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 mid-life associated with successful ageing and the primary prevention or delay of disability, dementia, frailty, and non-communicable chronic conditions

REPORT (v3)

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Review team Louise Lafortune*
Sarah Kelly*
Steven Martin
Isla Kuhn
Olivia Remes
Andy Cowan
Carol Brayne

* First co-authorship

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For further details please contact:

Dr Louise Lafortune
Senior Research Associate
Institute of Public Health, Forvie Site
University of Cambridge School of Clinical Medicine
Box 113 Cambridge Biomedical Campus
Cambridge, CB2 0SR
ll394@medschl.cam.ac.uk

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Abbreviations

ADL	Activities of Daily Living
AL	Alcohol
CIPH	Cambridge Institute of Public Health
CL	Combined Lifestyles
COPD	Chronic Obstructive Pulmonary Disease
CPH	Centre for Public Health
CPHE	Centre for Public Health Excellence
CVD	Cardiovascular disease
DG	Disadvantaged Groups
DH	Department of Health
DI	Diet
EC	Eye Care
HB	Health Behaviours
IADL	Instrumental Activities of Daily Living
LC	Leisure and Cognitive activities
LGBT	Lesbian, gay, bisexual and transsexual
NCCs	Non-communicable Chronic Conditions
NICE	National Institute for Health and Care Excellence
NIHR SPHR	National Institute of Health Research School of Public Health Research
OECD	Organisation for Economic Co-Operation and Development
PA	Physical Activity
RCT	Randomised controlled trials
SES	Socioeconomic status
SM	Smoking
WC	Weight Change (weight cycling)
WCRF	World Cancer Research Fund
WHO	World Health Organisation

Operational definitions

Successful ageing	Successful ageing is defined as survival to an advanced age while maintaining physical and cognitive function, functional independence and a full and active life. It means that morbidity and disability are compressed into a relatively short period before death, in line with the 'compression of morbidity' theory.
Disability	Disability will refer to any long-term restriction on the ability to perform an activity in the manner, or within the range, considered normal.
Dementia	Dementia will refer to a progressive, degenerative condition caused by diseases of the brain. Whether it occurs alone, in addition to, or as a combination of, chronic conditions, it is characterised by cognitive and non-cognitive symptoms of variable frequency and severity.
Frailty	Frailty will refer to a syndrome characterised by age-related declines in functional reserves where a small insult (e.g. infection, loss of partner) results in a striking and disproportionate change in health state. Frail older adults experience an increased risk of adverse outcomes such as falls, fractures, comorbidity, disability, dependency, hospitalisation, need for long-term care and mortality.
Non-communicable chronic conditions	Non-communicable chronic conditions will include cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases, obesity, visual and hearing conditions, and some cancers that may be associated with behavioural risk factors.
Disadvantaged populations	Disadvantaged populations will include (but are not limited to) low socioeconomic status, ethnic minority groups, lesbians, gay, bisexual and transsexual (LGBT) community groups, travellers and other groups with protected characteristics under the equality and diversity legislation.

EXECUTIVE SUMMARY

1. INTRODUCTION

1.1 Background

The Department of Health (DH) has asked the National Institute for Health and Care Excellence (NICE) to produce public health guidance on preventive approaches to be adopted in mid-life to delay the onset of disability, dementia and frailty in later life. Three evidence reviews and an economic model will underpin the guidance. The reviews look for evidence on a wide range of potential influences on well-being in later life (i.e. demographic, economic, geographical, physical, cultural and social factors), and at the effectiveness and cost effectiveness of available interventions to act on these factors. This second report presents the findings of the evidence review of behavioural risk factors in mid-life associated with successful ageing and the primary prevention or delay of disability, dementia, frailty and non-communicable chronic conditions.

1.2 Aims and review questions

The overarching research question for the suite of three evidence reviews is which primary prevention approaches to be adopted in mid-life are most effective and cost-effective to prevent and delay the onset of disability, dementia, frailty, and other non-communicable chronic conditions in later-life.

The specific question addressed in this review (Review 2) is:

- What behavioural risk factors in mid-life are associated with successful ageing and the primary prevention or delay of disability, dementia, frailty, and non-communicable chronic conditions? How strong are the associations and how does this vary for different subpopulations?

The two other reviews focus on key issues for people in mid-life that prevent or limit, or which help or motivate them to take up and maintain healthy behaviours (Review 1), and the effectiveness and cost effectiveness of mid-life interventions for increasing uptake and maintenance of healthy behaviours, and the extent to which different interventions to foster healthy behaviours prevent or delay ill health in later life (Review 3).

2. METHODS

The review reports quantitative evidence from observational studies (longitudinal cohort studies) for behavioural risk factors in mid-life (exposure) that are associated with successful ageing, and the primary prevention or delay of disability, dementia, frailty and non-communicable chronic conditions (outcomes).

Exposures of interest include:

- Behavioural risk factors including less sedentary behaviour, increased physical activity, improved diet, weight loss or control, cessation or reduction of smoking, reduction or modification of alcohol consumption, to maintain sufficient levels of social activity and avoid loneliness, avoidance of excessive exposure to noise and addressing hearing and/or sight loss, or to improve/modify multiple behavioural risk factors and health behaviours in general.
- Behavioural risk factors at individual, family, community, subnational or national level.
- Behavioural risk factors in a range of settings including primary and secondary care, and workplace and community settings in the private, public, voluntary or commercial sectors.

Outcomes of interest include: dementia, disability (activities of daily living (ADL), instrumental activities of daily living (IADL), independence, mobility), frailty, healthy life span and measures healthy ageing, quality of life, participation, non-communicable chronic conditions including cardiovascular diseases and stroke, renal disease, cancer, chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis and bone health.

The population covered by the review includes adults aged 40 to 64 years for the general population, and adults aged 18-39 from disadvantaged populations, with outcomes at follow-up in people aged 55 and over. The review does not cover people with and treated for pre-existing conditions (i.e. dementia, frailty, disability, non-chronic communicable conditions) nor does it cover the treatment (i.e. drugs, dietary supplements), diagnosis and care and management of these conditions.

We conducted a thorough search of the scientific and grey literature to identify studies published in English since 2000 that reported results of multivariate analyses for these associations. A minimum follow-up of five years was required for inclusion (as follow-up of less than five years is unlikely to be sufficient for the development and measurement of dementia, disability, frailty or pre-conditions associated with behavioural risk factors). Cross-sectional and qualitative studies are excluded.

Two reviewers screened the title and abstract of identified references independently. Primary studies that met the inclusion criteria were assessed for quality using available tools from NICE (CPH methods manual).

Quantitative evidence from cohort studies is synthesised descriptively by behavioural risk, for a range of late life outcomes. Data specific to health inequalities and vulnerable communities are assessed and findings are summarised separately where sufficient data is available.

For each key issue or factor of interest an evidence statement was generated which provides an aggregated summary of all of the relevant studies. Applicability ratings (i.e. directly applicable, partially applicable or not applicable) are proposed for each evidence statement to judge how similar the population(s), setting(s), intervention(s) and outcome(s) of the included studies are to those outlined in the review question.

3. RESULTS

Overall findings

This review includes 164 observational longitudinal cohort studies that have reported on the association between the following behavioural risk factors in midlife:

- Physical activity, physical inactivity
- Diet
- Smoking and smokeless tobacco (snus/snuff)
- Alcohol
- Weight change, weight cycling
- Combinations of lifestyle behaviours (combined lifestyles)
- Leisure, cognitive activity, social networks

and the following categories of outcomes:

- Successful ageing (including quality of life, well-being)
- Dementia
- Disability & frailty
- Overall mortality
- Cardiovascular outcomes (mortality; morbidity)
- Diabetes, metabolic syndrome, insulin sensitivity
- Cancer

- Mental health
- Other non-communicable chronic diseases

Studies reporting other behavioural risk factors (including behaviours related to vision and hearing) were sought but none were found that met the inclusion criteria.

The evidence for this review is reported in 3 tiers of data:

1. Overall summary tables are presented that summarise visually the overall trend of the data – showing whether outcomes are improved, poorer or null (based on statistical significance) for each health behaviour (Tables 1 through 8 below).
2. Summary tables of included studies for each health behaviour with a summary of the characteristics and data for each study and a summary of outcomes (Tables 9 through 17). Data presented in the tables is only from multivariate models. Where the authors report findings for multiple models, the most adjusted (or most relevant) model has been used in the summary tables and the evidence statements. Where a paper reports the same outcome at different timepoints that paper has not been excluded, the data at different timepoints has been reported but it has been pointed out in the evidence statements. It only applies to a few studies.
3. Full evidence tables (Appendix A) that show the full extracted data for each included study.

Overall, the quality of studies is good (most studies were rated as high or moderate quality) and most of them are directly or partially applicable to the UK context. Studies conducted in the UK were prioritised in the synthesis of data and the evidence and applicability statements.

EVIDENCE STATEMENTS (see page 141 onwards)

4. OVERALL SUMMARY

Supported by summary tables 1 through 8, below.

Physical activity (PA)

For PA and inactivity, 45 reports were included. The available data covers different levels and intensity of PA and a few studies report specific types of activity (e.g. walking, active commuting). There is consistent evidence that midlife physical activity has a beneficial effect

on later life healthy ageing, dementia, disability and other chronic disease outcomes. One study (out of 45 studies) reported a negative outcome, i.e. increased risk of bladder cancer in men participating in vigorous activity at midlife. Beneficial effects were reported for both men and women.

The promotion of physical activity in all midlife populations including men and women and different ethnic groups should be addressed by the guidance. All types of activity appear to have a positive relationship with outcomes.

Diet (DI)

For diet, 48 studies were included. Evidence was found covering midlife dietary patterns and consumption of dietary components, such macronutrients and for specific foods. There is some consistent evidence (but from a limited number of studies) that a healthy diet in general (studies included e.g. ADA diets) or Mediterranean diet, and fruit and vegetables have beneficial effects on late life outcomes. There is also consistent evidence (again from a limited number of studies) that higher consumption of saturated fat or processed and red meat (reported together) in midlife is associated with poorer ageing, disability, dementia, frailty outcomes and non-communicable conditions. There was some evidence (from a limited number of studies) that coffee consumption in moderation may be beneficial.

A healthy diet (standard guidelines) or Mediterranean-type diet could be recommended, also diets which minimise consumption of saturated fat, increase fruit and vegetable intake with moderate consumption of processed or red meat. Coffee consumption in moderation.

