ, Yip PK, Wu SC et al. (2007) Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. American Journal of Geriatric Psychiatry 15(9): 762-771.	
Choi JK, Kim MY, Kim JK et al. (2011) Association between short sleep duration and high incidence of metabolic syndrome in midlife women. Tohoku Journal of Experimental Medicine 225(3): 187-193.	Midlife outcomes

Cholesterol Treatment Trialists' (CTT) Collaboration. (2010) Effi cacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 376: 1670–81.	Statin therapy, drugs
Chou KL, Liang K, Mackenzie CS. (2011) Binge drinking and Axis I psychiatric disorders in community-dwelling middle-aged and older adults: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Journal of Clinical Psychiatry 72(5): 640-647.	Binge drinking and psychiatric disorders 3 yr follow up
Cosgrove MC, Franco OH, Granger SP et al. (2007) Dietary nutrient intakes and skin-aging appearance among middle-aged American women.[Erratum appears in Am J Clin Nutr. 2008 Aug;88(2):480]. American Journal of Clinical Nutrition 86(4): 1225-1231.	X-sect
Cournot M, Marquie JC, Ansiau D et al. (2006) Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology 67(7): 1208-1214.	Relation between BMI and cognition
Covinsky KE, Yaffe K, Lindquist K et al. (2010) Depressive symptoms in middle age and the development of later-life functional limitations: the long-term effect of depressive symptoms. Journal of the American Geriatrics Society 58(3): 551-556.	Exposure is depression
Crane PK, Gibbons LE, Arani K et al. (2009) Midlife use of written Japanese and protection from late life dementia. Epidemiology 20(5): 766-774.	Midlife use of Japanese but could have been learnt in childhood, not a midlife behaviour
Crichton GE, Murphy KJ, Bryan J. (2010) Dairy intake and cognitive health in middle-aged South Australians. Asia Pacific Journal of Clinical Nutrition 19(2): 161-171.	X-sectional
Czernichow S, Bruckert E, Bertrais S et al. (2007) Hypertriglyceridemic waist and 7.5-year prospective risk of cardiovascular disease in asymptomatic middle-aged men. International Journal of Obesity 31(5): 791-796.	Weight at midlife, 2 year follow up
Czernichow S, Mennen L, Bertrais S et al. (2002) Relationships between changes in weight and changes in cardiovascular risk factors in middle-aged French subjects: effect of dieting. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 26(8): 1138-1143.	Exposure is WC/TG
Dahl A, Hassing LB, Fransson E et al. (2010) Being overweight in midlife is associated with lower cognitive ability and steeper cognitive decline in late life. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 65(1): 57-62.	Exposure is OW, not health behaviour
Dahl AK, Hassing LB, Fransson EI et al. (2013) Body mass index across midlife and cognitive change in late life. International Journal of Obesity 37(2): 296-302.	Exposure is BMI

Dai Q, Borenstein AR Wu Y et al. (2006) Fruit and vegetable juices and Alzheimer's Disease: The Kame Project. The American Journal of Medicine 119(9): 751-759.	>65y at baseline
Danesh J, Saracci R, Berglund G et al. (2007) EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. European Journal of Epidemiology 22(2): 129-141.	No results, protocol
Danforth KN, Townsend MK, Lifford K et al. (2006) Risk factors for urinary incontinence among middle-aged women. American Journal of Obstetrics & Gynecology 194(2): 339-345.	X-sect
Daroszewski EB. (2004) Dietary fat consumption, readiness to change, and ethnocultural association in midlife African American women. Journal of Community Health Nursing 21(2): 63-75.	Not cohort study
Daviglus ML, Liu K, Pirzada A et al. (2003). Favorable cardiovascular risk profile in middle age and health-related quality of life in older age. Archives of Internal Medicine 163(20): 2460-2468.	Smoking but cannot separate smoking from other risk factors
Daviglus ML, Liu K, Pirzada A et al. (2005) Relationship of fruit and vegetable consumption in middle-aged men to medicare expenditures in older age: the Chicago Western Electric Study. Journal of the American Dietetic Association 105(11): 1735-1744.	Diet, outcome is health costs in older age
Daviglus ML, Liu K, Yan LL et al. (2003) Body mass index in middle age and health-related quality of life in older age: the Chicago heart association detection project in industry study. Archives of Internal Medicine 163(20): 2448-2455.	Midlife exposure is BMI
Daviglus ML, Liu K, Yan LL et al. (2004) Relation of body mass index in young adulthood and middle age to Medicare expenditures in older age. JAMA 292(22): 2743-2749.	Midlife exposure is BMI
Davis NC, Friedrich D. (2010) Age stereotypes in middle-aged through old-old adults. International Journal of Aging & Human Development 70(3): 199-212.	
de Lauzon-Guillain B, Balkau B, Charles MA et al. (2010) Birth weight, body silhouette over the life course, and incident diabetes in 91,453 middle-aged women from the French Etude Epidemiologique de Femmes de la Mutuelle Generale de l'Education Nationale (E3N) Cohort. Diabetes Care 33(2): 298-303.	Exposure is body silhouette
Deary IJ, Allerhand M, Der G. (2009) Smarter in middle age, faster in old age: a cross-lagged panel analysis of reaction time and cognitive ability over 13 years in the West of Scotland Twenty-07 Study. Psychology & Aging 24(1): 40-47.	Exposure is processing speed

Defina LF, Willis BL, Radford NB et al. (2013) The association between midlife cardiorespiratory fitness levels and later-life dementia: a cohort study.[Summary for patients in Ann Intern Med. 2013 Feb 5;158(3):I-36; PMID: 23381057]. Annals of Internal Medicine 158(3): 162-168.	Exposure is physical fitness
Delavar M, Lye M, Hassan S et al. (2011) Physical activity, nutrition, and dyslipidemia in middle-aged women. Iranian Journal of Public Health 40(4): 89-98.	X-sect
Demakakos P, Pierce MB, Hardy R. (2010) Depressive symptoms and risk of type 2 diabetes in a national sample of middle-aged and older adults: the English longitudinal study of aging. Diabetes Care 33(4): 792-797.	Exposure is depression
den Ouden ME, Schuurmans MJ, Brand JS et al. (2013) Physical functioning is related to both an impaired physical ability and ADL disability: a ten year follow-up study in middle-aged and older persons. Maturitas 74(1): 89-94.	Physical function measured at baseline
Denollet J, Maas K, Knottnerus A et al. (2009) Anxiety predicted premature all-cause and cardiovascular death in a 10-year follow-up of middle-aged women. Journal of Clinical Epidemiology 62(4): 452-456.	Exposure is anxiety
Deshpande N, Metter EJ, Guralnik J et al. (2013) Predicting 3-year incident mobility disability in middle-aged and older adults using physical performance tests. Archives of Physical Medicine & Rehabilitation 94(5): 994-997.	Exposure is physical performance, only 3 year follow up.
Dhingra R, Sullivan L, Jacques PF et al. (2007) Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community.[Erratum appears in Circulation. 2007 Dec 4;116(23):e557]. Circulation 116(5): 480-488.	Exposure is soft drink consumption, 4 year follow up, outcome is metabolic syndrome
Driscoll I, Beydoun MA, An Y et al. (2012) Midlife obesity and trajectories of brain volume changes in older adults. Human Brain Mapping 33(9): 2204-2210.	Exposure is obesity
Du H, van Bakel MME, Slimani N et al. (2009) Dietary glycaemic index, glycaemic load and subsequent changes of weight and waist circumference in European men and women. International Journal of Obesity 33(11): 1280-1288.	Not specifically midlife, age range is 20-78 years
Ecob R, Sutton G, Rudnicka A et al. (2008) Is the relation of social class to change in hearing threshold levels from childhood to middle age explained by noise, smoking, and drinking behaviour? International Journal of Audiology 47(3): 100-108.	Exposure in childhood, outcomes in middle age.
Ekelund U, Besson H, Luan JA et al. (2011) Physical activity and gain in abdominal adiposity and body weight: prospective cohort study in 288,498 men and women. American Journal of Clinical Nutrition. 93:4;826-835.	Not specifically midlife, broader age range. Results stratified by > or <50 y so may not be that useful for assessing midlife population specifically.

Elbaz A, Sabia S, Brunner E et al. (2013) Association of walking speed in late midlife with mortality: results from the Whitehall II cohort study. Age 35(3): 943-952.	Exposure is walking speed
Elovainio M, Kivimaki M, Ferrie JE et al. (2009) Physical and cognitive function in midlife: reciprocal effects? A 5-year follow-up of the Whitehall II study. Journal of Epidemiology & Community Health 63(6): 468-473.	Exposure is physical function in midlife
Emberson JR, Whincup PH, Morris RW et al. (2004) Social class differences in coronary heart disease in middle-aged British men: implications for prevention. International Journal of Epidemiology 33(2): 289-296.	Exposure is social class
Eriksson M, Udden J, Hemmingsson E et al. (2010) Impact of physical activity and body composition on heart function and morphology in middle-aged, abdominally obese women. Clinical Physiology and Functional Imaging Sep;30(5):354-9.	Intervention study 6 month follow up
Etgen T, Sander D, Huntgeburth U. (2010) Physical activity and incident cognitive impairment in elderly persons: the INVADE study. Archives of Internal Medicine 170(2):186-193.	Relevant PA - cognition but follow-up 2 years, mean age at baseline >65 y.
Falba T. (2005) Health events and the smoking cessation of middle aged Americans. Journal of Behavioral Medicine 28(1): 21-33.	Exposure is serious health events, outcome is smoking.
Farzadfar F, MM Finucane, Danaei G et al. (2011) National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet 377:578-86.	Cholesterol trends data not HB
Feinglass J, Lin S, Thompson J et al. (2007) Baseline health, socioeconomic status, and 10-year mortality among older middle-aged Americans: findings from the Health and Retirement Study, 1992 2002. Journals of Gerontology Series B-Psychological Sciences & Social Sciences 62(4): S209-217.	
Fernandez-Alonso AM, Trabalon-Pastor M, Vara C et al. (2012) Life satisfaction, loneliness and related factors during female midlife. Maturitas 72(1): 88-92.	X-sect
Field AE, Wing RR, Manson JE et al. (2001) Relationship of a large weight loss to long-term weight change among young and middle-aged US women. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 25(8): 1113-1121.	Weight as exposure
Fitzpatrick AL, Kuller LH, Lopez OL et al. (2009) Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Archives of Neurology 66(3): 336-342.	Exposure is obesity, outcome is dementia