Alcohol (AL)

Twenty-four prospective cohort studies were included on alcohol intake. Evidence specific to midlife alcohol consumption was mixed. Some studies reported negative outcomes e.g. for dementia, mortality and cancer and some more positive outcomes e.g. for ageing and mental health. However studies found were sparsely distributed among different outcomes. Two studies reported moderate quality evidence of higher risk of dementia in non-drinkers and heavy drinkers compared to moderate drinkers, but limited evidence was available specific to midlife. There was limited evidence, from one study, that for people in lower SES groups high alcohol intake (>21 drinks/week) at midlife is related to poorer cognitive performance in later life.

It is not clear from the findings of this review whether there is a safe level of alcohol consumption, so caution should be exercised in making recommendations in that respect.

Smoking (SM)

The review found a wealth of evidence from longitudinal cohort studies (n=57) relating to the association between midlife smoking and late life outcomes. There is consistent evidence that midlife smoking has a detrimental effect on later life dementia, disability and other chronic disease outcomes including: healthy ageing, mobility, dementia, CVD outcomes, cancer (lung, pancreatic, colorectal, cancer mortality) and total mortality. Smoking had a detrimental effect on all populations for which studies were found, including men and women and in different ethnic groups.

Smokeless tobacco (SNUS)

Only one study was found which suggested that smokeless tobacco may be associated with improved diabetes related outcomes but evidence for midlife relationship with later outcomes was very limited.

Weight change, weight cycling (WC)

Four studies were included that reported an association between weight change patterns in midlife and later outcomes. One study reported increased risk of hip fracture in those losing greater than 10% of their body weight (as determined from maximum weight during follow up). Two studies reported null relationships with weight loss/gain or cycling, one with mortality as an outcome and one with diabetes as an outcome. One study reported increased risk of dementia with weight change in midlife (independent of the direction of weight change). There was some limited evidence that being overweight or obese appeared to be a more important factor in the association with diabetes than weight change in midlife.

Combined healthy lifestyle programmes (CL)

There is some consistent evidence (from 3 studies) that combinations of lifestyle behaviours (not smoking, fruit and veg intake, maintaining healthy weight, regular exercise, moderate alcohol intake) have beneficial outcomes for ageing well, disability, dementia, frailty outcomes and non-communicable conditions.

Consideration could be given to programmes which combine at least two or more aspects of healthy behaviour (from PA, healthy diet, non-smoking, alcohol in moderation, leisure activities)

Leisure activities/social activities

There is some evidence that those who participate in a diverse range of intellectual, passive, physical and leisure activities in midlife have better cognitive outcomes, however the number of studies specific to midlife with later life outcomes was limited and activities varied across studies. There was insufficient consistent data in midlife to determine if the relationship was causal or related to baseline cognitive ability.

Consideration could be given to improving social support and access to activities. This could be incorporated into healthy lifestyle programmes (with evaluation to build the evidence base).

Other health-related behaviours

Evidence was sought but not found within the inclusion criteria for other behaviours including vision and hearing related behaviours.

Disadvantaged groups/health inequalities

Data relating to disadvantaged groups was also limited with some sparse data on people with low SES, ethnic minority groups and gender in midlife with relevant outcomes. This data is summarised above for each health behaviour. No relevant data was found for other groups covered by the equality and diversity legislation.

5. DISCUSSION

This review aimed to identify if there were any specific issues or behavioural risk factors at midlife that should be considered by the PHAC team when designing the guidance. It synthesises the evidence from observational studies (longitudinal cohort studies) for the association between modifiable behavioural risk factors in midlife (age 40-65 years) and dementia, disability and frailty, and non-communicable conditions in later life (age >65 years).

Included studies reported follow up from 5 years to 36 years. Most of the data used to assess behaviour was self-reported with little objective data, although many of the smoking studies used biochemical confirmation of smoking status. In general outcome data was assessed objectively using clinical data and medical records or registers. Included studies were mainly from OECD countries and most were from Europe and the US with a fairly good representation of studies from the UK.

Limitations & gaps in evidence - Limited evidence was found specifically relating to midlife behaviours for leisure activities including cognitive activities and social networks, weight change and weight cycling, smokeless tobacco, and sight and hearing risks. While many diet-related studies were found they covered a broad range of diets and dietary components. There were some diets or dietary components for which studies specifically pertaining to midlife were not found. Data relating to disadvantaged groups was also limited. Some sparse data on people with low SES, ethnic minority groups and gender in midlife was found. No longitudinal data was found relevant to other groups covered by the equality and diversity legislation such as LGBT groups or travellers.

Limitation of the review - The remit of this review was specifically to identify midlife behavioural risk factors for dementia, disability, frailty outcomes and common NCCs in later life. Determinants of these outcomes over the whole lifecourse were not included. Also, the review only includes longitudinal observational studies, which can show an association between midlife risk factors and later life outcomes, but not causality.

Due to the wide scope of the review, the large amount of literature covering behavioural risk factors and the outcomes of interest, and the timescales for the review, the searches were focused on studies with midlife-related terms in the title, abstract or related MeSH indexing to identify those studies that specifically aimed to report on midlife exposure. The implication of this pragmatic approach is that cohort studies that have followed individuals from mid- to late life and reported associations of interest without specifying midlife terms in the title or abstract were not identified by the searches. This might explain some of the gaps in evidence and further work is ongoing (though beyond the scope of this report) to address this limitation.

Because a very large amount of data was found for a wide range of risks and outcomes, the search limitations are unlikely to have an impact on the overall findings. In fact, it appears that a lot of what we know of the associations between behavioural risk factors and late life outcomes comes from studies conducted in people in mid-life. So, where caution should be exercised is in extrapolating the mid-life associations to older age groups – the direction and magnitude of these associations vary across the life cycle. This is the focus of several work packages undertaken by NIHR SPHR Ageing Well programme, which should complement the findings of this review with regards to identifying behavioural risk factors that are amenable to change for improved health outcomes in later life.

Table 1. Overall summary of studies of PHYSICAL ACTIVITY/INACTIVITY and dementia, disability, frailty, chronic disease*

Successful ageing	Disability and frailty	Dementia	Total mortality	CVD outcomes (events and mortality)	Diabetes (MetS)	Cancer (and cancer mortality)	Other chronic diseases	Mental health
2.3.1PA	**2.3.2PA**	**2.3.3PA**	**2.3.4PA**	**2.3.5PA**	**2.3.6PA**	**2.3.7PA**		**2.3.8PA**
√√√ [+][++][++] UK,UK,US	√√√√√ 0 [+][+][-][+][-] [+] UK,It,Ice,Fin,US, Fin	(√√)(√√)√√ 00 ([+])([+])[+][-] [++][-] UK,Swe,US,Ice, Swe, US (2 light but not heavy √)	(√√)√√√ ([+])[+][+][+] UK,Fin,Den,Ger	(√√)(√√√)√√√√ ([+])([+])[+][+][++][+] UK,Fin,Swe,Ger,Gre,Den	√√ (√√√) [+]([+]) UK,Nor	0(√0X)0√ [+]([+])[+][+] UK,UK,UK,Fin X=increased risk of bladder cancer/vig act (OR= 2.1 (95%CI 1.1-4.0)		√ 0 (5 y not 10y) [+][-] UK,Aust
Physical inactivity								
	0 [-] Den		0 [+] Fin	(X0) [+] Fin				

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

Table 2. Overall summary of studies of DIET (DI) and dietary component*

Evidence statement ref.	Diet or components of diet	Successful ageing	Disability & frailty	Dementia	Total mortality	CVD outcomes	Diabetes (MetS)	Cancer	Other chronic diseases	Mental health
2.5.1DI	Healthy dietary pattern	√√	√				√	0		√
2.5.1DI	Mediterranean diet	√				√√				√
2.5.1DI	Western diet	X								
2.5.2DI	Fruit and vegetables		√ 0 0	√ 0	√√ 0	√ 0	 0	 0 0	√	
2.5.3DI	Fat (saturated)		X	X		0	X			
2.5.3DI	Fat (polyunsaturated)			√		0				
2.5.3DI	Fat (monounsat)					0				
2.5.3DI	Fat (total)					0		X		
2.5.4DI	Fish				X	√ 0	√ women 0 men		√	
2.5.5DI	Meat		√ (>1 per 2 d)			√ (1-2/wk)				
2.5.5DI	Red and processed meat					X	X	X X		
2.5.6DI	Coffee		0	√ 0		X (heavy)	√√		√√	0
2.5.6DI	Tea								√	0
2.5.6DI	Caffeine								√	0
2.5.7DI	Milk							√		

2.5.8DI	Salt							X		
2.5.9DI	Glycaemic index/GL					√0				
2.5.10DI	Protein					0		0		
2.5.11DI	Chocolate					√ (1-3 times/month only)				
2.5.12DI	Fibre							0		
2.5.13DI	Micronutrients			0				√		0
2.5.13DI	Flavonoids			0		√		0		

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

Table 3. Overall summary of studies of SMOKING (SM) and dementia, disability, frailty, chronic disease*

Successful ageing	Disability and frailty	Dementia	Total mortality	CVD outcomes (events and mortality)	Diabetes (MetS)	Cancer (and cancer mortality)	Other chronic diseases	Mental health
2.6.1SM	**2.6.2SM**	**2.6.3SM**	**2.6.4SM**	**2.6.5SM**	**2.6.6SM**	**2.6.7SM**	**2.6.9SM**	**2.6.8SM**
XXX	XX (mobility) 0X0X (fract)	XXXXXX (dementia) 00XXX (cognition)	X(XXX)XXX √√√√√ (Ex-smokers)	XXXXXX0 (mortality) XXXXXXXXXXX0 (CVD)	XXX0 (Dia) X0 (MetS)	XXXXXX (lung, pancreatic,colorectal,cancer)	X (kidney disease) 0 (ex smoker)	No studies
All [+]	[+][-] (mobility) All [+] (fracture)	All [+]	All [+]	All [+] (mortality) 3[++] 9[+] (CVD)	All [+]	All [+]	[+]	
UK,Fin,US	Swe,US Swe,Swe,UK,Aust	US,US,US,Kor,US,US Us,Nor, UK,UK,NL	UK,3Fin,Jp,Sing, Is	US,Cz,Jp,Jp,Is,SingCh UK,UK,Jp,Jp,Swe,Jp,Swe,Swe,US,US,Swe	UK,Fin,Jp,Nor	UK,UK,Jp,Jp,Jp,Sing	Jp	

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

Review 4. Overall summary of studies of ALCOHOL (AL) and dementia, disability, frailty, chronic disease*