Flood A, Rastogi T, Wirfalt E et al. (2008) Dietary patterns as identified by factor analysis and colorectal cancer among middle-aged Americans. American Journal of Clinical Nutrition 88(1): 176-184.	
Flugsrud GB, Nordsletten L, Espehaug B et al. (2007) The effect of middle-age body weight and physical activity on the risk of early revision hip arthroplasty: a cohort study of 1,535 individuals. Acta Orthopaedica 78(1): 99-107.	Not primary incidence of hip arthroplasty but subsequent loosening of hip replacements
Franco, M, Ordunez P, Caballero B et al. (2007) Impact of energy intake, physical activity, and population-wide weight loss on cardiovascular disease and diabetes mortality in Cuba, 1980-2005. American Journal of Epidemiology 166:12;1374-1380.	Not specifically midlife, age 15-74
Fratiglioni L , Paillard-Borg S, Winblad B. (2004) An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurology Jun;3(6):343-53.	Review, not SR, social networks and dementia. Only 1 study in midlife (Hulsch 1999), rest all mean age >65y.
Freedman VA, Martin LG, Schoeni RF et al. (2008) Declines in late-life disability: the role of early- and mid-life factors. Social Science & Medicine 66(7): 1588-1602.	No HB at midlife
Gallo LC, Jimenez JA, Shivpuri S et al. (2011) Domains of chronic stress, lifestyle factors, and allostatic load in middle-aged Mexican-American women. Annals of Behavioral Medicine 41(1): 21-31.	Exposure is stress, outcome is allostatic load. Age 40-65. X-sect
Gallo LC, Troxel WM, Matthews KA et al. (2003) Marital status and quality in middle-aged women: Associations with levels and trajectories of cardiovascular risk factors. Health Psychology 22(5): 453-463.	Exposure is marital status/quality
Gautam P, Cherbuin N, Sachdev PS et al. (2011) Relationships between cognitive function and frontal grey matter volumes and thickness in middle aged and early old-aged adults: the PATH Through Life Study. Neuroimage 55(3): 845-855.	X-sect. Exposure is grey matter volume. Outcome is cog fn.
George ES, Rosenkranz RR, Kolt GS. (2013) Chronic disease and sitting time in middle-aged Australian males: findings from the 45 and Up Study. International Journal of Behavioral Nutrition & Physical Activity 10:20.	X-sect analysis.
Ginty AT, Carroll D, Roseboom TJ et al. (2013) Depression and anxiety are associated with a diagnosis of hypertension 5 years later in a cohort of late middle-aged men and women. Journal of Human Hypertension 27(3): 187-190.	Exposure is depression and anxiety.
Goon JA, Aini AH, Musalmah M et al. (2009) Effect of Tai Chi exercise on DNA damage, antioxidant enzymes, and oxidative stress in middle-age adults. Journal of Physical Activity & Health 6(1): 43-54.	Exposure is Tai Chi, sedentary behaviour. Outcome is DNA damage but not specific health conditions.

Gray L, Hart CL, Smith GD et al. (2010) What is the predictive value of established risk factors for total and cardiovascular disease mortality when measured before middle age? Pooled analyses of two prospective cohort studies from Scotland. European Journal of Cardiovascular Prevention & Rehabilitation 17(1): 106-112.	Age 15-35 at baseline
Gray L, Lee IM, Sesso HD et al. (2011) Blood pressure in early adulthood, hypertension in middle age, and future cardiovascular disease mortality: HAHS (Harvard Alumni Health Study). Journal of the American College of Cardiology 58(23): 2396-2403.	Links between blood pressure and later CVD, mortality - pre-conditions
Guan JW, Huang CH, Li YH et al. (2011) No association between hypertension and risk for Alzheimer's disease: a meta-analysis of longitudinal studies. Journal of Alzheimer's Disease 27(4): 799-807.	Exposure is hypertension
Guo X, Pantoni L, Simoni M et al. (2006) Midlife respiratory function related to white matter lesions and lacunar infarcts in late life: the Prospective Population Study of Women in Gothenburg, Sweden. Stroke 37(7): 1658-1662.	Exposure is respiratory function, age 70-92 at baseline.
Gureje O, Ogunniyi A, Kola L et al. (2011) Incidence of and risk factors for dementia in the Ibadan study of aging. Journal of American Geriatric Society 59(5):869-74.	Age >65 at baseline
Gustafsson PE, Janlert U, Theorell T et al. (2012) Do peer relations in adolescence influence health in adulthood? Peer problems in the school setting and the metabolic syndrome in middle-age. PLoS One 7(6): e39385.	Exposure is peer problems in adolescence (16y). Outcome is metabolic syndrome in midlife.
Guthrie JR, Dennerstein L, Taffe JR et al. (2004) The menopausal transition: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project. Climacteric 7(4): 375-389.	
Hall MH, Muldoon MF, Jennings JR et al. (2008) Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. Sleep 31(5): 635-643.	X-sect
Hall MH, Okun ML, Sowers M, et al. (2012) Sleep is associated with the metabolic syndrome in a multi-ethnic cohort of midlife women: the SWAN Sleep Study. Sleep 35(6):783-90.	X-sect
Ham E, Choi H, Seo JT et al. (2009) Risk factors for female urinary incontinence among middle-aged Korean women. Journal of Women's Health 18(11):1801-6.	X-sect
Hamer M, Chida Y. (2009) Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychological Medicine 39: 03-11.	Exposure is fitness, 3 yr follow-up

Hamer M, Steptoe A. (2009) Prospective study of physical fitness, adiposity, and inflammatory markers in healthy middle-aged men and women. American Journal of Clinical Nutrition 89(1): 85-89.	SR, most studies in people age >65. 3 studies <65 - check primary for inclusion - Chen 2005, Rovio 2005, Yamada 2003.
Hart CL, Hole DJ, Lawlor DA et al. (2007) How many cases of Type 2 diabetes mellitus are due to being overweight in middle age? Evidence from the Midspan prospective cohort studies using mention of diabetes mellitus on hospital discharge or death records. Diabetic Medicine 24(1):73-80.	Exposure is BMI
Hartman-Stein PE, Potkanowicz ES. (2003) Behavioral determinants of healthy aging: good news for the baby boomer generation. Online Journal of Issues in Nursing 8(2): 6.	Review but not SR
Haseli-Mashhadi N, Pan A, Ye X et al. (2009) Self-rated health in middle-aged and elderly Chinese: distribution, determinants and associations with cardio-metabolic risk factors. BMC Public Health 9:368.	X-sect, exposure is self-rated health
Hassing LB, Dahl AK, Pedersen NL et al. (2010) Overweight in midlife is related to lower cognitive function 30 years later: a prospective study with longitudinal sssessments. Dement and Geriatric Cognitive Disorders 29: c543-552.	Exposure is overweight in midlife
Hassing LB, Dahl AK, Thorvaldsson D et al. (2009) Overweight in Midlife and Risk of Dementia: A 40-Year Follow-up Study. International Journal of Obesity (8):893-8.	Exposure is overweight in midlife
Hatch SL, Feinstein L, Link BG et al. (2007) The Continuing Benefits of Education: Adult Education and Midlife Cognitive Ability in the British 1946 Birth Cohort. Journal of Gerontology: Social Sciences 62B(6): S404–S414.	Outcomes at midlife
Haveman-Nies A, De Groot LCPGM, van Stavern WA. (2003) Dietary quality, lifestyle factors and healthy ageing in Europe: the SENECA study. Age & Ageing 32: 427-434.	Age 70-75 at baseline.
Hawkley LC, Thisted RA, Masi CM et al. (2010) Loneliness predicts increased blood pressure: five-year cross-lagged analyses in middle-aged and older adults. Psychology and Aging 25(1): 132-41.	Exposure is loneliness (poss relevant?) but follow up is 4 yrs.
Heir T, T. Erikssen J, Sandvik L. (2011) Overweight as predictor of long-term mortality among healthy, middle-aged men: A prospective cohort study. Preventive Medicine 52: 223-226.	Exposure is overweight
Henriksson K, Lindblad U, Gullberg B et al. (2002) Development of hypertension over 6 years in a birth cohort of young middle-aged men: the Cardiovascular Risk Factor Study in southern Sweden (CRISS). Journal of Internal Medicine 252: 21-26.	Baseline ages 37,40,43, follow up 6 years but only to 49 years mas (<55 y)
Henriksson KM, Lindblad U, Agren B et al. (2001) Associations between body height, body composition and cholesterol levels in middle-aged men. The coronary risk factor study in southern Sweden (CRISS). European Journal of Epidemiology 17: 521-526.	Baseline ages 37,40,43, follow up 6 years but only to 49 years mas (<55 y)

Henriksson KM, Lindblad U, Gullberg B et al. (2003) Body composition, ethnicity and alcohol consumption as determinants for the development of blood pressure in a birth cohort of young middle-aged men. European Journal of Epidemiology 18: 955-963.	Baseline ages 37,40,43, follow up 6 years but only to 49 years mas (<55 y)
Heraclides A, Chandola T, Witte DR et al. (2009) Psychosocial stress at work doubles the risk of type 2 diabetes in middle-aged women: evidence from the Whitehall II study. Diabetes Care 32(12): 2230-5.	Psychosocial stress as risk factor
Hernelahti M, Kujala UM, Kaprio J et al. (2002) Long-term vigorous training in young adulthood and later physical activity as predictors of hypertension in middle-aged and older men. International Journal of Sports Medicine 23(3): 178-82.	Population is elite athletes, includes young adulthood, not midlife specifically
Hirokawa W, Nakamura K, Sakurai M et al. (2010) Mild metabolic abnormalities, abdominal obesity and the risk of cardiovascular diseases in middle-aged Japanese men. Journal of Atherosclerosis and Thrombosis 17(9):934-43.	Exposure is BP, lipids, glucose, obesity.
Hjerkinn EM, Sandvik L, Hjermann I et al. (2004) Effect of diet intervention on long-term mortality in healthy middle-aged men with combined hyperlipidaemia. Journal of Internal Medicine 255(1): 68-73.	Intervention study - review 3
Ho SH, Li CS, Liu CC. (2009) The influence of chronic disease, physical function, and lifestyle on health transition among the middle-aged and older persons in Taiwan. Journal of Nursing Research 17(2): 136-43.	Relevant lifestyle behaviours but 4 yr follow up (Taiwan)
Hoffman BM, Blumenthal JA, Babyak MA et al. (2008). Exercise fails to improve neurocognition in depressed middle-aged and older adults. Medicine & Science in Sports & Exercise 40(7): 1344-1352.	Intervention study - review 3?
Hoffman GJ, Lee J, Mendez-Luck CA. (2012) Health behaviors among baby boomer informal Caregivers. The Gerontologist 52(2): 219-230.	X-sect analysis
Holahan CK. (2003) Stability and change in positive self-appraisal from midlife to later aging. International Journal of Aging and Human Development 56(3): 247-67.	Exposure is self-appraisal of having lived up to one's abilities'
Holm K, Dan A, Wilbur J et al. (2002) A longitudinal study of bone density in midlife women. Health Care For Women International 23(6-7): 678-91.	2 year follow up but relevant exposures and outcomes
Holmberg AH, Nilsson PM, Nilsson J-Å et al. (2008) The Association between Hyperglycemia and Fracture Risk in Middle Age. A Prospective, Population-Based Study of 22,444 Men and 10,902 Women. The Journal of Clinical Endocrinology & Metabolism 93(3):815-22.	Exposure is fasting glucose
Holtermann A, Mortensen OS, Burr H et al. (2010) Long work hours and physical fitness: 30-year risk of ischaemic heart disease and all-cause mortality among middle-aged Caucasian men. Heart 96(20):1638-44.	Exposure is long worl hours/fitness