Successful ageing	Disability and frailty	Dementia	Total mortality	CVD outcomes (events & mortality)	Diabetes (MetS)	Cancer (and cancer mortality)	Other chronic diseases	Mental health
2.7.1AL	**2.7.2AL**	**2.7.3AL**	**2.7.4AL**	**2.7.5AL**	**2.7.6AL**	**2.7.7AL**	**2.7.8AL**	**2.7.9AL**
√X	X (ADL) 0X (fract)	X0 (dementia APOE4) 0 (cognition) XX (Abstainers (compared to mod or infreq) XXX Heavy drinkers (APOE4 compared to non-drinkers)	X	000 XX (Heavy cf occasional) √ (Reg cf occasional)	X (Diabetes - mod or high) X0√ (MetS)	000X	0 (COPD)	√
[++][+]	[-] [+][+]	All[+][	[++]	[+][++][+] [++][+] [+]	[+] [+][+][+]	[+][+][++][+]	[-]	[-]
US, US	US Swe, UK	Fin, UK FR Fin,UK Fin,Fr,Fin	UK	UK, Ch, NL UK, Jp UK	Jp UK,UK,US	UK,UK,US,Jp	Europe	Aust

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

Table 5. Overall summary of studies of WEIGHT CHANGE/CYCLING (WC) and dementia, disability, frailty, chronic disease*

Successful ageing	Disability and frailty	Dementia	Total mortality	CVD outcomes (events and mortality)	Diabetes (MetS)	Cancer (and cancer mortality)	Other chronic diseases	Mental health
2.8.1WC	**2.8.2WC**	**2.8.3WC**	**2.8.4WC**	**2.8.5WC**	**2.8.6WC**	**2.8.7WC**	**2.8.8WC**	**2.8.9WC**
	Weight loss of > 10% from max	Weight variability	Weight cycling		Weight cycling when OW at midlife			
	X (hip fracture)	X	0		X			
	[+]	[+]	[+]		[++]			
	US	Israel	US		US			

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

TABLE 6. Overall summary of studies of ACTIVITIES (LC) and dementia, disability, frailty, chronic disease*

Successful ageing	Disability and frailty	Dementia	Total mortality	CVD outcomes (events and mortality)	Diabetes (MetS)	Cancer (and cancer mortality)	Other chronic diseases	Mental health
2.9.1LC	**2.9.2LC**	**2.9.3LC**	**2.9.4LC**	**2.9.5LC**	**2.9.6LC**	**2.9.7LC**	**2.9.8LC**	**2.9.9LC**
0	0	√ (dementia) √√√ (cognition)						
[+]	[-]	[-] [++][++][++]						
UK	Swe	US Aust, US, Swe						

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

TABLE 7. Overall summary of studies of COMBINED HEALTHY LIFESTYLE (CL) and dementia, disability, frailty, chronic disease*

Successful ageing	Disability and frailty	Dementia	Total mortality	CVD outcomes (events and mortality)	Diabetes (MetS)	Cancer (and cancer mortality)	Other chronic diseases	Mental health
2.10.1CL	**2.10.2CL**	**2.10.3CL**	**2.10.4CL**	**2.10.5CL**	**2.10.6CL**	**2.10.7CL**	**2.10.8CL**	**2.10.9CL**
		√0 (cog) [++][+] US, UK	√ √ [++][+] US, UK (no of healthy behaviours)	√0 [++][+] US, UK (no of healthy behaviours)	0 [+] UK	0 [+] UK		

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

TABLE 8. Overall summary of studies of SMOKELESS TOBACCO and dementia, disability, frailty, chronic disease*

Successful ageing	Disability and frailty	Dementia	Total mortality	CVD outcomes (events and mortality)	Diabetes (MetS)	Cancer (and cancer mortality)	Other chronic diseases	Mental health
2.11ST					**2.11.1ST**			
					√ (insulin, weight) [+] Swe			

√ = study that shows improved outcomes; 0 = study that shows no significant association; X = study that shows poorer outcomes

[++/+/-] Quality of study; country where study conducted

1. INTRODUCTION

1.1 Background

Non-communicable chronic conditions and disability in later life are heavily influenced by behaviours across the life course, which in turn are influenced by a variety of wider contextual social, economic, and organisational factors (Kuh 2002; Clegg 2013). Although these outcomes manifest themselves in later life, the processes leading to ill health have been shown to start in mid-life (Newman et al. 2011; Singh-Manoux et al. 2011; Wills et al. 2011). The four main behavioural risk factors[1], i.e. smoking, excessive consumption of alcohol, poor diet and low levels of physical activity, contribute to close to half of the burden of illness in developed countries (WHO 2002). And it is well known that these risks, which tend to co-occur or cluster, are unequally distributed in the population.

It is encouraging that European and UK specific epidemiology data over the last two decades show that it is possible to prevent or delay morbidity and mortality related to behavioural risk factors (Barnes and Yaffe 2011). Data also shows that people who adopt healthy behaviours are more likely to age successfully and have improved quality of life (Khaw et al. 2008; Myint et al. 2011; Sabia et al. 2012). However, finding effective ways to change people's behaviours is a challenging task without a good understanding as to why people engage in unhealthy behaviours, or do not undertake unhealthy ones.

Although many good systematic reviews have looked at the links between specific and multiple behavioural risk factors and individual chronic conditions, evidence on the association between these behaviours in *mid-life* across a range of late life outcomes and for subgroups of the population has yet to be comprehensively assessed. That is particularly true for the relationship between behavioural risk factors and frailty, where the operational definition of this complex syndrome is still controversial; and for dementia where the many unknowns about the natural history of the disease make the development of effective preventive interventions even more challenging. A good understanding of cultural, ethnic, and geographic differences in how people view and interpret health risks and health behaviours is also necessary for these interventions to work.

[1]The collective term for these risk factors is the subject of much debate, with people from different fields preferring different terminology, each having a view about what is pejorative and what is not. Phrases used range from 'unhealthy or healthy behaviours' and 'poor health behaviours', health promoting behaviours, 'lifestyle risks', behavioural risk factors. We will use the terms healthy behaviours and behavioural risk factors interchangeably in this report.

In that context, the Department of Health (DH) has asked National Institute for Health and Care Excellence (NICE) to produce public health guidance on preventive approaches to be adopted in mid-life to delay the onset of disability, dementia and frailty in later life. Three evidence reviews and an economic model underpin the guidance. The reviews looked for evidence on a wide range of potential influences on well-being in later life (i.e. demographic, economic, geographical, physical, cultural and social factors), and at the effectiveness and cost effectiveness of available interventions to act on these factors. This second report presents the findings of the evidence review of behavioural risk factors in mid-life associated with successful ageing and the primary prevention or delay of disability, dementia, frailty and non-communicable chronic conditions.

1.2 Aims of the review

This review is the second of three to be conducted to inform the guidance on which primary prevention behaviours to be adopted in mid-life are most effective and cost-effective to prevent and delay the onset of disability, dementia, frailty in later life. The full scope of the guidance is available in the final scope document (Final Scope, NICE 2013) that incorporates stakeholder comments from a 4-week public consultation (21 March to 18 April 2013).

1.3 Research questions

The specific question addressed in this review (Review 2) is:

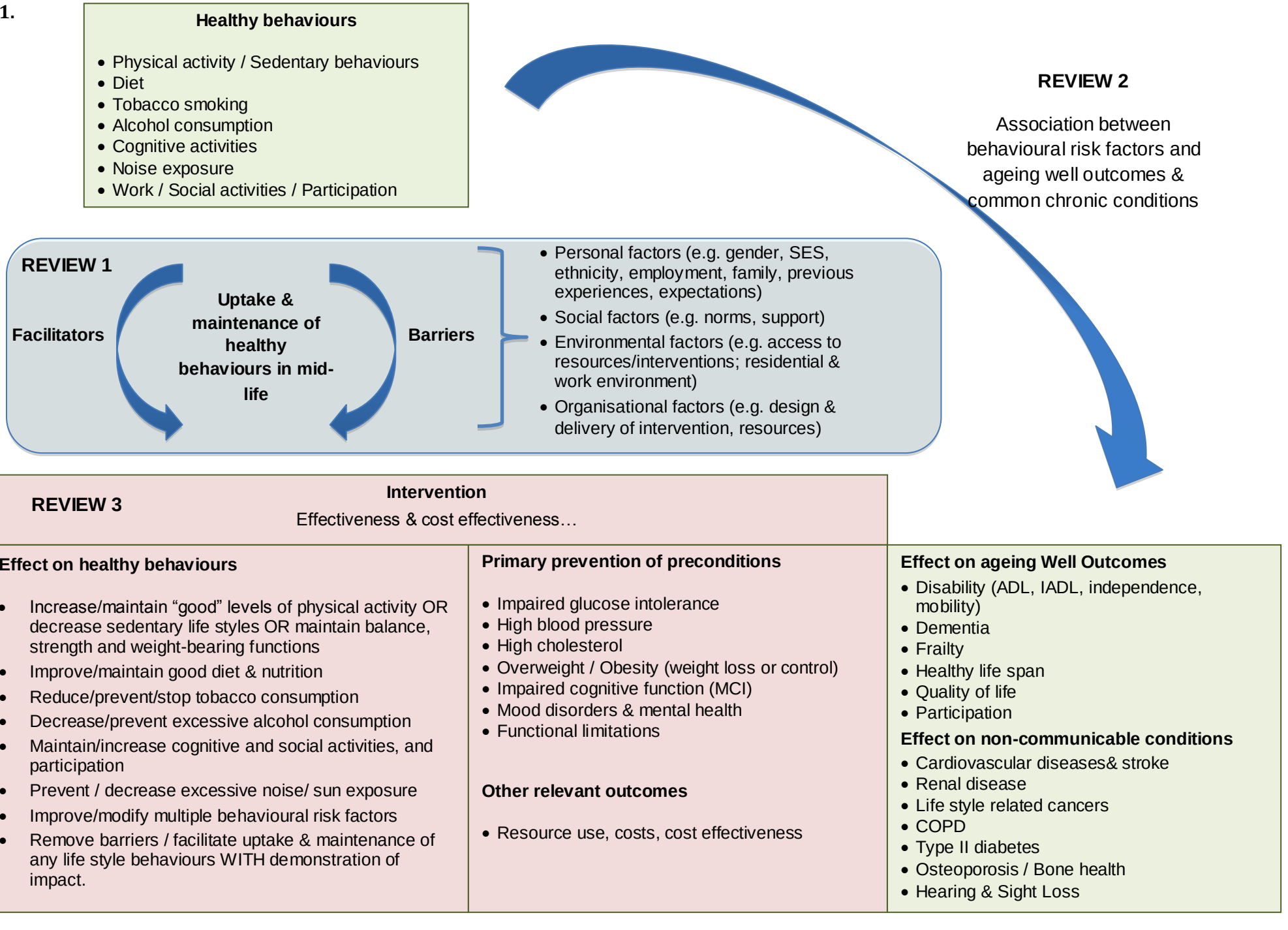
- What behavioural risk factors in mid-life are associated with successful ageing and the primary prevention or delay of disability, dementia, frailty, and non-communicable chronic conditions? How strong are the associations and how does this vary for different subpopulations?

The two other evidence reviews (presented separately) address the following questions:

- Review 1: What are the key issues for people in mid-life that prevent or limit, or which help or motivate them to take up and maintain healthy behaviours, and to what extent do they have an effect? How does this differ for subpopulations, for example by ethnicity, socioeconomic status or gender?
- Review 3: What are the most effective and cost-effective mid-life interventions for increasing the uptake and maintenance of healthy behaviours? To what extent do the different health behaviours prevent or delay disability and frailty related to modifiable behavioural risk factors? To what extent do the different health behaviours prevent or delay dementia? To what extent do the different health behaviours prevent or delay non-communicable chronic conditions?

A conceptual overview of the three reviews and how Review 2 fits into the overall scheme is presented in Figure 1. The model details behavioural risk factors in mid-life, interventions to improve or maintain healthy behaviours, intermediate biological risk factors that can be influenced by healthy behaviours and preventable outcomes relating to dementia, disability, frailty or non-communicable chronic conditions in later life. The model was used to inform the searches and selection of studies for the review.

Figure 1.


Healthy behaviours
Physical activity / Sedentary behaviours
Diet
Tobacco smoking
Alcohol consumption
Cognitive activities
Noise exposure
Work / Social activities / Participation
REVIEW 2
Association between behavioural risk factors and ageing well outcomes & common chronic conditions
REVIEW 1
Facilitators
Uptake & maintenance of healthy behaviours in mid-life
Barriers
Personal factors (e.g. gender, SES, ethnicity, employment, family, previous experiences, expectations)
Social factors (e.g. norms, support)
Environmental factors (e.g. access to resources/interventions; residential & work environment)
Organisational factors (e.g. design & delivery of intervention, resources)
REVIEW 3
Intervention
Effectiveness & cost effectiveness…
Effect on healthy behaviours
Increase/maintain "good" levels of physical activity OR decrease sedentary life styles OR maintain balance, strength and weight-bearing functions
Improve/maintain good diet & nutrition
Reduce/prevent/stop tobacco consumption
Decrease/prevent excessive alcohol consumption
Maintain/increase cognitive and social activities, and participation
Prevent / decrease excessive noise/ sun exposure
Improve/modify multiple behavioural risk factors
Remove barriers / facilitate uptake & maintenance of any life style behaviours WITH demonstration of impact.
Primary prevention of preconditions
Impaired glucose intolerance
High blood pressure
High cholesterol
Overweight / Obesity (weight loss or control)
Impaired cognitive function (MCI)
Mood disorders & mental health
Functional limitations
Other relevant outcomes
Resource use, costs, cost effectiveness
Effect on ageing Well Outcomes
Disability (ADL, IADL, independence, mobility)
Dementia
Frailty
Healthy life span
Quality of life
Participation
Effect on non-communicable conditions
Cardiovascular diseases& stroke
Renal disease
Life style related cancers
COPD
Type II diabetes
Osteoporosis / Bone health
Hearing & Sight Loss

1.4 Operational definitions

- Successful ageing is defined as survival to an advanced age while maintaining physical and cognitive function, functional independence and a full and active life. It means that morbidity and disability are compressed into a relatively short period before death, in line with the 'compression of morbidity' theory (Fries 2011).
- Disability will refer to any long-term restriction on the ability to perform an activity in the manner, or within the range, considered normal.
- Dementia will refer to a progressive, degenerative condition caused by diseases of the brain. Whether it occurs alone, in addition to, or as a combination of, chronic conditions, it is characterised by cognitive and non-cognitive symptoms of variable frequency and severity.
- Frailty will refer to a syndrome characterised by age-related declines in functional reserves where a small insult (e.g. infection, loss of partner) results in a striking and disproportionate change in health state. Frail older adults experience an increased risk of adverse outcomes such as falls, fractures, comorbidity, disability, dependency, hospitalisation, need for long-term care and mortality (Clegg 2013).
- Non-communicable chronic conditions (NCCs) will include cardiovascular diseases, diabetes, chronic obstructive pulmonary diseases, obesity, visual and hearing conditions, and some cancers that may be associated with behavioural risk factors.
- Disadvantaged populations will include (but are not limited to) low socioeconomic status, ethnic minority groups, lesbians, gay, bisexual and transsexual (LGBT) community groups, travellers and other groups with protected characteristics under the equality and diversity legislation.

1.5 Equality and equity issues

A core aim of this programme of evidence review is to identify prevention approaches that are tailored to mid-life populations, focusing on those that have the greatest potential to maintain well-being in later life and avoid or reduce inequalities. The reviews synthese and highlight the evidence pertaining to groups or subgroups of the population that are at increased risk of ill health or less likely to benefit from preventive interventions because of biological, psychosocial factors, environmental factors – or a combination thereof (Ben-Shlomo 2003).

It is hoped that the combined outputs will summarise an evidence base that address key areas of concern for government and society – how to optimise health and well-being, and reduce inequalities in our ageing societies; how to tackle at a population level increasing

health and social care demand; and how to change policy and practice through better use of research.

1.6 Review team

The expertise of the review team and the role of each member in the review are presented in Appendix D.

2. METHODOLOGY

2.1 Searches

An iterative approach involving the whole team was undertaken to develop the search strategies. The key steps were:

a) Initial team discussions around research questions.

b) Initial drafting of search building at least (but not exclusively) on the final scope for this guidance, comments received from key stakeholders on the draft scope, high quality peer-review systematic reviews (when available) on same or similar topics for each key domains of the strategy, (e.g. health, preventative interventions, behaviours, etc.);

c) Testing of individual components and development of the review specific strategies in key databases;

d) Refining of specific review strategies upon discussion with information specialist;

e) Updating of search strategies based on reviewers comments;

f) Adaptation of strategies to individual databases (i.e. Mesh terms or filters in one database don't usually apply to other databases);

g) Running of search and uploading of references in individual Endnote data bases (for specified time period, i.e. since 2000);

h) Create a combined Endnote database (master file); delete duplicate and prepare for title screening;

i) Identification of potential included studies; selection of full text for further assessment; identification of included and excluded studies.

Searching was conducted in two stages: 1) searching for primary longitudinal cohort studies using an observational study search filter agreed with CPH), and 2) where there are no primary studies covering a topic or area, targeted searches were conducted for relevant systematic reviews in adults in general as appropriate, using a systematic review search filter agreed with CPH.

We searched the following electronic databases for peer-reviewed studies published since year 2000 (with host platform):

- MEDLINE (including MEDLINE – in-process) (Ovid)
- EMBASE (Ovid)
- PsycINFO (Ovid)
- CINAHL (EBSCO host)
- Health Management Information Consortium (Ovid)
- Social Science Citation Index (Web of Knowledge)

The following additional databases were searched for systematic reviews published since year 2000:

- HTA database
- The Cochrane Collaboration databases (www.thecochranelibrary.com)
    - Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effectiveness

Searches were restricted to publications in English language. The detailed search strategies used to identify primary studies and systematic reviews are presented in Appendix E.

Finally, we conducted a thorough grey literature search (simultaneously for all three reviews) to identify publications that may provide a source of relevant data. The websites searched are:

- NHS Evidence Search (www.evidence.nhs.uk)
- Open Grey (www.opengrey.eu)
- Public Health Observatories (www.apho.org.uk)
- Health Evidence Canada (www.healthevidence.org)
  Alzheimer's Society (www.alzheimers.org.uk)
- RNIB (www.fightforsight.org.uk)
- Fight for Sight (www.fightforsight.org.uk)
- Action on Hearing Loss (www.actiononhearingloss.org.uk)
- Beth Johnson Foundation (www.bjf.org.uk)
- British Library (http://www.bl.uk)
- Campbell Collaboration (http://www.campbellcollaboration.org)
- Department of Health (https://www.gov.uk/government/publications)
- E-Print Network (http://www.osti.gov/eprints/)
- Google Scholar (http://scholar.google.co.uk)
- Grey Literature Report (http://www.greylit.org)

- Lenus (http://www.lenus.ie/hse/)
- OAIster (http://www.oclc.org)
- Public Health Europe (http://ec.europa.eu/health/index_en.htm)
- RAND Health (http://www.rand.org/health.html)
- Scirus (http://www.scirus.com)
- World Health Organisation (http://www.who.int/en/)

We did not conduct additional hand searches nor did we contact authors for additional data. However, the publication list of the Behaviour and Health Research Unit at the University of Cambridge (led by Professor Theresa Marteau) was searched for relevant publications as well as the responses to the NICE call for evidence relating to this guidance conducted between 31/5/2013 and 28/6/2013.

Records retrieved from the searches are reported according to Appendix C of the CPHE methods manual in Appendix F.

2.2 Population

The populations covered by this review include:

- Adults aged 40-64 years, with a particular focus on people at increased risk of disability, dementia, frailty, or other non-communicable chronic conditions (NCCs) due to behavioural risk factors.
- Adults aged 39 and younger from disadvantaged populations (as they are at increased risk of ill health and more likely to develop multiple morbidities). Disadvantaged populations include (but is not limited to) low socioeconomic status; ethnic minority groups; lesbian, gay, bisexual, transsexual (LGBT) groups; travellers, and other groups with protected characteristics under the equality and diversity legislation.

This review does not cover the following populations:

- Adults with any type of dementia or pre-existing cognitive impairments in mid-life.
- Adults who are receiving treatment for a non-communicable chronic condition.
- Adults who have a disability associated with behavioural risk factors will not be included for that particular condition or disability.

2.3 Behavioural risk factors – scope

This review focuses on:

- Behavioural risk factors for people in mid-life (aged 40 to 64) that are associated with successful ageing or the development and progression of: disability, dementia, frailty

(including bone health) and common NCCs in older age (age 55 and over). Examples of the latter include cardiovascular diseases and stroke, type 2 diabetes, chronic obstructive pulmonary disease, renal disease, osteoporosis and bone health, visual and hearing conditions and some cancers that may be associated with lifestyle (these may be defined by the types of studies found).

- Behavioural risk factors for younger adults (aged 18 to 39) from disadvantaged populations (as defined in section 2.2) that are associated with successful ageing or the development and progression of: disability, dementia, frailty (including bone health) and common non-communicable chronic conditions in older age (age 55 and over). As disability, frailty and common non-communicable chronic conditions may present earlier in people from disadvantaged populations, outcomes for this group would not be restricted to those in people aged 55 and over.