Horsten M, Mittleman MA, Wamala SP et al. (2000) Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. European Heart Journal 21(13):1072-80	In women with existing CHD
Houston DK, Cai J, Stevens J. (2009) Overweight and obesity in young and middle age and early retirement: The ARIC Study. Obesity 17, 143–149.	Exposure is OW/obesity, outcome is early retirement
Hu Y, Block G, Sternfeld B et al. (2009) Dietary glycemic load, glycemic index, and associated factors in a multiethnic cohort of midlife women. The Journal of the American College of Nutrition 28(6):636-47.	X-sect analysis
Hultsch DF, Hertzog C, Small BJ et al. (1999) Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? Psychology and Aging 14(2), 245.	Social networks and dementia - only midlife paper identified from Fratiglioni review but 1999 so pre-2000.
Huuskonen J, Väisänen SB, Kröger H et al. (2000) Determinants of bone mineral density in middle aged men: a population-based study. Osteoporos International 11(8):702-8.	Exposure is BMI
Huuskonen J, Väisänen SB, Kröger H et al. (2001) Regular physical exercise and bone mineral density: a four-year controlled randomized trial in middle-aged men. The DNASCO study. Osteoporos International 12(5):349-55.	Intervention study - review 3?
Hwang GS, Choi JW, Choi SH et al. (2012) Effects of a tailored health promotion program to reduce cardiovascular disease risk factors among middle-aged and advanced-age bus drivers. Asia Pac Journal of Public Health 24(1):117-27.	Intervention - rev 3?
Hwang LC, Chen SC, Chen CJ. (2011) Increased risk of mortality from overweight and obesity in middle-aged individuals from six communities in Taiwan. Journal of the Formosan Medical Association 110(5):290-8.	Exposure is BMI
Imagama S, Ito Z, Wakao N, et al. (2013) Influence of sagittal balance and physical ability associated with exercise on quality of life in middle-aged and elderly people. Archives of Osteoporos 6:13–20	X-sect analysis
Imano H, Kitamura A, Sato S et al. (2009) Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: the Circulatory Risk in Communities Study (CIRCS). Stroke 40(5):1571-7.	BP exposure
Inoue M, Hanaoka T, Sasazuki S et al. (2004) Impact of tobacco smoking on subsequent cancer risk among middle-aged Japanese men and women: data from a large-scale population-based cohort study in Japan - the JPHC study. Preventive Medicine 38(5):516-22.	X-sect analysis

Iso H, Imano H, Nakagawa Y et al. (2002) One-year community-based education program for hypercholesterolemia in middle-aged Japanese: a long-term outcome at 8-year follow-up. Atherosclerosis 164(1):195-202.	Intervention study - review 3?
Jain P, Jain P, Bhandari S et al. (2008) A case-control study of risk factors for coronary heart disease in urban Indian middle-aged males. Indian Heart Journal 60(3):233-40.	X-sectional analysis
Jakovljević B, Stojanov V, Lović D et al. (2011) Obesity and fat distribution as predictors of aortoiliac peripheral arterial disease in middle-aged men. European Journal of Internal Medicine 22(1):84-8.	Exposure is obesity
Jang SY, Ju EY, Choi S et al. (2012) Prehypertension and obesity in middle-aged Korean men and women: the third Korea national health and nutrition examination survey (KNHANES III) study. Journal Of Public Health 34(4):562-9.	Exposure is obesity
Jayalath VH, de Souza RJ, Sievenpiper, JL et al. (2013) Effect of dietary pulses on blood pressure: a systematic review and meta-analysis of controlled feeding trials. American Journal of Hypertension *27*(1): 56-64.	Review of intervention studies - consider for rev 3
Jeong JY, Lee SK, Kang YW et al. (2011) Relationship between ED and depression among middle-aged and elderly men in Korea: Hallym aging study. International Journal of Impotence Research 23(5): 227-34.	Exposure is erectile dysfunction
Jin L, Huang Y, Bi Y et al. (2011) Association between alcohol consumption and metabolic syndrome in 19,215 middle-aged and elderly Chinese. Diabetes Research and Clinical Practice 92(3):386-92.	X-sect
Johansson E, Leijon O, Falkstedt D et al. (2012) Educational differences in disability pension among Swedish middle-aged men: role of factors in late adolescence and work characteristics in adulthood. Journal of Epidemiology and Community Health 66(10): 901-907.	X-sect in midlife, exposure in adolescence
Johansson L, Guo X, Hällström T et al. (2013) Common psychosocial stressors in middle-aged women related to longstanding distress and increased risk of Alzheimer's disease: a 38 year longitudinal population study. BMJ Open 3(9): e003142.	Exposure is psychosocial stressors
Johansson S, Wilhelmsen L, Welin C et al. (2010) Obesity, smoking and secular trends in cardiovascular risk factors in middle-aged women: data from population studies in Göteborg from 1980 to 2003. Journal of Internal Medicine 268(6):594-603.	Prevalence/trends
Jood K, Jern C, Wilhelmsen L et al. (2004) Body mass index in mid-life is associated with a first stroke in men: a prospective population study over 28 years. Stroke 35(12): 2764-9.	Exposure is BMI
Joosten H, van Eersel ME, Gansevoort RT et al. (2013) Cardiovascular risk profile and cognitive function in young, middle-aged, and elderly subjects. Stroke 44(6):1543-9.	X-sect

Jovanovic GK, Zezelj SP, Malatestinić Đ et al. (2010) Diet quality of middle age and older women from Primorsko-Goranska County evaluated by healthy eating index and association with body mass index. Collegium Antropologicum 34 Suppl 2: 155-160.	X-sect
Kaffashian S, Dugravot A, Brunner EJ et al. (2013) Midlife stroke risk and cognitive decline: A 10-year follow-up of the Whitehall II cohort study. Alzheimers & Dementia 9(5):572-9.	Exposure is stroke risk - includes smoking but cannot be separated from other stroke risk factors
Kalmijn S, van Boxtel MP, Ocké M et al. (2004) Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology 62(2): 275-80.	X-sect, midlife outcomes
Kalmijn S, van Boxtel MP, Verschuren MW et al. (2002) Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age. American Journal of Epidemiology 156(10): 936-44.	Outcomes are midlife
Kamijo T, Murakami M. (2009) Regular physical exercise improves physical motor functions and biochemical markers in middle-age and elderly women. Journal of Physical Activity and Health 6(1): 55-62.	Intervention study review 3?
Karp A, Andel R, Parker MG et al. (2009) Mentally stimulating activities at work during midlife and dementia risk after age 75: follow-up study from the Kungsholmen Project. American Journal of Geriatric Psychiatry 17(3): 227-36.	Exposure is mentally stimulating work
Karp A, Kåreholt I, Qiu C et al. (2004) Relation of education and occupation-based socioeconomic status to incident Alzheimer’s disease.. American Journal of Epidemiology 159(2): 175-183.	Exposure is level of education/SES
Karp A, Paillard-Borg S, Wang HX et al. (2006) Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. Dementia and Geriatric Cognitive Disorders 21(2): 65-73.	Exposure is in over 75 years age
Karpansalo M, Manninen P, Lakka TA et al. (2002) Physical workload and risk of early retirement: prospective population-based study among middle-aged men. Journal of Occupational and Environmental Medicine 44(10): 930-9.	Outcome is early retirement
Karvonen-Gutierrez CA, Ylitalo KR. (2013) Prevalence and correlates of disability in a late middle-aged population of women. Journal of Aging and Health 25(4): 701-17.	X-sect
Kim J, Chu SK, Kim K et al. (2011) Alcohol use behaviors and risk of metabolic syndrome in South Korean middle-aged men. BMC Public Health 22;11:489.	X-sect
Kim JW, Lee DY, Lee BC et al. (2012). Alcohol and cognition in the elderly: a review. Psychiatry Investigation 9(1): 8-16.	Review, not SR, in elderly

Kivimäki M, Lawlor DA, Smith GD et al. (2007) Socioeconomic position, co-occurrence of behavior-related risk factors, and coronary heart disease: the Finnish Public Sector study. American Journal of Public Health 97(5): 874-9.	Exposure is SES
Kivimaki M, Nyberg ST, Batty GD et al. (2012) Job strain as a risk factor for coronary heart disease: A collaborative meta-analysis of individual participant data. The Lancet 380(9852): 1491-1497.	Exposure is job strain
Kivipelto K, T Ngandu, Laatikainen T et al. (2006) Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population based study. Lancet Neurology 5(9): 735-41.	Review, not SR, not midlife.
Kivipelto M, Helkala EL, Laakso MP et al. (2002) Apolipoprotein E ε4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Annals of Internal Medicine 137(3): 149-155.	Exposure is BP, serum cholesterol
Kivipelto M, Helkala EL, Laakso MP et al. (2001). Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 322(7300): 1447-1451.	Exposure is BP, serum cholesterol
Kivipelto M, Solomon A. (2006) Cholesterol as a risk factor for Alzheimer's disease – epidemiological evidence. Acta Neurologica Scandinavica 114 (Suppl. 185): 50–57	Exposure is a general dementia risk score (includes obesity)
Kloppenborg RP, van den Berg E, Kappelle LJ et al. (2008).Diabetes and other vascular risk factors for dementia: Which factor matters most? A systematic review. European Journal of Pharmacology 585(1) 97-108.	SR, not midlife specifically, exposures are diabetes, BP, lipids, obesity
Knopman D, Boland LL, Mosley T et al. (2001) Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 56(1): 42-8.	For smoking, mean age at baseline 57, follow up 6 years
Kozakova M, Palombo C, Mhamdi L et al. (2007) Habitual physical activity and vascular aging in a young to middle-age population at low cardiovascular risk. Stroke 38(9): 2549-55.	Outcome is carotid wall stiffness
Kremen WS, Vinogradov S, Poole JH et al. (2010) Cognitive decline in schizophrenia from childhood to midlife: a 33-year longitudinal birth cohort study. Schizophrenia Research 118(1-3): 1-5.	Cognitive deficit before and after schizophrenia onset
Kristenson H, Osterling A, Nilsson JA et al. (2002). Prevention of alcohol-related deaths in middle-aged heavy drinkers. Alcoholism: Clinical and Experimental Research 26(4): 478-84.	Out of range
Kuh D, Cooper R, Hardy R et al. (2009) Lifetime cognitive performance is associated with midlife physical performance in a prospective national birth cohort study. Psychosomatic Medicine 71(1): 38-48.	Exposure is cognitive performance, outcome is phys perf at age 53