- Behavioural risk factors by people in mid-life (aged 40 to 64) that are associated with the development and progression of 'preconditions' for disability, dementia, frailty (including bone health) and common non-communicable chronic conditions in later life (age 55 and over). Such preconditions include high blood pressure, impaired glucose intolerance, high cholesterol, overweight/obesity, impaired cognitive function, mood disorders, and functional limitations.

- Behavioural risk factors for younger adults (aged 18 to 39) from disadvantaged populations (as defined in section 2.2) that are associated with the development and progression of preconditions for disability, dementia, frailty (including bone health) and common non-communicable chronic conditions in later life.

The scope of the review includes:

- Behavioural risk factors including less sedentary behaviour, increased physical activity, improved diet or components of diet (e.g. fat intake, fruit and vegetable intake), weight loss or control, cessation or reduction of smoking, reduction or modification of alcohol consumption, to maintain sufficient levels of social activity and avoid loneliness, avoidance of excessive exposure to noise and addressing hearing and/or sight loss, or to improve/modify multiple behavioural risk factors and health behaviours in general.
- Behavioural risk factors at individual, family, community, subnational or national level (these may be targeted at specific groups, particularly those who are at increased risk, or who are from disadvantaged groups, or at healthcare professionals).

- Behavioural risk factors in a range of settings including primary and secondary care, and workplace and community settings in the private, public, voluntary or commercial sectors.

Associations between health-related behaviours in mid-life and ageing well outcomes and NCCs, and between health-related behaviours and 'preconditions' such as overweight or obesity, or hypertension or raised cholesterol are covered by the scope of the review and the guidance. However, associations in people with existing dementia, disability, frailty or NCCs fall outside the scope of this review and the guidance. Associations between preconditions and dementia, disability, frailty or NCCs also fall outside the scope of this review.

Finally, the scope of the review does not cover:

a. Use of drugs to prevent or treat dementia and non-communicable chronic conditions;
b. Use of dietary supplements;
c. Diagnosis and care of disability, dementia, frailty and common non-communicable chronic conditions;
d. Management of existing disability, dementia, frailty and common non-communicable chronic conditions;
e. Recreational drug use;
f. Management of obesity, including medical and surgical interventions for obesity;
g. Organisational interventions, policies and laws.

2.4 Review outcomes

Evidence for behavioural risk factors in mid-life that are associated with successful ageing, and the primary prevention or delay of disability, dementia, frailty and non-communicable chronic conditions, namely quantitative evidence of associations.

These quantitative outcomes include the extent of the association between the type, level and amount of behavioural risk factor and ageing well or morbid outcomes including dementia, disability, frailty and NCCs.

2.5. Inclusion criteria – types of studies

a) The first tier of evidence for this review include primary longitudinal cohort studies that provide information on the association between behavioural risk factors at mid-life and ageing well or morbid outcomes including disability, dementia, frailty, and NCCs.

Only cohort studies that have conducted multivariate analyses are included in this review. Studies that conducted only univariate analysis are excluded.

Cross-sectional studies are excluded from the review as they would only show a cross-sectional association, and would not provide information on the impact of behavioural risk factors in later life. Any cross-sectional analyses reported in studies in addition to longitudinal analyses are excluded also.

Qualitative studies are excluded from the review, as they would not provide any quantitative evidence of an association between behavioural risk factors and ageing well or morbid outcomes in later life.

Abstracts, letters and editorials are excluded. Theses are excluded, although we sought relevant published peer-reviewed papers based on thesis data. Where found theses were included if they meet the inclusion criteria for the review.

b) The protocol stated that where no primary longitudinal cohort studies in mid-life populations are found to cover a potentially relevant topic or area of interest, systematic reviews or meta-analyses of quantitative longitudinal observational studies in adult populations in general were to be searched for and included if appropriate. We did not conduct specific searches of systematic reviews (because coverage from primary studies was deemed sufficient) but we did assess the systematic reviews identified in the primary searches and those identified through Review 1. In the end, no systematic reviews were included.

2.6 Inclusion criteria – Dates of studies to be included

Systematic reviews and primary studies published from year 2000 onwards.

2.7 Inclusion criteria – observational studies

For the purposes of this review, we included longitudinal cohort studies.

Population:

Studies in adults at mid-life (aged 40 to 64 years for the general population) with outcomes at follow-up in people aged 55 and over. A younger age cut point (i.e. 55 years as opposed to 60 or 65 years) was selected with recognition of the fact that disease processes can be accelerated in disadvantaged populations.

Studies in adults from disadvantaged populations (as defined in section 2.2) aged 18-39 with outcomes at follow-up in later life, even if not in people aged 55 and over.

Studies would not be excluded on basis of country of origin, however, where the study was conducted was considered in the applicability ratings.

Exposure:

Behavioural risk factors in the populations described above including (but not limited to) increase/maintain physical activity or decrease sedentary lifestyles; maintain balance, strength and weight-bearing functions; improve/maintain good diet (or components of diet) and nutrition; smoking cessation or reduction or prevention of smoking; decrease/moderate alcohol consumption or prevent excessive consumption; improve/modify multiple behavioural risk factors; healthy behaviours in general, increase/maintain social activity or prevent loneliness; increase or maintain/address management of sight loss or hearing loss, body weight, avoid excessive exposure to noise.

Outcomes**:** Dementia, disability (activities of daily living (ADL), instrumental activities of daily living (IADL), independence, mobility), frailty, healthy life span, quality of life, participation, NCCs including cardiovascular diseases and stroke, renal disease, cancer, chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis and bone health.

Timescale: Follow-up of 5 years or over (follow-up of less than 5 years is unlikely to be sufficient for the development and measurement of dementia, disability, frailty or pre-conditions associated with behavioural risk factors)

Language: English language studies only.

2.8 Inclusion criteria – systematic reviews

Population, exposure and outcomes to be included as for observational studies (section 2.7).

Systematic reviews or meta-analyses of longitudinal cohort studies in adults that have reported multivariate analyses and have follow-up of 5 years or longer were to be included if they answer the review question. None were included.

The process for using review level material is described in more detail below.

2.9 Identification of relevant studies

Titles and abstracts were screened independently by SK and SM using the inclusion criteria described above. Differences between reviewer's results were resolved by discussion and when necessary in consultation with a third reviewer (LL). If after discussion, there was still

doubt about a study's relevance for the review the full paper was obtained.

Full paper copies were obtained (AC, SK, LL) for studies identified by the title/abstract screening. For primary studies, decisions were made based on inclusion and exclusion criteria. Full paper screening was carried out independently by SK and SM. Any differences of opinion about inclusion/exclusion were resolved during discussion between the two reviewers or by consultation with a third reviewer (LL or NS). If after discussion, there was still doubt about a study's relevance for the review, the paper was retained and reassessed after quality assessment and data extraction.

A flow chart summarises the number of papers included and excluded at each stage of the process (Figures 2). Studies excluded at the full paper screening stage are listed in Appendix G along with the reason for exclusion.

2.10 Quality Assessment

Only primary studies (longitudinal cohort) are included in the review. Study design was assigned using the glossary of study designs (appendix D, CPHE methods manual) and the algorithm for classifying study designs (appendix E, CPHE methods manual).

Quality appraisal of cohort studies was done (SM, OR, SK) using the relevant quality appraisal checklist in the NICE methods manual (Appendix D; CPHE methods manual). Each full paper was assessed by one reviewer and checked for accuracy by another. A minimum of 10% of the studies was fully double assessed. Any discrepancy between reviewers was resolved by discussion.

2.11 Description of overall Quality Ratings

++ All or most of the checklist criteria have been fulfilled; where they have not been fulfilled the conclusions are very unlikely to alter.

\+ Some of the checklist criteria have been fulfilled, where they have not been fulfilled or adequately described the conclusions are unlikely to alter.

\- Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter

QA ratings included in evidence summary statements: [++]/[+]/[-]

2.12 Data extraction

Data was extracted (SM, OR, SK, LL) on study detail, population and setting, study design, outcomes and method of analysis, and results. To ensure accurate reporting the data extraction pro-forma was piloted against on a selection of papers. Due to the number of studies and the timeframe we had to complete the review, we did not doubly extract data for 10% of the papers as specified in the protocol; data extraction was instead verified while writing the evidence statements.

2.13 Synthesis of evidence

Only quantitative evidence is included in this review. Findings are narratively synthesised and presented to inform guidance. Data specific to health inequalities and vulnerable communities are assessed and findings are summarised separately where sufficient data is available.

Information about included studies is presented in both narrative and evidence table sections of the review, and in sufficient detail, to ensure clear and transparent links between recommendations and evidence (Section 5, Appendix K, CPHE methods manual).

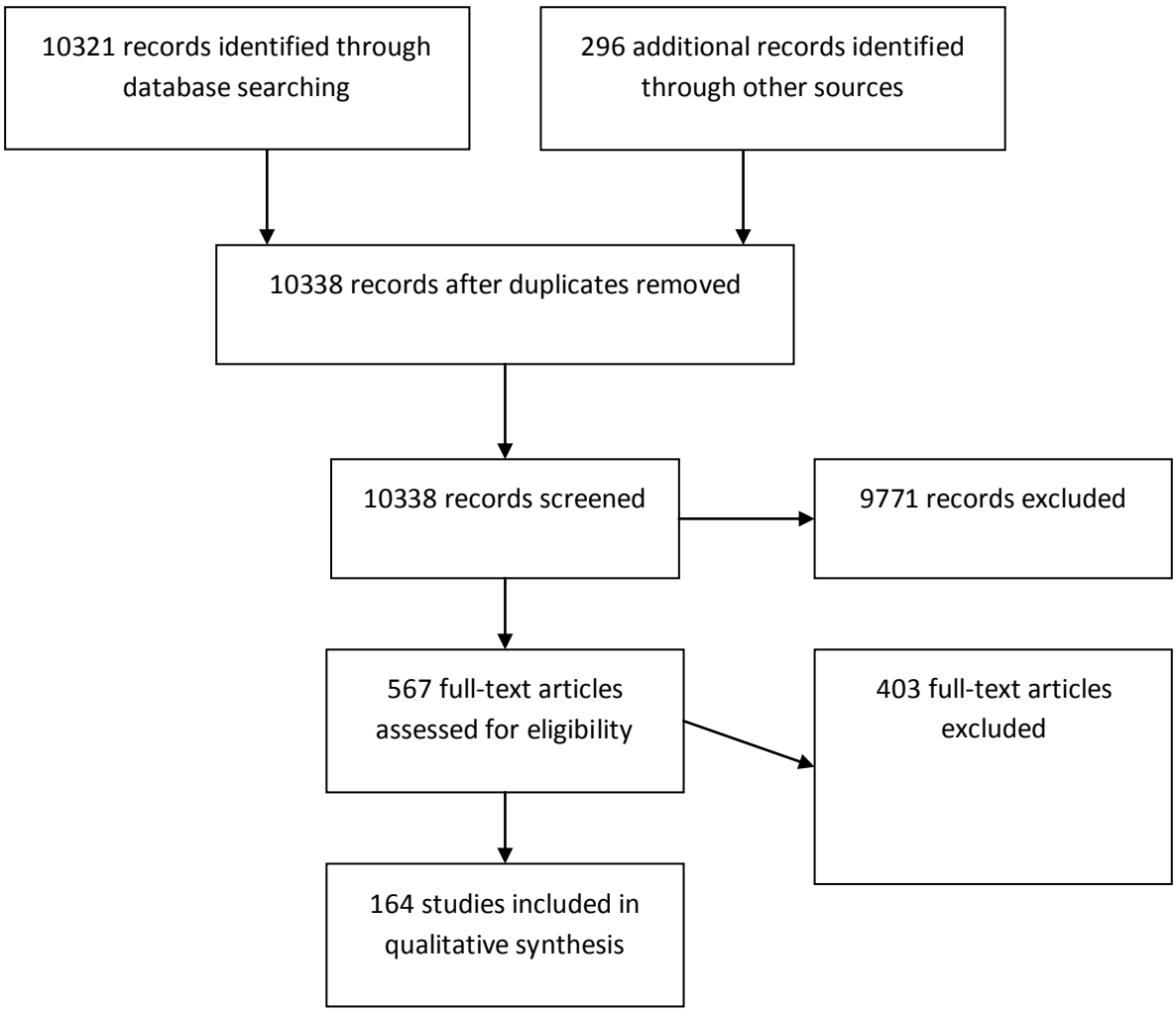
For each key question or issue an evidence statement provide an aggregated summary of all of the relevant studies (Sections 5.5.1 to 5.5.5 CPHE methods manual). Applicability ratings are used to assess each evidence statement to judge how similar the population(s), setting(s), exposure(s) and outcome(s) of the included studies are to those outlined in the review question (Section 5.6 CPHE methods manual). Each evidence statement has been rated as ‘directly applicable, partially applicable or not applicable’ by the reviewers.