Kuh D, Hardy R, Butterworth S et al. (2006) Developmental origins of midlife physical performance: evidence from a British birth cohort. American Journal of Epidemiology 164(2): 110-21.	Exposure is developmental performance from childhood, outcomes age 53
Kukuljan S, Nowson CA, Sanders K et al. (2009) Effects of resistance exercise and fortified milk on skeletal muscle mass, muscle size, and functional performance in middle-aged and older men: an 18-mo randomized controlled trial. Journal of Applied Physiology 107(6): 1864-73.	Intervention - review 3?
Kumari M, Marmot M. (2005) Diabetes and cognitive function in a middle-aged cohort: Findings from the Whitehall II study. Neurology 65(10): 1597-603.	X-sect. Exposure is diabetes
Kuo CW, Chang TH, Chi WL et al. (2008) Effect of cigarette smoking on bone mineral density in healthy Taiwanese middle-aged men.Journal of Clinical Densitometry 11(4): 518-24.	X-sect. Exposure is diabetes
Kuper H, Adami HO, Theorell T et al. (2006) Psychosocial determinants of coronary heart disease in middle-aged women: a prospective study in Sweden American Journal of Epidemiology 164(4): 349-57.	Exposure is subjective rate of aging
Kurishima K, Satoh H, Ishikawa H et al. (2001) Lung cancer in middle-aged patients. Oncology Reports 8(4): 851-3.1.	Comparison of incidence between younger and older case-control patients.
Kurl S, Sivenius J, Mäkikallio TH et al. (2008) Exercise workload, cardiovascular risk factor evaluation and the risk of stroke in middle-aged men. Journal of Internal Medicine 265(2):229-37.	Exposure is physical performance (max exercise workload)
Laaksonen DE, Niskanen L, Punnonen K et al. (2005) The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: a prospective cohort study. Journal of Clinical Endocrinolgy & Metabolism 90(2): 712-9.	Exposure is MS-outcome hypogonadism
Lachman ME, Agrigoroaei S.Lahti. (2010) Promoting functional health in midlife and old age: Long-term protective effects of control beliefs, social support, and physical exercise. PLoS One 11;5(10): e13297.	Age 24-75 at baseline, 32-84 at FU, mean age 47
Lallukka T, Chandola T, Hemingway Het al. (2009).Job strain and symptoms of angina pectoris among British and Finnish middle-aged employees. Journal of Epidemiology & Community Health 63(12): 980-5.	X-sect, exp job strain
Lamb SE, Bartlett HP, Ashley A et al. (2002) Can lay-led walking programmes increase physical activity in middle aged adults? A randomised controlled trial. Journal of Epidemiology & Community Health 56(4): 246-52.	Intervention - rev 3?

Laukkanen JA, Kurl S, Lakka TA et al. (2001) Exercise-induced silent myocardial ischemia and coronary morbidity and mortality in middle-aged men. Journal of the American College of Cardiology 38(1): 72-9.	Exposure is ischaemia
Laukkanen JA, Rauramaa R, Kurl S. (2008) Exercise workload, coronary risk evaluation and the risk of cardiovascular and all-cause death in middle-aged men. European Journal of Cardiovascular Prevention & Rehabilitation 15(3): 285-92.	Exposure is physical performance (not PA)
Launer LJ, Hughes T, Yu B et al. (2010) Lowering mid-life levels of systolic blood pressure as a public health strategy to reduce late-life dementia: Perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. Hypertension 55(6): 1352-9.	Exposure is BP
Launer LJ, Ross GW, Petrovitch H et al. (2000) Midlife blood pressure and dementia: the Honolulu–Asia aging study. Neurobiology of Aging 21(1): 49-55.	Exposure is BP
Laurin D, Verreault R, Lindsay J et al. (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. Archives of Neurolgy 58(3): 498-504.	>65 y at baseline
Lee DM, Rutter MK, O'Neill TW et al. (2009) Vitamin D, parathyroid hormone and the metabolic syndrome in middle-aged and older European men. European Journal of Endocrinology 161(6): 947-54.	X-sect
Lee JS, Kawakubo K, Kobayashi et al. (2001) Effects of ten year body weight variability on cardiovascular risk factors in Japanese middle-aged men and women. International Journal of Obesity & Related Metabolic Disorders 25(7): 1063-1067.	X-sect
Lee PG, Cigolle CT, Ha J et al. (2013) Physical function limitations among middle-aged and older adults with prediabetes. Diabetes Care 36(10): 3076-83.	X-sect
Lee SA, Cai H, Yang G et al. (2010) Dietary patterns and blood pressure among middle-aged and elderly Chinese men in Shanghai. British Journal of Nutrition 104(2): 265-75.	Exposure is adiposity
Lee WC, Ory MG. (2013) The Engagement in physical activity for middle-aged and older adults with multiple chronic conditions: findings from a community health assessment. Journal of Aging Research 2013: 152868.	X-sect
Lee YH, Lee SH, Jung ES et al. (2010) Visceral adiposity and the severity of coronary artery disease in middle-aged subjects with normal waist circumference and its relation with lipocalin-2 and MCP-1. Atherosclerosis 213(2): 592-597.	X-sect
Lee IP, Skerrett J. (2001) Physical activity and all-cause mortality: what is the dose-response relation? Medicine Science Sports Exercise 33(6 Suppl): S459-71.	X-sect

Lêng CH, Wang JD. (2013) Long term determinants of functional decline of mobility: An 11-year follow-up of 5464 adults of late middle aged and elderly. Archives of Gerontology & Geriatrics 57(2): 215-20.	50-97 at baseline, mean age >65 at baseline
Leskinen T, Sipilä S, Kaprio J, Kainulainen H et al. (2013) Physically active vs. inactive lifestyle, muscle properties, and glucose homeostasis in middle-aged and older twins. Age (Dordr) 35(5): 1917-26.	Outcome is physical composition performance rather than illness/frailty related
Letenneur L, Larrieu S, Barberger-Gateau P. (2004) Alcohol and tobacco consumption as risk factors of dementia: a review of epidemiological studies. Biomedicine & Pharmacotherapy 58 95–99.	Review but not systematic review
Levinger I, Howlett KF, Peake J et al. (2010) Akt, AS160, metabolic risk factors and aerobic fitness in middle-aged women. Exercise Immunology Review 16:98-104.	X-sect, metabolic inflamm markers, fitness
Lewis TT, Everson-Rose SA, Karavolos K et al. (2009) Hostility is associated with visceral, but not subcutaneous, fat in middle-aged African-American and white women. Psychosomatic Medicine 71(7): 733-40.	Exposure is hostility
Lewis TT, Kravitz HM, Janssen I et al. (2011) Self-reported experiences of discrimination and visceral fat in middle-aged African-American and Caucasian women. American Journal of Epidemiology 173(11): 1223-31.	Exposure is discrimination
Li F, Harmer P, Cardinal BJ et al. (2009) Built environment and changes in blood pressure in middle aged and older adults. Preventive Medicine 48(3): 237-41.	Relevant but 1 year follow up
Li Y, Yatsuya H, Iso H, Tamakoshi K et al. (2010) Incidence of metabolic syndrome according to combinations of lifestyle factors among middle-aged Japanese male workers. Preventive Medicine 51(2): 118-22.	Relevant but 3 year follow up
Lida T, Ikeda H, Shiokawa M et al. (2012) Longitudinal study on physical fitness parameters influencing bone mineral density reduction in middle-aged and elderly women: bone mineral density in the lumbar spine, femoral neck, and femur. Hiroshima Journal of Medical Science 61(2): 23-8.	1 year follow-up, mainly physical fitness but reports mean amount of exercise
Lida T, Ikeda H, Shiokawa M et al. (2012) Longitudinal study on physical fitness parameters influencing bone mineral density reduction in middle-aged and elderly women: bone mineral density in the lumbar spine, femoral neck, and femur. Hiroshima Journal of Medical Science. 61(2): 23-8.	1 year follow-up, mainly physical fitness but reports mean amount of exercise
Lidfeldt J, Nyberg P, Nerbrand C et al. (2002) Biological factors are more important than socio-demographic and psychosocial conditions in relation to hypertension in middle-aged women. The Women's Health in the Lund Area (WHILA) Study. Blood Pressure 11(5): 270-8.	X-sect

Lim NK, Park SH, Choi SJ et al. (2012) A risk score for predicting the incidence of type 2 diabetes in a middle-aged Korean cohort – the Korean Genome and Epidemiology Study. Circulation Journal 76(8): 1904-10.	Overall risk score rather than individual behaviours
Lin YC, Chen JD, Chen PC. (2011) Excessive 5-year weight gain predicts metabolic syndrome development in healthy middle-aged adults. World Journal of Diabetes 2(1): 8-15.	Mean age 32
Lin YC, Hsiao TJ, Chen PC. (2009) Persistent rotating shift-work exposure accelerates development of metabolic syndrome among middle-aged female employees: a five-year follow-up. Chronobiology International 26(4): 740-55.	Mean age 32
Lin YC, Hsiao TJ, Chen PC. (2009) Shift work aggravates metabolic syndrome development among early-middle-aged males with elevated ALT. World Journal of Gastroenterology 15(45): 5654-61	Mean age 32
Lindsay J, Laurin D, Verreault R et al. (2002) Risk factors for Alzheimer’s disease: a prospective analysis from the Canadian Study of Health and Aging. American Journal of Epidemiology 156(5): 445-53.	>65years at baseline
Lindström I, Pallasaho P, Luukkonen R et al. (2011) Reduced work ability in middle-aged men with asthma from youth- a 20-year follow-up. Respiratory Medicine 105(6): 950-5.	Exposure is childhood asthma
Lindström M, Hanson BS, Brunner E et al. (2000) Socioeconomic differences in fat intake in a middle-aged population: report from the Malmö Diet and Cancer Study. International Journal of Epidemiology 29(3): 438-48.	X-sect, SES in fat intake
Liu C, Yu Z, Li H et al. (2010) Associations of alcohol consumption with diabetes mellitus and impaired fasting glycemia among middle-aged and elderly Chinese. BMC Public Health 19;10:713.	X-sect
Liu K, Daviglus ML, Loria CM et al. (2012) Healthy lifestyle through young adulthood and presence of low cardiovascular disease risk profile in middle age: the Coronary Artery Risk Development in (young) Adults (CARDIA) Study. Circulation 125(8): 996-1004.	X-sect
Liu-Ambrose T, Donaldson MG. (2009) Exercise and cognition in older adults: is there a role for resistance training programmes? British Journal of Sports Medicine 43: 25–27.	Review of resistance training programmes, >65y at baseline
Loef M, Walach H. (2012) Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. The Journal of Nutrition, Health & Aging 16(7): 626-30.	SR on midlife obesity and dementia
Lu Y, Lu J, Wang S et al. (2012) Cognitive function with glucose tolerance status and obesity in Chinese middle-aged and aged adults. Aging & Mental Health 16(7): 911-4.	Exposures in young adulthood, outcomes in middle-age

Ma E, Sasazuki S, Iwasaki M et al. (2010) 10-Year risk of colorectal cancer: Development and validation of a prediction model in middle-aged Japanese men. Cancer Epidemiology 34(5): 534-41.	Prediction model for colorectal cancer
Maatouk I, Wild B, Herzog W et al. (2012) Longitudinal predictors of health-related quality of life in middle-aged and older adults with hypertension: results of a population-based study. Journal of Hypertension 30(7): 1364-72.	Patients with existing hypertension
Mahamat A, Richard F, Arveiler D et al. (2003) Body mass index, hypertension and 5-year coronary heart disease incidence in middle aged men: the PRIME study. Journal of Hypertension 21(3): 519-24.	Exposure is hypertension and BMI
Malhotra A. (2013). Saturated fat is not the major issue. BMJ 347: f6340.	Letter
Malmberg JJ, Miilunpalo SI, Vuori IM et al. (2002) Improved functional status in 16 years of follow-up of middle aged and elderly men and women in north eastern Finland. Journal of Epidemiology and Community Health 56(12): 905-12.	Data captured in Malberg 2006.
Mann J, McLean R, Te Morenga L. (2013) Evidence favours an association between saturated fat intake and coronary heart disease. BMJ 2013; 347.	Letter
Marmot MG, Syme SL, Kagan A et al. (1975) Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: prevalence of coronary and hypertensive heart disease and associated risk factors. American Journal of Epidemiology 102(6): 514-25.	Background paper for methodology
Marques-Vidal P, Arveiler D, Evans A et al. (2002) Awareness, treatment and control of hyperlipidaemia in middle-aged men in France and northern ireland in 1991-1993: the PRIME study. Prospective epidemiological study of myocardial infarction. Acta Cardiologica 57(2): 117-23.	X-sect analysis
Marques-Vidal P, Arveiler D, Evans A et al. (2000) Patterns of alcohol consumption in middle-aged men from France and Northern Ireland. The PRIME Study. European Journal of Clinical Nutrition 54(4): 321-8.	X-sect
Marques-Vidal P, Montaye M, Haas B et al. (2001) Relationships between alcoholic beverages and cardiovascular risk factor levels in middle-aged men, the PRIME study. Atherosclerosis 157(2): 431-40.	X-sect
Martínez-González MA, Guillén-Grima F, De Irala J et al. (2012) The Mediterranean diet is associated with a reduction in premature mortality among middle-aged adults. Journal of Nutrition 142(9):1672-8.	Relevant but mean age at baseline 38, FU 7 years so outcomes at < 55 years
Masel MC, Raji M, Peek MK. (2010) Education and physical activity mediate the relationship between ethnicity and cognitive function in late middle-aged adults. Ethnicity and Health 15(3): 283-302.	X-sect

Matthews KA, Abrams B, Crawford S et al. (2001) Body mass index in mid-life women: relative influence of menopause, hormone use, and ethnicityInternational Journal of Obesity & Related Metabolic Disorders 25(6): 863-873.	X-sect analysis, BMI exposure
Matthews KA, Räikkönen K, Sutton-Tyrrell K et al. (2004) Optimistic attitudes protect against progression of carotid atherosclerosis in healthy middle-aged women. Psychosomatic Medicine 66(5): 640-4.	Exposure is optimism/pessimism
Medraś M, Słowińska-Lisowska M, Jozkow P et al. (2005) Impact of recreational physical activity on bone mineral density in middle-aged men. Aging Male 8(3-4): 162-5.	X-sect analysis, retrospective identification of cases, controls.
Michikawa T, Inoue M, Sawada N et al. (2012) Development of a prediction model for 10-year risk of hepatocellular carcinoma in middle-aged Japanese: The Japan Public Health Center-based Prospective Study Cohort II. Preventive Medicine 55(2): 137-43.	Prediction model
Mielke MM, Zandi PP, Shao H et al. (2010) The 32-year relationship between cholesterol and dementia from midlife to late life. Neurology 75: 1888-1895.	Exposure is cholesterol
Missault L, Witters N, Imschoot J. (2010) High cardiovascular risk and poor adherence to guidelines in 11,069 patients of middle age and older in primary care centres. European Journal of Cardiovascular Prevention & Rehabilitation 17(5): 593-8.	X-sect, outcome is CV risk prediction rather than actual events
Mitnitski A, Song X, Rockwood K. (2007) Improvement and decline in health status from late middle age: Modeling age-related changes in deficit accumulation. Experimental Gerontology 42(11): 1109-15.	Time trends for changes in health states
Miyake Y. (2000) Risk factors for non-fatal acute myocardial infarction in middle-aged and older Japanese. Fukuoka Heart Study Group. Japanese Circulation Journal 64(2): 103-9.	X-sectional
Mohamed S, Bondi MW, Kasckow JW et al. (2006) Neurocognitive functioning in dually diagnosed middle aged and elderly patients with alcoholism and schizophrenia. International Journal of Geriatric Psychiatry 21(8): 711-8.	Participants had existing schizophrenia
Morgan GS, Gallacher J, Bayer A et al. (2012) Physical activity in middle-age and dementia in later life: findings from a prospective cohort of men in Caerphilly, South Wales and a meta-analysis. Journal of Alzheimer's Disease 31(3): 569-580.	PA - dementia 16 yr Fup of Caerphilly cohort study
Mostofsky E, Levitan EB, Wolk A et al. (2010) Chocolate intake and incidence of heart failure a population-based prospective study of middle-aged and elderly women. Circulation: Heart Failure 3(5): 612-616.	

Mozaffarian D, Micha R, Wallace S. (2010) Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Medicine 7(3): e1000252.	SR includes a number of studies in middle-aged people - check cited references
Murray ET, Hardy R, Strand BH et al. (2011) Gender and life course occupational social class differences in trajectories of functional limitations in midlife: findings from the 1946 British birth cohort. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 66(12): 1350-9.	Prevalence study of functional limitation at midlife
Nakanishi N, Nakamura K, Matsuo Y et al. (2000) Cigarette smoking and risk for impaired fasting glucose and type 2 diabetes in middle-aged Japanese men. Annals of Internal Medicine 133(3): 183-91.	Age 46-47 at baseline, followed for 5 years, so outcomes at age <55 years.
Nakanishi N, Nakamura K, Suzuki K et al (2000) Relation of body weight change to changes in atherogenic traits; a study of middle-aged Japanese obese male office workers. Industrial Health-Kawasaki 38(2): 233-238.	Mean age 44-47 at baseline, 1 year follow up, intentional weight reduction
Nakanishi N, Suzuki K, Tatara K. (2003) Alcohol consumption and risk for development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. Diabetes Care 26(1):48-54	Age 45-47 at baseline, 7 years of FU so outcomes at age <55years
Nakanishi N, Suzuki K. (2005) Daily life activity and the risk of developing hypertension in middle-aged Japanese men. Archives of Internal Medicine 165(2): 214-20.	Mean age 47-48 at baseline, range 35-59, 7 yr FU. Outcomes at age <55 years. Have excluded other papers from this cohort as outcomes <55 y. This one is borderline but just under age 55 yr cut off.
Nakanishi N, Takatorige T, Suzuki K. (2005) Cigarette smoking and the risk of the metabolic syndrome in middle-aged Japanese male office workers. Industrial Health 43(2): 295-301.	Age 46-47 at baseline, followed for 7 years, so outcomes at age <55 years.
Nakanishi N, Yoshida H, Nakamura K et al. (2001) Alcohol consumption and risk for hypertension in middle-aged Japanese men. Journal of Hypertension 19(5): 851-5.	Age 42-45 at baseline, 9 years of FU so outcomes <55 years.
Nakanishi N, Kawashimo H, Nakamura K et al. (2001) Association of alcohol consumption with increase in aortic stiffness: a 9-year longitudinal study in middle-aged Japanese men.Industrial Health 39(1): 24-28.	Outcome is aortic stiffness
Naya M, Morita K, Yoshinaga K et al. (2011). Long-term smoking causes more advanced coronary endothelial dysfunction in middle-aged smokers compared to young smokers. European Journal of Nuclear Medicine and Molecular Imaging 38(3): 491-8.	Comparison of smoking cessation between young and midlife smokers

Novak M, Björck L, Giang KW et al. (2012) Perceived stress and incidence of Type 2 diabetes: a 35-year follow-up study of middle-aged Swedish men. Diabetic Medicine 30(1): e8-16.	Exposure is perceived stress
Okazaki T, Himeno E, Nanri H et al. (2001) Effects of a community-based lifestyle-modification program on cardiovascular risk factors in middle-aged women. Hypertension Research 24(6): 647-53.	Intervention - review 3
Opree SJ. (2012) Exploring casual effects of combining work and intergenerational support on depressive symptoms among middle-aged women. Ageing and Society 1(1): 1-17.	X-sect
Otsuka R, Imai T, Kato Y et al. (2010) Relationship between number of metabolic syndrome components and dietary factors in middle-aged and elderly Japanese subjects. Hypertension Research 33(6): 548-54.	X-sect
Owen CG, Whincup PH, Orfei L et al. (2009). Is body mass index before middle age related to coronary heart disease risk in later life? Evidence from observational studies. International Journal of Obesity 33(8): 866-77.	Exposure is BMI
Pajak A, Kawalec E. (2005) Lifestyle characteristics and hypertension in the middle-aged population of Kraków. Blood Pressure Supplement 2: 17-21.	X-sect
Pan A, Malik VS, Schulze MB et al. (2011) Plain-water intake and risk of type 2 diabetes in young and middle-aged women. American Journal of Clinical Nutrition 95(6): 1454-60.	Mean age at baseline 36, range 25-42
Paterson DH, Warburton DER. (2010) Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. International Journal of Behavioral Nutrition and Physical Activity 7: 38.	SR in adults >65 yrs
Peacock JM, Folsom AR, Knopman DS et al. (2000). Dietary antioxidant intake and cognitive performance in middle-aged adults. Public Health Nutrition 3(3): 337-43.	X-sect
Peila R, White LR, Petrovich H et al. (2001) Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu-Asia Aging Study. Stroke 32(12): 2882-9.	Exposure is BP/APOE
Pereira MA, Schreiner PJ, Pankow JS et al. (2000) The family risk score for coronary heart disease: associations with lipids, lipoproteins, and body habitus in a middle-aged bi-racial cohort: the ARIC study. Annals of Epidemiology 10(4): 239-45.	Combined risk factor score, includes non behavioural RF.
Pereira SMP, Ki M, Power C. (2012) Sedentary behaviour and biomarkers for cardiovascular disease and diabetes in mid-life: the role of television-viewing and sitting at work. PLoS One 7(2): e31132.	X-sect