3. FINDINGS

3.1 Searches

The searches for primary studies and the grey literature (Figure 2; Appendix F) located 10,338 articles after removing duplicates, 567 of which had relevant titles and abstracts. Of the 567 selected for full text assessment, 164 are included in the review. In light of the number of primary studies included in this review, we did not search for systematic reviews. None of the systematic reviews identified via the searches conducted for Review 1 were included. Appendix G lists the excluded studies and the reasons for exclusion. In total, 164 studies are included in the review and form the basis of the evidence statements.

Figure 2. Search results for primary studies



3.2 Characteristics of included studies

This review includes 164 longitudinal cohort studies reporting on the association between the following behavioural risk factors:

- Physical activity, physical inactivity
- Diet
- Smoking and smokeless tobacco (SNUS)
- Alcohol
- Weight change, weight cycling
- Combined lifestyles
- Leisure, cognitive activity, social networks

and the following categories of outcomes:

- Successful ageing (including quality of life, well-being)
- Dementia
- Disability & frailty
- Overall mortality
- Cardiovascular outcomes (mortality; morbidity)
- Diabetes, metabolic syndrome, insulin sensitivity
- Cancer
- Other chronic diseases
- Mental health

An overview of included studies is provided in Tables 9 to 17, with more details provided in the evidence tables (Appendix A).

Table 9. Overview of included studies – Physical activity

PHYSICAL ACTIVITY – SUCCESSFUL AGEING Note: A positive association (+) with PA is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Britton 2008	UK (England)	5823	35-55	17 years	Self-reported questionnaire Frequency and number of hours per week.	Successful aging: free from major disease (coronary heart disease, stroke, cancer, diabetes mellitus, depression, metabolic syndrome and with good physical and mental functioning.	Self-reported questionnaires, medication use, clinical examinations, evidence from GPs and hospitals.	<u>Successful aging</u> Men: **+** Women: **+**	+/++
Hamer 2013	UK (England)	3454	63.7 (SD 8.9)	8 years	Self-reported Questionnaire (shown to have moderate correlation with objective measure of accelerometry) Frequency and intensity of participation in PA.	Healthy ageing defined as: (1) being free from major chronic disease; (2) having no major impairment of cognitive function; (3) having no major limitation of physical functions and (4) and having good mental health.	Disease status: self-reported physician diagnosis of major chronic diseases Cognitive function: neuropsychological tests. Mental health: validated depression scale	<u>Healthy ageing</u> <u>Baseline PA:</u> Inactive: 1 Moderate: **+** Vigorous: **+** <u>Change in PA</u> Remained inactive: 1.00 Became active: **+** Remained active: **+**	++/++

Sun 2010	US	13535	60 (mean age)	14 years	Self-reported Questionnaire Leisure PA	Successful survival - no history of 11 major chronic diseases and no cognitive impairment, physical impairment, or mental health limitations.	Telephone Interview for Cognitive Status (TICS), which is modelled on the Mini-Mental State Examination administered by trained study nurses.	<u>Successful survival</u> (Mean) METS 0.9h/wk 1 3.6 0 7.9 **+** 16.2 **+** 37.1 **+**	++/+

Footnotes (applies to all tables):

i. Data is from multivariate models.
ii. Where multiple models have been reported data from the most adjusted (or most relevant) model has been used.
iii. + = significant positive association, – = significant inverse association, 0 = no significant association

PHYSICAL ACTIVITY – DEMENTIA OUTCOMES Note: A negative association (-) with PA is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Andel 2008 (case control study)	Sweden	264 dementia 2870 controls (90 twin pairs)	Mean 48.1 (SD 4.9)	31.4 years	Self-reported Questionnaire (4 point scale)	Dementia (and sub-analysis for Alzheimer's disease)	Screening for cognitive impairment followed by full clinical evaluation	<u>Dementia</u> Hardly any: 1 Light: **–** Regular: – Heavy: **0** <u>Alz Dis</u> Hardly any: 1 Light: **–** Regular: – Heavy: **0**	+/ +
Carlson 2008	US	147 twin pairs	45 (SD 3)	20-40 years	Self-reported questionnaire Frequency of participation on a scale of 1 to 5	Dementia	Screening for cognitive impairment followed by dementia questionnaires and neurological and neuropsychological testing	<u>Dementia</u> Dementia risk: **0**	++/+
Chang 2010	Iceland	4761	51	26 years	Interview and self-report of no. of hours per week in 3 categories	Cognitive function	Cognitive function assessed using cognitive tests	<u>Better cognitive function</u> Those who were more active in mid-life had better cognitive function None 1.00 </= 5h/wk: **+** >5h/wk: **+**	-/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Chang 2010	Iceland	4945	51 (SD 7)	26 years	Interview (2 questions) and self-report of no. of hours per week in 3 categories	Dementia	DSM-IV dementia diagnosed according to 3 step protocol: MMSE or digit symbol substitution test; diagnostic cognitive test battery; neurological test and interview	Dementia None: 1 </= 5h/wk: – >5h/wk: **0**	-/+
Elwood 2013 (Caerphilly cohort study)	UK (Wales)	2235	45-59	30 years	Self-reported (method?) Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit	Cognitive impairment Dementia	Interview, examination, primary care and hospital records.	Cog impairment: – Dementia: –	+/++
Morgan 2012 (Caerphilly cohort study)	UK (Wales)	1005	45-59	16 years	Self-reported questionnaire data assessed: *work-related physical activity *leisure-time physical activity: *Composite type, frequency, and duration of leisure-time physical activity score	Dementia	Cognitive function screening using CAMCOG *Clinical assessment	Dementia Leisure time PA: **0** Occupational PA: **0**	+/++

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Sabia 2009	England	5123	44 (mean)	17 years (85-88 to 02-04)	Self-reported Questionnaire	Cognitive function	Cognitive tests to measure executive function (reasoning, verbal fluency measures)	<u>Short-term association (5y)</u> Low PA: 1 High PA: **+** <u>Long-term association (17y)</u> Low PA: 1 High PA: **0**	+/++
Friedland 2001 (case-control study)	US	193 cases/358 controls (for total study, not reported for 40-59 year olds)	40-59	>12 (not fully reported)	Self reported or surrogate reported (for cases); Questionnaire Physical intensity: total hours/month – sports, garde-ning, walking	Alzheimer's Disease	Neuropsychological, laboratory, and neurological exams and all had x-ray computed tomography or MRI scans of the brain.	<u>Phys intensity</u>**:** **0**	-/+
Rovio 2005	Sweden	2000	50	21 years	Self-reported Questionnaire Leisure time PA	Dementia Alzheimer's disease	Cognitive status by MMSE was determined, and participants who scored 24 or less were referred for further neurological and cardiovascular exams.	<u>Dementia</u> Sedentary: 1 PA at least 2/wk: **–** <u>Alzheimer's disease</u> Sedentary: 1 PA at least 2/wk: **–**	+/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Rovio 2007 (same study as Rovio 2005)	Sweden	1449	50	21 years	Self-reported questionnaire Occupational commuting PA	Dementia Alzheimer's disease	Cognitive status by MMSE was determined, and participants who scored ≤24 were referred for further neurological cardiovascular exams.	<u>Dementia</u> Sedentary 1 PA at least 2/wk **0** <u>Alzheimer's disease</u> Sedentary 1 PA at least 2/wk **0**	+/+