Peters R, Beckett N, Forette F, et al. (2008) Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurology 7: 683-89.	Exposure is hypertension
Peters R, Peters J, Warner J et al. (2008) Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age and Ageing 37(5): 505-512.	SR in those >65 yrs
Peters R, Poulter R, Warner J et al. (2008) Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatrics 8(1): 36.	SR in those >65 yrs
Peters R. (2012) Blood pressure, smoking and alcohol use, association with vascular dementia. Experimental Gerontology 47(11): 865-872.	Review, not SR, not midlife
Piazza-Gardner AK, Gaffud TJB et al. (2013) The impact of alcohol on Alzheimer's disease: A systematic review. Aging & Mental Health 17(2): 133-146.	Alcohol SR, not midlife
Plassman, BL, Williams JW. (2010) Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Annals of Internal Medicine 153: 182-193.	Older adults, not midlife, I yr FU
Platz EA, Willett WC, Colditz GA et al. (2000) Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. Cancer Causes Control 11(7): 579-88.	Combined risk factor score - includes non-behavioural risk factors
Podewils LJ, Guallar E, Kuller LH et al. (2005) Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. American Journal of Epidemiology 161(7): 639-651.	>65 at baseline
Pope SK, Sowers M. (2005) Functional status and hearing impairments in women at midlife. Journals of Gerontology Series B: Psychological Sciences and Social Sciences 55(3):S190-4.	X-sect
Pope SK, Sowers MF, Welch GW et al. (2001) Functional limitations in women at midlife: the role of health conditions, behavioral and environmental factors. Womens Health Issues 11(6): 494-502.	X-sect
Power MC, Weuve J, Gagne JJ et al. (2011) The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. Epidemiology 22(5): 646-659.	Exposure is BP
Profenno LA, Porsteinsson AP, Faraone SV. (2010) Meta-analysis of Alzheimer’s disease risk with obesity, diabetes, and related disorders. Biological Psychiatry 67: 505-512..	Exposure is BMI, diabetes, MetS
Prospective Studies Collaboration. (2007) Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. Lancet 370: 1829-39.	Exposure is BP and cholesterol

Pullen C, Noble Walker S. (2002) Midlife and older rural women's adherence to US dietary guidelines across stages of change in healthy eating. Public Health Nursing 19(3):170-8.	X-sect
Qin L, Corpeleijn E, Jiang C et al. (2010) Physical activity, adiposity, and diabetes risk in middle-aged and older Chinese population. Diabetes Care 33(11):2342-8	X-sect
Rantakömi SH, Laukkanen JA, Sivenius J et al. (2013) Hangover and the risk of stroke in middle-aged men. Acta Neurologic Scandinavica 127(3): 186-91.	Exclude - drinking patterns - atherosclerosis as measured by ultrasound, not specific health conditions
Rantanen T. (2013) Midlife fitness predicts less burden of chronic disease in later life. Clinical Journal of Sports Medicine 23(6): 499-500.	Exposure is physical fitness
Rasmussen M, Holstein BE, Due P. (2012) Tracking of overweight from mid-adolescence into adulthood: consistent patterns across socio-economic groups. European Journal of Public Health 22 (6): 885–887.	Exposure is overweight in adolescence
Ravaglia G, Forti P, Lucicesare A et al. (2008) Physical activity and dementia risk in the elderly. Findings from a prospective Italian study. Neurology. 70(19 Pt 2): 1786-94.	Age >65 at baseline
Reis JP, Hankinson AL, Loria CM et al. (2013) Duration of abdominal obesity beginning in young adulthood and incident diabetes through middle age: the CARDIA study. Diabetes Care 36(5):1241-7.	Exposure is obesity
Rhee EJ, Oh KW, Lee WY et al. (2004) Age, body mass index, current smoking history, and serum insulin-like growth factor-I levels associated with bone mineral density in middle-aged Korean meen. Journal of Bone and Mineral Metabolism 22(4):392-8.	X-sect
Richards M, Hardy R, Wadsworth ME. (2005) Alcohol consumption and midlife cognitive change in the British 1946 birth cohort study. Alcohol and Alcoholism 40(2): 112-7.	Outcomes in midlife
Richards M, Jarvis MJ, Thompson N et al. (2003) Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. American Journal of Public Health 93(6): 994-8	Outcomes in midlife
Ridley NJ, Draper B, Withall A. (2013) Alcohol-related dementia: an update of the evidence. Alzheimer's Research & Therapy 5:3.	Review but not SR
Ritchie K, Carrière I, De Mendonca A et al. (2007) The neuroprotective effects of caffeine. A prospective population study (the Three City Study). Neurology 69(6): 536-45.	>65 y at baseline
Rohr G, Støvring H, Christensen K et al. (2005) Characteristics of middle-aged and elderly women with urinary incontinence. Scandinavian Journal of Primary Health Care 23(4): 203-8.	X-sect

Rönnlund M, Sundström A, Sörman DE et al. (2013). Effects of perceived long-term stress on subjective and objective aspects of memory and cognitive functioning in a middle-aged population-based sample. Journal of Genetic Psychology 174(1): 25-41.	Exposure is perceived stress
Rundberg J, Lidfeldt J, Nerbrand C et al. (2008) Abstinence, occasional drinking and binge drinking in middle-aged women. The Women's Health in Lund Area (WHILA) Study. Nordic Journal of Psychiatry 62(3): 186-91.	X-sect
Sabia S, Guéguen A, Marmot MG et al. (2010) Does cognition predict mortality in midlife? Results from the Whitehall II cohort study. Neurobiology of Aging 31(4): 688-95.	Exposure is cognition
Sakurai M, Nakamura K, Miura K et al. (2012) Self-reported speed of eating and 7-year risk of type 2 diabetes mellitus in middle-aged Japanese men. Metabolism 61(11): 1566-71.	Age 46 at baseline, 7 y FU so outcomes at age <55y
Santos-Eggimann B, Cuénoud P, Spagnoli J et al. (2009). Prevalence of frailty in middle-aged and older community-dwelling europeans living in 10 countries. Journals of Gerontology Series A Biological Sciences & Medical Sciences 64(6): 675-81.	X-sect
Savonen KP, Kiviniemi V, Laaksonen DE et al. (2011) Two-minute heart rate recovery after cycle ergometer exercise and all-cause mortality in middle-aged men. Journal of Internal Medicine 270(6): 589-96.	Exposure is fitness related
Savonen KP, Lakka TA, Laukkanen JA et al (2006) Heart rate response during exercise test and cardiovascular mortality in middle-aged men. European Heart Journal 27(5): 582-8.	Exposure is fitness related
Savva GM, Blossom CMS. (2010) Epidemiological studies of the effect of stroke on incident dementia: a systematic review. Stroke 41:e41-e46.	Exposure is stroke risk - includes smoking but cannot be separated from other stroke risk factors
Scarmeas N, Luchsinger JA, Schupf N et al. (2009) Physical activity, diet, and risk of Alzheimer disease. JAMA 302 (6): 627-37.	Mean age 76-82 at baseline
Scarmeas N, Stern Y, Mayeux R et al. (2006) Mediterranean diet, Alzheimer disease, and vascular mediation. Archives of Neurology 63(12): 1709-17.	X-sect analysis
Schuit AJ, Feskins EJM, Launer LJ et al. (2001) Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. Medicine & Science in Sports & Exercise 33(5): 772-7.	Mean age 74 at baseline
Schult A, Eriksson H, Wallerstedt S et al. (2011) Overweight and hypertriglyceridemia are risk factors for liver cirrhosis in middle-aged Swedish men. Scandinavian Journal of Gastroenterology 46(6): 738-44.	OW/LTG as exposures
Schulze MB, Manson JE, Ludwig DS et al. (2004). Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 292(8): 927-34.	Mean age 36 at baseline

Seki A, Takigawa T, Ito T et al. (2002) Obesity and the risk of diabetes mellitus in middle-aged Japanese men. Acta Medica Okayama 56(5): 255-60.	Exposure is obesity
Shaper AG, Wannamethee SG. (2000) Alcohol intake and mortality in middle-aged men with diagnosed coronary heart disease. Heart 83(4): 394-9.	Study in those with existing CHD
Sharp SI, Aarsland D, Day S et al. (2011) Hypertension is a potential risk factor for vascular dementia: systematic review. International Journal of Geriatric Psychiatry 26(7): 661-669.	Exposure is BP
Shay CM, Stamler J, Dyer AR et al. (2012) Nutrient and food intakes of middle-aged adults at low risk of cardiovascular disease: the international study of macro-/ micronutrients and blood pressure (INTERMAP). European Journal of Nutrition 51(8): 917-26.	X-sect
Shepherd JP, Shepherd I, Newcombe RG et al. (2009) Impact of antisocial lifestyle on health: chronic disability and death by middle age. Journal of Public Health 31(4): 506-11.	Outcomes at 48 y (<55y), antisocial lifestyle
Sheu WH, Chuang SY, Lee WJ et al. (2006) Predictors of incident diabetes, metabolic syndrome in middle-aged adults: A 10-year follow-up study from Kinmen, Taiwan. Diabetes Research & Clinical Practice 74(2): 162-8.	Exposure is baseline components of MetS
Shi J, Song X, Yu P et al. (2011) Analysis of frailty and survival from late middle age in the Beijing Longitudinal Study of Aging. BMC Geriatrics 20;11:17.	Exposure is frailty - mortality outcomes
Shimizu S, Kawata Y, Kawakami N et al. (2001) Effects of changes in obesity and exercise on the development of diabetes and return to normal fasting plasma glucose levels at one-year follow-up in middle-aged subjects with impaired fasting glucose. Environmental Health and Preventive Medicine 6(2): 127-131.	Intervention, consider review 3
Shlomo YB, Kuh D. (2002) A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. International Journal of Epidemiology 31: 285-193.	Model, not a primary study
Siervo M, Nasti G, Stephan BC et al. (2012) Effects of intentional weight loss on physical and cognitive function in middle-aged and older obese participants: a pilot study. Journal of the American College of Nutrition 31(2): 79-86.	Int - rev 3? Not midlife realtionship with older outcomes
Singh-Manoux A, Marmot M. (2005) High blood pressure was associated with cognitive function in middle-age in the Whitehall II study. Journal of Clinical Epidemiology 58(12): 1308-15.	Exposure is BP
Skretteberg PT, Grundvold I, Kjeldsen SE et al. (2013) Seven-year increase in exercise systolic blood pressure at moderate workload predicts long-term risk of coronary heart disease and mortality in healthy middle-aged men. Hypertension 61(5): 1134-40.	Exposure is BP

Sluijs I, Beulens JW, Grobbee DE et al. (2009) Dietary Carotenoid Intake Is Associated with Lower Prevalence of Metabolic Syndrome in Middle-Aged and Elderly Men. Journal of Nutrition 139(5): 987-92.	X-sect
Smith ML, Honoré Goltz H, Ahn S et al. (2012) Correlates of chronic disease and patient–provider discussions among middle-aged and older adult males: Implications for successful aging and sexuality. The Aging Male 15(3): 115-23.	X-sect
Smith-DiJulio K, Anderson D. (2009) Sustainability of a multimodal intervention to promote lifestyle factors associated with the prevention of cardiovascular disease in midlife Australian women: a 5-year follow-up. Health Care for Women International 30(12): 1111-30	Int - rev 3?
Sofi F, Ceasri F, Abbate R et al. (2008) Adherence to Mediterranean diet and health status: meta-analysis. BMJ 337: a1344.	SR Med diet and health, not spec midlife, not spec follow up to older age. Checked ref list for midlife studies - Check Lagiou 2006, Fung 2006, Gao 2007, Mitrou 2007
Sofi F, Valecchi D, Bacci D et al. (2011) Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. Journal of Internal Medicine 269(1): 107-17.	SR, not spec midlife, checked included studies list for midlife papers.
Soloman A, Kivipelto M, Wolozin B et al. (2009) Midlife serum cholesterol and increased risk of Alzheimer’s and vascular dementia three decades later. Cognitive Disorders 28(1):75-80.	
Solomon A, Kåreholt I, Ngandu T et al. (2007) Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. Neurology 6;68(10): 751-6.	Exposure is cholesterol
Song Y, Ridker PM, Manson JE et al. (2005) Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older US women. Diabetes Care 28(6): 1438-4.	X-sect
Sowers M, Zheng H, Tomey K et al. (2007) 6-year changes in body composition in women at mid-life: ovarian and chronological aging. Journal of Clinical Endocrinology & Metabolism 92(3): 895-901.	Age- body composition
Stavem K, Aaser E, Sandvik L et al. (2005) Lung function, smoking and mortality in a 26-year follow-up of healthy middle-aged males. European Respiratory Journal 25(4): 618-25.	Exposure is baseline lung fn
Steptoe A, Owen N, Kunz-Ebrecht SR et al. (2004) Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. Psychoneuroendocrinology 29(5): 593-611.	Not DDF outcomes

Stewart R, White LR, Xue QL et al. (2007) Twenty-six–year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. Archives of Neurology 64(1): 103-107.	Exposure is cholesterol
Strandberg A, Strandberg TE, Salomaa VVet al. (2004) A follow-up study found that cardiovascular risk in middle age predicted mortality and quality of life in old age. Journal of Clinical Epidemiology 57(4): 415-21.	High vs low risk combined score includes non-behavioural RF
Strandberg TE, Sirola J, Pitkälä KH et al. (2012) Association of midlife obesity and cardiovascular risk with old age frailty: a 26-year follow-up of initially healthy men. International Journal of Obesity 36(9): 1153-7.	Exposure is midlife obesity/CVD risk
StStrandberg TE, Saijonmaa O, Tilvis RS et al. (2011) Association of telomere length in older men with mortality and midlife body mass index and smoking. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 66(7): 815-20.	Outcome is telomere length, not directly DDF outcomes
Sun Q, Townsend MK, Okereke OI et al. (2009) Adiposity and weight change in mid-life in relation to healthy survival after age 70 in women: prospective cohort study. BMJ 339: b3796.	Exposure is BMI or weight change from 18 to midlife
Swanepoel de W, Eikelboom RH, Hunter ML et al. (2013) Self-reported hearing loss in baby boomers from the Busselton Healthy Ageing Study: audiometric correspondence and predictive value. Journal of the American Academy of Audiology 24(6): 514-21.	Not a prospective study, comparison of self-reported hearing loss with objectively measured hearing loss.
Takwoingi Y, Hopewell S, Tovey D et al. (2013) A multicomponent decision tool for prioritising the updating of systematic reviews. BMJ 347: f7191.	Not relevant topic
Tanno K, Sakata K, Ohsawa M et al. (2009) Associations of ikigai as a positive psychological factor with all-cause mortality and cause-specific mortality among middle-aged and elderly Japanese people: Findings from the Japan Collaborative Cohort Study. Journal of Psychosomatic Research 67(1): 67-75.	Ikigai' psychological factor as exposure
Tatsuno I, Terano T, Nakamura M et al. (2013) Lifestyle and osteoporosis in middle-aged and elderly women: Chiba bone survey. Endocrinology Journal 60(5): 643-50.	X-sect
Thom DH, Brown JS, Schembri M et al. (2010) Incidence of and risk factors for change in urinary incontinence status in a prospective cohort of middle-aged and older women: The Reproductive Risk of Incontinence Study in Kaiser (RRISK). Journal of Urology 184(4): 1394-401.	Not behavioural risk factors
Thornton EW, Sykes KS, Tang WK. (2004) Health benefits of Tai Chi exercise: improved balance and blood pressure in middle-aged women. Health Promotion International 19(1): 33-8.	Intervention - rev 3?
Tice JA, Kanaya A, Hue T et al. (2006) Risk factors for mortality in middle-aged women. Archives of Internal Medicine 166(22): 2469-77.	Smoking, 9y FU, mean age 68 at baseline

Tourlouki E, Matalas AL, Panagiotakos DB. (2009) Dietary habits and cardiovascular disease risk in middle-aged and elderly populations: a review of evidence. Clinical Interventions in Aging 4: 319-30.	Review, not SR, >65 yrs
Tsai CC, Hsieh MH, Li AH et al. (2013) Dietary supplementation and engaging in physical activity as predictors of coronary artery disease among middle-aged women. Journal of Clinical Nursing 22(17-18): 2487-98.	X-sect
Tsai SP, Donnelly RP, Wendt JK. (2006) Obesity and mortality in a prospective study of a middle-aged industrial population. Journal of Occupational & Environmental Medicine 48(1): 22-7.	Exposure is obesity
Tsuboi S, Hayakawa T, Kanda H et al. (2009) The relationship between clustering health-promoting components of lifestyle and bone status among middle-aged women in a general population. Environmental Health & Preventive Medicine 14(5): 292-298.	X-sect
Tunstall-Pedoe H. (2013) The decline in coronary heart disease; did it fall or was it pushed? BMJ 344: d7809.	Editorial
van Dam RM, Willett WC, Manson JE et al. (2006) Coffee, Caffeine, and Risk of Type 2 Diabetes: a prospective cohort study in younger and middle-aged U.S. women. Diabetes Care 29(2): 398-403.	Age 26-46 at baseline
Van Gelder BM, Buijsse B, Tijhuis M et al. (2007) Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. European Journal of Clinical Nutrition 61(2): 226-232.	>65 at baseline
Van Gelder BM, Tijhuis MAR, Kalmijn S et al. (2004) Physical activity in relation to cognitive decline in elderly men. The FINE Study. Neurology 63(12): 2316-21.	>65 at baseline
van Gool CH, Kempen GI, Penninx BW et al. (2005) Impact of depression on disablement in late middle aged and older persons: results from the Longitudinal Aging Study Amsterdam. Social Science & Medicine 60(1): 25-36.	Exposure is depression
van Vliet P. (2012) Cholesterol and late-life cognitive decline. Journal of Alzheimer’s Disease 30: S147–S162.	Exposure is cholesterol
Verghese J, Lipton RB, Katz MJ et al. (2003) Leisure activities and the risk of dementia in the elderly. New England Journal of Medicine 348: 2508-16.	>75y at baseline
Verghese J, Wang C, Katz MJ et al (2009) Leisure activities and risk of vascular cognitive impairment in older adults. Journal of Geriatric Psychiatry and Neuroogy 22(2): 110-118.	Age 75-85 y at baseline
Villegas R, Liu S, Gao YT et al. (2007) Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Archives of Intern Medicine 167(21): 2310-6.	FU 4.7 y (<5 y)

Virtanen JK, Voutilainen S, Rissanen TH et al. (2006) High dietary methionine intake increases the risk of acute coronary events in middle-aged men. Nutrition, Metabolism & Cardiovascular Diseases 16(2): 113-20.	Exposure is dietary methionine
Voss R, Cullen P, Schulte H et al. (2002) Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Münster Study (PROCAM) using neural networks. International Journal of Epidemiology 31(6): 1253-62.	Neural network modelling
Vuorinen M, Solomon A, Rovio S et al. (2011) Changes in vascular risk factors from midlife to late life and white matter lesions: a 20-year follow-up study. Dementia and Geriatric Cognitive Disorders 31(2): 119-25.	Outcome is white matter lesions but not specific health conditions. Exposures are BP, TC, BMI, ApoE.
Waetjen LE, Liao S, Johnson WO et al. (2007) Factors associated with prevalent and incident urinary incontinence in a cohort of midlife women: a longitudinal analysis of data study of women's health across the nation. American Journal of Epidemiology 165(3): 309-18.	Social support is one exposure - relevant?, Mean age 45 (range 42-52), 5y follow-up so outcomes at <55y
Weirich G, Bemben DA, Bemben MG. (2010) Predictors of balance in young, middle-aged, and late middle-aged women. Journal of Geriatric Physical Therapy 33(3): 110-117.	No behaviour

Weng LC, Steffen LM, Szklo M et al. (2013) A diet pattern with more dairy and nuts, but less meat is related to lower risk of developing hypertension in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. Nutrients 5(5): 1719-1733.	The exposure we are interested in is diet and the outcome is hypertension/blood pressure (as a precondition for dementia, disability and frailty). Baseline measurements were taken at 1987-89 and follow-up at 1990-92 (Exam 2), 1993-95 (Exam 3) and 1996-98 (Exam 4). From the tables (3 and 4) the data seems to be reported for 1987-1998. So the outcome hypertension data was taken from exam 4 (1996-98). So between baseline measurements and Exam 4 there is about 9 years of follow-up. However, between exam 3 and exam 4 there is only 3 years of follow-up and it is not clear from the data reported how much of the analysis was based on 9 year follow-up and how much on 3 year follow up data.
Wennberg P, Andersson T, Bohman M. (2000) Associations between different aspects of alcohol habits in adolescence, early adulthood, and early middle age: a prospective longitudinal study of a representative cohort of men and women. Psychology of Addictive Behaviors 14(3): 303-307.	Adolescent exposure - midlife outcomes
Whalley LJ, Dick FD, McNeil G. (2006) A life-course approach to the aetiology of late-onset dementias. Lancet Neurology 5: 87-96.	Review and model
Whisman MA. (2010) Loneliness and the metabolic syndrome in a population-based sample of middle-aged and older adults. Health Psychology 29(5): 550-554.	X-sect
White L. (2010) Educational attainment and mid-life stress as risk factors for dementia in late life. Brain 133: 2180-2184.	18 months
White SM, Wójcicki TR, McAuley E. (2012) Social cognitive influences on physical activity behavior in middle-aged and older adults. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 64(5): 543-50.	Model