PHYSICAL ACTIVITY – DISABILITY & FRAILTY

Note: a negative association (-) with PA is the better outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Englund 2011 (case-control study)	Sweden	81 cases/ 156 controls	57 (SD 5)	11 years	Self-reported questionnaire Commuting activities, occupational physical activity, exercise, leisure time activities, walking and bicycling activities	Hip fracture	All fracture cases were identified from a prospective injury database	<u>Walking:</u> Low: 1 Mod: – High: **0** <u>Spare time activity:</u> Low: 1 Mod: – High: –	-/+
Englund 2013 (case-control study)	Sweden	376 cases/402 controls	54 (SD 6)	11 years	Self-reported questionnaire Commuting activities, occupational physical activity, exercise, leisure time activities, walking,bicycling activities.	Wrist fracture	All fracture cases were identified from a prospective injury database	<u>Commuting activity:</u> Low: 1 Mod: 0 High: – <u>Occupational activity:</u> Low: 1 Mod: 0 High: 0 <u>Training activity:</u> 0 <u>Cycling:</u> Low: 1 Mod: 0 High: 0	-/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Lang 2007	UK [England (ELSA study), and US]	8702 (US)& 1507 (UK) (from 2 studies	50-69 (mean 60.2 & 58)	6 years	Questionnaire (frequency and intensity)	Physical mobility	Self-reported questionnaire (US study), clinician applied Physical Performance Battery (UK study)	<u>Incidence of impaired physical mobility</u> <u>UK study (ELSA):</u> – <u>US study:</u> –	+/++
Ostbye 2002	US	7845 (HRS study) 5037	51-61	5-6 yrs	Self-reported Questionnaire Intensity and frequency of PA	Disability (impairment that limits amount of paid work; ADL in activities necessary for survival IADL for activities necessary to manage in society) Self- reported health Health care use	Questions with yes/no options for disability, ADL, IADL. Health care use. For self- reported health - categories	<u>Disability</u> Light: – Mod: – Heavy: – <u>ADL & IADL</u> Light: – Mod: – Heavy: – <u>Stairs/Blocks</u> Light: – Mod: – Heavy: – <u>Poor health</u> Light: – Mod: – Heavy: – <u>Hospitalised</u> Light: – Mod: – Heavy: –	-/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Patel 2006	Italy	1001	40-60	7 years	Retrospective recall at age 74 of PA in mid-life (age 40-60)	Mobility	Ability to walk 400m	Unable to walk 400 meters: <u>Men</u> Low Reference Moderate **0** Vigorous **–** p for trend p = <0.001 <u>Women</u> Low Reference Moderate **0** Vigorous **0** p for trend p = 0.620	+/+
Szoeke 2006	US	224	50 (mean)	11 years	Self-reported Questionnaire (1 question, daily PA, no PA)	Osteoarthritis (hand and knee)	X-rays	<u>Osteoarthritis</u> PA **0**	+/+

PHYSICAL ACTIVITY – DISABILITY & FRAILTY Note: A positive association (+) with PA is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Chang 2013 (same study as Chang 2010, different outcomes)	Iceland	4753	51 (SD 7)	25 years	Interview (2 questions) and self-report of no. of hours per week in 3 categories	Lower extremity function	Gait speed (6m walk) Timed up and go test Knee extension strength	<u>Better lower extremity function (LEF)</u> Those who were active in mid-life had better LEF Inactive: 1 Active: **+**	-/+
Lahti 2010	Finland	5437 women, 1257 men	49-51	5-7 years	Self-reported Questionnaire Leisure time PA Commuting PA: volume, intensity	Physical health function	SF-36 Physical health function questionnaire	<u>Better physical function</u> **Women:** Inactive vs Conditioning PA: **+** Inactive vs active mod, active vig, very active mod, very active vig PA: **0** **Men:** Inactive vs active mod, active vig, very active mod, very active vig, conditioning PA: **0**	+/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Malmberg 2006	Finland	1791	40-64	16 years	Self-reported Questionnaire Leisure time PA (intensity, frequency, duration)	Mobility (stair climbing, difficulty in walking)	Self -reported	Difficulty walking **Men:** Fitness activity: ≥3 times /wk: 1 2 times/wk: **+** Once/wk: **+** <once/wk: **+** None : **+** Global LTPA**:** **0** LTPA energy ex **0** LTPA freq – int **0** Commuting **0** **Women:** Fitness activity: **0** Global LTPA**:** **0** LTPA energy ex **0** LTPA freq – int **0** Commuting **0**	+/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association [a,b,c] (-/+/0)	Quality/ Applicability
Nokes 2012	US	244	35-45	6 years	Accelerometer (over 7 days) PA volume and intensity	Change in bone mineral density (BMD)	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)	<u>Gain in bone mineral density:</u> Low PA volume: 1 Moderate: **+** Moderate-high: **+** PA intensity: **0**	+/+
Patel 2006	Italy	1001	40-60	7 years	Retrospective recall at age 74 of PA in mid-life (age 40-60)	Mobility	Short Physical Performance Battery	<u>Better physical perf</u> Short Physical Performance Battery Men b weight (SE) Low 1 Moderate **0** Vigorous **+** p for trend p = 0.023 Women b weight (SE) Low 1 Moderate **0** Vigorous **+** p for trend p = 0.024	+/+

PHYSICAL ACTIVITY – OVERALL MORTALITY

Note: A negative association (-) with PA is the better outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Hu 2005	Finland	47212	25-64 (mean age 41-46)	17.7 years	Self-reported Questionnaire Occupational/ Leisure PA	All cause mortality	National and hospital registers	**Men** Total mortality Low 1.00 Moderate: – High: – P-value for trend <0.001 **Women** Total mortality Low 1.00 Moderate: – High: – P-value for trend <0.001	+/+
Holtermann 2009	Denmark	4952	40-59	30 years	Self-reported questionnaire Occupational/ leisure PA	All cause mortality	Official national registers	*Among men with moderate physical work demands:* All cause mortality Low Leisure PA : 1 Mod Leisure PA: – High Leisure PA : –	+/+
Menotti 2006	Italy	1712	40-49	5 years	Self-reported questionnaire	All cause mortality	Death certificates, hospital and medical records, interviews with physicians and relatives.	All cause mortality: –	+/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association [a,b,c] (-/+/0)	Quality/ Applicability
Yu 2003 (Caerphilly cohort study)	UK (Wales)	1975	45-59	10.5 years	Self- reported Questionnaire (Minnesota Leisure Time Physical Activity). Leisure-time PA Total energy expenditure on activities Occupational PA	**CVD**, cancer, mortality from all causes	National Health Service Central Registry	<u>Heavy intensity activity</u> All-cause death: –	+/++
Elwood 2013 (Caerphilly cohort study)	UK (Wales)	2235	45-59	30 years	Self-reported (method?) Regular exercise: walking ≥2 miles to work each day, cycling ≥ten miles to work each day, 'vigorous' exercise described as a regular habit	Death	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	Death: –	++/++

PHYSICAL ACTIVITY – CARDIOVASCULAR OUTCOMES Note: A negative association (-) with PA is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Harmsen 2006	Sweden	6193	47-55	28 years	Self-reported questionnaire Leisure time PA	Stroke	Hospital records, national register	<u>Risk of stroke:</u> Low leisure PA: **0**	+/+
Hu 2004	Finland	18892	25-74 (mean age 42-48)	9.8 years	Self-reported Questionnaire Occupational/ Leisure PA	CVD	National and hospital registers	<u>Risk of CVD</u> **Men** Physical activity Low: 1.00 Moderate: **–** High: **–** P trend 0.007 Women Physical activity Low: 1.00 Moderate: **–** High: **–** P trend 0.02	+/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Hu 2005	Finland	47212	25-64 (mean age 41-46)	17.7 years	Self-reported Questionnaire Occupational/ Leisure PA	CVD	National and hospital registers	**Men** Cardiovascular mortality Low 1.00 Moderate – High – P-value for trend <0.001 **Women** Cardiovascular mortality Low 1.00 Moderate: – High: – P-value for trend <0.001	+/+
Hu 2007	Finland		25-64 (mean age 42-49)	18.9 years	Self-reported Questionnaire Occupational/ Leisure PA	CHD	National and hospital registers	CHD events **Men** Occupational PA Low: 1 Moderate: – High: – P trend 0.007 **Women** Physical activity Low: 1 Moderate: – High: – P trend 0.02	+/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Yu 2003 (Caerphilly cohort study)	UK (Wales)	1975	45-59	10.5 years	Self- reported Questionnaire (Minnesota Leisure Time Physical Activity Questionnaire). Leisure-time PA Total energy expenditure on activities Occupational PA	CVD	National Health Service Central Registry	<u>Total activity:</u> CHD death: **–** (trend p-value=0.039) <u>Heavy intensity activity</u> CVD death: **–** CHD death: **–**	+/++
Meisinger 2007	Germany	3501 men, 3475 women	45-74	8.6 years	Interview (4 level graded activities: none, < 1h/wk; 1-2 h/wk, >2 h/wk)	Myocardial Infarction	In and out of hospital registries	<u>Myocardial infarction</u> <u>Men: Leisure sports</u> None: 1 Low **0** Med: **0** High: **0** <u>Women:</u> None: 1 Low **0** Med: **–** High: **–**	+/+
Pitsavos 2004	Greece (Corfu)	529	49 ±6	40 years	Physical activity levels were assessed by self reports of habitual, occupational and leisure-time	Stroke mortality	Previous clinical records filled out by the study's research group, or by hospital records, or by necroscopy records, or by info from family or hospital doctors, other specialists, family or	<u>Presence of LVH</u> PA status Sedentary: 1 Moderate **–** Hard **0** <u>Absence of LVH</u> PA status	++/+

					activities		relatives, friends and any other witnesses.	Sedentary) 1 Moderate **–** Hard **0**	
Holtermann 2009	Denmark	4952	40-59	30 years	Self-reported questionnaire Occupational/ leisure PA	Ischaemic heart disease	Official national registers	*Among men with moderate physical work demands:* <u>IHD mortality</u> Low Leisure PA: 1 High Leisure PA: **–**	+/+
Elwood 2013 (Caerphilly cohort study)	UK (Wales)	2235	45-59	30 years	Self-reported (method?) Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit	Vascular disease	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	Vascular disease**: 0**	+/++

PHYSICAL ACTIVITY – DIABETES / METABOLIC SYNDROME/INSULIN SENSITIVITY Note: A negative association (-) with PA is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Hu 2003	Finland	13290	35-64	12 years	Self-reported Questionnaire Occupational/ Leisure Commuting PA	Type 2 diabetes	National registers	<u>Occupational physical activity</u> **Men 0** **Women 0** **Men and women combined** Light 1.00 Moderate: **–** Active: **–** p value for trend 0.020 <u>Commuting physical activity</u> Men **0** Women **0** Men and women combined ≥30 min **–** p value for trend 0.048 <u>Leisure-time physical activity</u> Men: **0** Women: **0** Men and women	+/+

								combined Low 1.00 Moderate: **0** High: **0**	
Elwood 2013 (Caerphilly cohort study)	UK (Wales)	2235	45-59	30 years	Self-reported (method?) Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit	Diabetes	Interview, examination, primary care and hospital records..	Diabetes: —	++/++
Ekelund 2005	UK (England)	605	53 (mean)	5.6 years	Physical activity energy expenditure measured using the flex heart rate method	Metabolic syndrome	Blood samples	<u>PA energy expenditure</u> Metabolic syndrome summary score: **–**	+/++