Whitley E, Lee IM, Sesso HD et al. (2012) Association of cigarette smoking from adolescence to middle-age with later total and cardiovascular disease mortality: theHarvard Alumni Health Study. Journal of the American College of Cardiology 60(18): 1839-1840.	Letter not primary study
Whitmer RA, Gunderson EP, Barrett-Connor E et al. (2005). Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 330(7504): 1360.	Exposure is obesity
Whitmer RA, Gunderson EP, Quesenberry CP et al. (2007) Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Current Alzheimer Research 4(2): 103-109.	Exposure is BMI
Whitmer RA, Karter AJ, Yaffe K et al. (2009) Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009 Apr 15;301(15):1565-72	
WHO Ageing Website (accessed 26.11.13)	Information sheet only, not primary study
Wilbur J, A Vassalo, Chandler P et al. (2005) Midlife women's adherence to home-based walking during maintenance. Nursing Research 54(1): 33-40.	Possible for rev 1 - check again
Wilson D, Peters R, Ritchie K et al. (2011) Latest advances on interventions that may prevent, delay or ameliorate dementia. Therapeutic Advances in Chronic Disease 2(3) 161-173.	Review but not SR, check refs
Wolinsky FD, Malmstrom TK, Miller JP et al. (2009) Antecedents of global decline in health-related quality of life among middle-aged African Americans. Journals of Gerontology Series B-Psychological Sciences & Social Sciences 64(2): 290-295.	No behaviour
Woodside JV, Yarnell JW, Patterson CC et al. (2012) Do lifestyle behaviours explain socioeconomic differences in all-cause mortality, and fatal and non-fatal cardiovascular events? Evidence from middle aged men in France and Northern Ireland in the PRIME Study. Preventive Medicine 54(3-4): 247-253.	No behaviour
World Cancer Research Fund/American Institute for Cancer Research. (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC: AICR.	
Wray LA, Alwin DF, McCammon RJ et al. (2006) Social status, risky health behaviors, and diabetes in middle-aged and older adults. Journals of Gerontology Series B-Psychological Sciences & Social Sciences 61(6): S290-298.	Clearly relevant exposures and outcomes but cannot tell which data is longitudinal > 5 years or cross-sectional so excluded on that basis. Contact authors?

Wright JL, Sherriff JL, Dhaliwal SS et al. (2011) Tailored, iterative, printed dietary feedback is as effective as group education in improving dietary behaviours: results from a randomised control trial in middle-aged adults with cardiovascular risk factors. International Journal of Behavioral Nutrition & Physical Activity 8: 43.	Int - rev 3?
Xu WL, Atti AR, Gatz M et al. (2011) Midlife overweight and obesity increase late-life dementia risk: a population-based twin study. Neurology 76(18): 1568-1574.	Exposure is OW/Obesity
Yaffe K, Barnes D, Nevitt M et al. (2001) A prospective study of physical activity and cognitive decline in elderly women. Archives of Internal Medicine 161(14): 1703-1708.	Exclude >65 at baseline
Yagci N, Cavlak U, Aslan UB et al. (2007) Relationship between balance performance and musculoskeletal pain in lower body comparison healthy middle aged and older adults. Archives of Gerontology & Geriatrics 45(1): 109-119.	Balance not behaviour
Yamada M, Kasagi F, Sasaki H et al. (2003) Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. Journal of the American Geriatrics Society 51(3): 410-414.	Mean age <40 y
Yan LL, Daviglus ML, Liu K et al. (2006) Midlife body mass index and hospitalization and mortality in older age. JAMA 295(2): 190-198.	Cannot separate health behaviour data from other risk factors
Yang G, Shu XO, Gao YT et al. (2007) Impacts of weight change on prehypertension in middle-aged and elderly women. International Journal of Obesity 31(12): 1818-1825.	X-sect
Yang L, Kuper H, Sandin Set al. (2009). Reproductive history, oral contraceptive use, and the risk of ischemic and hemorrhagic stoke in a cohort study of middle-aged Swedish women. Stroke 40(4): 1050-1058.	Exposure is oral contraceptive use.
Yarnell JW, Patterson CC, Thomas HF et al. (2000) Comparison of weight in middle age, weight at 18 years, and weight change between, in predicting subsequent 14 year mortality and coronary events: Caerphilly Prospective Study. Journal of Epidemiology & Community Health 54(5): 344-348.	Smoking - BMI relationship but smoking appears to be assessed at age 18 so not midlife.
Ye X, Gao X, Scott T et al. (2011) Habitual sugar intake and cognitive function among middle-aged and older Puerto Ricans without diabetes. British Journal of Nutrition 106(9): 1423-1432.	X-sect analysis
Yoshida M, Ishikawa M, Kokaze A et al. (2003) Association of life-style with intraocular pressure in middle-aged and older Japanese residents. Japanese Journal of Ophthalmology 47(2): 191-8.	X-sect analysis of lifestyle, intraocukar pressure. Age range 29-79 so not midlife specifically
Zhang X, Zhang S, Li Y et al. (2009) Association of obesity and atrial fibrillation among middle-aged and elderly Chinese. International Journal of Obesity 33(11): 1318-1325.	X-sect

APPENDIX H – Methodology checklists

H.1 Quality assessment for quantitative studies (cohort)

<table>
<tr><td>Study identification: Include full citation details</td><td colspan="2"></td></tr>
<tr><td>Study design:
Refer to the glossary of study designs (appendix D) and the algorithm for classifying experimental and observational study designs (appendix E) to best describe the paper's underpinning study design</td><td colspan="2"></td></tr>
<tr><td>Guidance topic:</td><td colspan="2"></td></tr>
<tr><td>Assessed by:</td><td colspan="2"></td></tr>
<tr><td colspan="3">Section 1: Population</td></tr>
<tr><td>1.1 Is the source population or source area well described?
Was the country (e.g. developed or non-developed, type of health care system), setting (primary schools, community centres etc), location (urban, rural), population demographics etc adequately described?</td><td>++
+
−
NR
NA</td><td>Comments:</td></tr>
<tr><td>1.2 Is the eligible population or area representative of the source population or area?
Was the recruitment of individuals, clusters or areas well defined (e.g. advertisement, birth register)?
Was the eligible population representative of the source? Were important groups underrepresented?</td><td>++
+
−
NR
NA</td><td>Comments:</td></tr>
<tr><td>1.3 Do the selected participants or areas represent the eligible population or area?
Was the method of selection of participants from the eligible population well described?
What % of selected individuals or clusters agreed to participate? Were there any sources of bias?
Were the inclusion or exclusion criteria explicit and appropriate?</td><td>++
+
−
NR
NA</td><td>Comments:</td></tr>
</table>

Section 2: Method of selection of exposure (or comparison) group		
2.1 Selection of exposure (and comparison) group. How was selection bias minimised? • How was selection bias minimised?	++ + – NR NA	**Comments:**
2.2 Was the selection of explanatory variables based on a sound theoretical basis? • How sound was the theoretical basis for selecting the explanatory variables?	++ + – NR NA	**Comments:**
2.3 Was the contamination acceptably low? • Did any in the comparison group receive the exposure? • If so, was it sufficient to cause important bias?	++ + – NR NA	**Comments:**
2.4 How well were likely confounding factors identified and controlled? • Were there likely to be other confounding factors not considered or appropriately adjusted for? • Was this sufficient to cause important bias?	++ + – NR NA	**Comments:**
2.5 Is the setting applicable to the UK? • Did the setting differ significantly from the UK?	++ + – NR NA	**Comments:**

Section 3: Outcomes		
3.1 Were the outcome measures and procedures reliable? • Were outcome measures subjective or objective (e.g. biochemically validated nicotine levels ++ vs self-reported smoking −)? • How reliable were outcome measures (e.g. inter- or intra-rater reliability scores)? • Was there any indication that measures had been validated (e.g. validated against a gold standard measure or assessed for content validity)?	**++** **+** **−** **NR** **NA**	**Comments:**
3.2 Were the outcome measurements complete? • Were all or most of the study participants who met the defined study outcome definitions likely to have been identified?	**++** **+** **−** **NR** **NA**	**Comments:**
3.3 Were all the important outcomes assessed? • Were all the important benefits and harms assessed? • Was it possible to determine the overall balance of benefits and harms of the intervention versus comparison?	**++** **+** **−** **NR** **NA**	**Comments:**
3.4 Was there a similar follow-up time in exposure and comparison groups? • If groups are followed for different lengths of time, then more events are likely to occur in the group followed-up for longer distorting the comparison. • Analyses can be adjusted to allow for differences in length of follow-up (e.g. using person-years).	**++** **+** **−** **NR** **NA**	**Comments:**
3.5 Was follow-up time meaningful? • Was follow-up long enough to assess long-term benefits and harms? • Was it too long, e.g. participants lost to follow-up?	**++** **+** **−**	**Comments:**

	NR **NA**	
Section 4: Analyses		
4.1 Was the study sufficiently powered to detect an intervention effect (if one exists)? • A power of 0.8 (i.e. it is likely to see an effect of a given size if one exists, 80% of the time) is the conventionally accepted standard. • Is a power calculation presented? If not, what is the expected effect size? Is the sample size adequate?	**++** **+** **−** **NR** **NA**	**Comments:**
4.2 Were multiple explanatory variables considered in the analyses? • Were there sufficient explanatory variables considered in the analysis?	**++** **+** **−** **NR** **NA**	**Comments:**
4.3 Were the analytical methods appropriate? • Were important differences in follow-up time and likely confounders adjusted for?	**++** **+** **−** **NR** **NA**	**Comments:**
4.6 Was the precision of association given or calculable? Is association meaningful? • Were confidence intervals or p values for effect estimates given or possible to calculate? • Were CIs wide or were they sufficiently precise to aid decision-making? If precision is lacking, is this because the study is under-powered?	**++** **+** **−** **NR** **NA**	**Comments:**
Section 5: Summary		
5.1 Are the study results internally valid (i.e. unbiased)? • How well did the study minimise sources of bias	**++** **+**	**Comments:**

(i.e. adjusting for potential confounders)? • Were there significant flaws in the study design?	−	
5.2 Are the findings generalisable to the source population (i.e. externally valid)? • Are there sufficient details given about the study to determine if the findings are generalisable to the source population? • Consider: participants, interventions and comparisons, outcomes, resource and policy implications.	++ + −	**Comments:**