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Holme 2007 (Oslo study)	Norway	6382	40-49	28 years	Self-reported physical activity at work and leisure	Metabolic syndrome Diabetes	Metabolic syndrome presence of at least 3 out of the following 5 criteria: 1) triglycerides >=1.7 mmol/l adjusted for the last meal, 2) glucose >= 6.1 mmol/l adjusted for the last meal, 3) BMI >=30 kg/m2, 4) blood pressure >= 135/85 mmHg, and 5) HDL cholest <1.03 mmol/l Diabetes definition included self-reported diabetes, antidiabetic medication, insulin use or non-fasting glucose >=11.1 mmol/l	Metabolic syndrome sedentary/light PA: ref: moderate: – mod vig: – vigorous: – Diabetes sedentary/light PA: ref: moderate: – mod vig: – vigorous: –	+/+
Riserus 2007	Sweden	770	50	20 yrs (70-73 to 91-95)	Self-reported Questionnaire Leisure-time PA was assessed using a validated questionnaire with 4 activity levels: sedentary, moderate, regular, athletic.	Insulin sensitivity	Hyperinsulinemic – euglycemic clamp used to calculate glucose infusion rate	Insulin sensitivity Leisure PA: –	+/+

PHYSICAL ACTIVITY – CANCER Note: A negative association (-) with PA is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (–/+/0)**	**Quality/ Applicability**
Stevens 2009	England and Scotland	1.29 million women	50-64 (mean 56)	96-01 to 2005-07 Mean yrs of follow-up: 7.2 for cancer incidence; 8.9 for mortality	Self-reported Questionnaire Strenuous exercise/Any exercise	Incident and fatal pancreatic cancer	National Health Service Central Register (deaths, cancer registrations with ICD codes)	<u>PA (times per week) and incidence/mortality):</u> <1 : 1.00 1 **0** 2-3: **0** >/= 4 **0**	+/++
Wannamethee 2001	UK (England)	7630	40-59	18.8 years	Self- reported Questionnaire Total PA (total physical activity score based on frequency and type (intensity) of activity.	Cancer	Death certificates, cancer registry, postal questionnaires.	<u>Total cancer:</u> No PA 1.00 Occasional PA **–** Vigorous PA **–** p for trend <0.0001 <u>Upper digestive tract cancer (oral, esophagus, stomach cancer)</u> No PA 1.00 Moderate-vigorous PA **–** <u>Bladder cancer</u> No PA 1.00 Vigorous PA **+** *vigorous exercise was associated with a significantly *increased* risk of bladder cancer.	+/++

								Prostate cancer No PA 1.00 Vigorous PA – No sig association found for lung, stomach, colorectal, lymphatic/haematopoetic cancers.	
Hu 2005	Finland	47212	25-64 (mean age 41-46)	17.7 years	Self-reported Questionnaire Occupational/ Leisure PA	CVD Cancer All cause mortality	National and hospital registers	**Men** <u>Total mortality</u> Low 1.00 Moderate: – High: – P-value for trend <0.001 <u>Cardiovascular mortality</u> Low 1.00 Moderate – High – P-value for trend <0.001 <u>Cancer mortality</u> Low 1.00 Moderate: **0** High: – P-value for trend 0.05 **Women** <u>Total mortality</u> Low 1.00	+/+

								Moderate: – High: – P-value for trend <0.001 <u>Cardiovascular mortality</u> Low 1.00 Moderate: – High: – P-value for trend <0.001 <u>Cancer mortality</u> Low 1.00 Moderate: – High: – P-value for trend 0.005	
Elwood 2013 (Caerphilly cohort study)	UK (Wales)	2235	45-59	30 years	Self-reported (method?) Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit	Cancer	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	Cancer: **0**	+/++

PHYSICAL ACTIVITY – MENTAL HEALTH

Note: A negative association (-) with PA is the better outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Wiles 2007 (Caerphilly cohort study)	UK (Wales)	2512	45-59	10 years	Self- reported Questionnaire (Minnesota Leisure Time Physical Activity Questionnaire). Leisure-time PA Total energy expenditure on activities Occupational PA	Common mental disorders, comprising anxiety and depression	Validated psychiatric disorders screening questionnaire, report of antidepressant/ anxiolytic use.	*5-year follow-up: <u>Mental disorders</u> Total leisure PA Low: 1 Med: 0 High: 0 % time in heavy PA Low: 1 Med: – High: – *<u>10-year follow-up:</u> Total leisure PA Low: 1 Med: 0 High: 0 % time in heavy PA Low: 1 Med: 0 High: 0	++/++
Xu 2010	South East Queensland, Australia	564	45-60 yrs (mean 55)	2001-06	Self-reported Questionnaire Four options including “none,” “1–2 times/week,” “3–times/week” 4 times/week,” and “5–6 times/week” The intensity and	General mental well-being, and psychological symptoms	SF-36 and the self-reported Greene Climacteric Scale (GCS) questionnaire	Correlations between PA and 1) anxiety, 2) depression, 3) psychological symptoms, 4) SF-36 mental health: <u>For 1, 2,3,4 above separately</u> None ref	**-/+**

					the duration of exercise were not measured.			1-2/wk 0 3-4/wk 0 5-6/wk 0	

Table 10. Overview of included studies – Physical Inactivity

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association (-/+/0)	Quality/ Applicability
Christensen 2006	Denmark	376	50, 60, 70	25 years	Self-reported physical inactivity in leisure time assessed in 5 categories	Disability at age 75	Functional ability assessed by interviewer-administered Mob-T scale that measures tiredness after performing mobility activities.	<u>Disability at age 75</u> At age 50: **0** At age 60: </= 7 y school: **0** > 7 y school: **0**	-/+
Haapanen-Niemi 2000	Finland	2212 (295 PA)	35-63	16 years	Leisure time physical activity (LTPA): 1) an index for total energy expenditure in LTPA (23 questions) 2) a single-item self-assessment of physical activity.	Mortality: all cause; CHD and CVD	National census data (Finland)	<u>CVD mortality</u> <u>1) LTPA index:</u> High: 1.00 Mod: **0** Low: **0** <u>2) Single item LTPA</u> Vigorous: 1.00 None: **+** <u>All cause mortality</u> <u>1) LTPA index:</u> High: 1.00 Mod: **0** Low: **0** <u>2) Single item LTPA</u> Vigorous: 1.00 None: **0**	+/+

Footnote: where multiple outcomes have reported the most adjusted data in this table; sig = p</=0.05; ns = not significant (p>0.05)

Table 11. Overview of included studies – Diet and components of diet

DIET – SUCCESSFUL AGING Note: a positive association (+) with diet is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Akbaraly (2013)	UK	8815	35-55 years	18 years	Dietary patterns and adherence to the Alternative Healthy Eating Index (AHEI) Clinical examination, self-reported questionnaire, food-frequency questionnaire	Mortality, chronic diseases, and functioning	Hospital data, register linkage, and screenings every 5 years	<u>Ideal aging</u> <u>Western-type diet</u> (high intakes of fried and sweet food, processed food and red meat, refined grains, and high-fat dairy products) Top tertile compared to the bottom tertile: **–** <u>Healthy diet pattern:</u> Top tertile compared to the bottom tertile: **0**	+/++
Britton (2008)	UK	5823	35-55 years (mean: 44)	20 years	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	Successful aging: free from major disease (coronary heart disease, stroke, cancer, diabetes mellitus, depression, metabolic syndrome) with good physical and mental functioning	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,	<u>Men</u> Good diet vs poor diet: **+**	+/++

					or vegetables eaten less often than daily. Self-reported questionnaires				
Samieri (2013)	United States	10670	Upper 50s, lower 60s (SD: 59)	15.2 years	Dietary patterns Self-reported FFQ Alternative Healthy Eating Index-2010 (AHEI-2010) and Alternate Mediterranean diet scores.	"Healthy" aging was defined as survival to 70 years or older with maintenanceof 4 health domains: no major chronic diseases or major impairments in cognitive or physical function or mental health.	Questionnaire on disease incidence every 2 years. Telephone interviews for cognitive status	<u>Healthy ageing</u> <u>Healthy eating index diet:</u> Q1 low ref 1.00 Q2 **0** Q3 **0** Q4 **+** Q5 **+** P trend<0.001 <u>Med diet score</u> Q1 low ref 1.00 Q2 **+** Q3 **+** Q4 **+** Q5 **+** P trend =0.002	+/+

DIET – DISABILITY/FRAILTY OUTCOMES (1)

Note: a negative association (-) with diet is the better outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Nakamura (2009)	Japan	2316	47-60 years	19 years	Diet Telephone interviews. Face-to-face interviews at home. Self-administered lifestyle questionnaire	Activities of daily living (ADL)	Participants were asked about 5 basic ADL items	Impaired ADL Meat (no. times in 2 days) <1/2 d ref 1.00 ≥1/2 days – (less impaired ADL) Fish <1/day 1.00 ≥1/day 0 Egg <1/day 1.00 ≥1/day 0 Mortality Meat, fish, egg: **0**	+/+
Elwood (2013)	UK (Caerphilly)	2235	45-59 years	30 years	3+ portions of fruit and veg/day Self-report, food-frequency questionnaire, cognitive function tests	Diabetes Vascular disease Cancer Cognitive impairment Dementia Death	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	Cog impairment: **0**	+/++
Eskelinen (2008)	Finland	1449	SD: 50.2	21 years	Dietary fat intake (total, saturated, polyunsaturated, monounsaturated) Self-reported	Cognitive impairment (MCI)	Mini Mental State Examination, immediate word recall tests, Category Fluency Test. psychomotor speed with Purdue Peg Board task letter digit substitution	Cognitive impairment: Total fat Low (0-38 g/d): 1 High(>38 g/d) **+** Sat fat	+/+

					validated semi-quantitative food-frequency questionnaire		test. Executive function with the Stroop test .	Low (0-21.6 g/d): 1 High(>21.6 g/d) **+**	
Laitala (2009)	Finland	2606	Mean age 46-52	28 years	Coffee intake Self-reported questionnaire, telephone interviews (TELE, TICS, MMSE)	Cognitive performance (MCI)	TELE screening and the Telephone Interview for Cognitive Status (TICS) *TELE and TICS are sensitive and specific and correlate well with the MMSE	<u>MCI</u> <u>Coffee (cups/d)</u> 0-3 (ref) 1 3.5-8 **0** >8 **0**	++/+

DIET – DISABILITY/FRAILTY OUTCOMES (2)

Note: a positive association (+) with diet is the better outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Kesse-Guyot (2012)	France	3054	SD: 52.1	13.4 years	Diet Self-reported 24-h dietary records. 'Healthy pattern' -+ve: fruit,veg, wholegrains, fresh dairy products, vegetables,, breakfast cereal, tea, vegetables, vegetable fat, nuts, fish. 'Traditional pattern' - +ve: vegetables, vegetable fat, meat, poultry.	Cognitive performance	Clinical examination, neuropsychological evaluation (verbal fluency, the RI-48 cued recall test, the trail-making test, and forward and backward digit span). Three composite variables, for global cognitive function, verbal memory, and executive functioning, were reported.	<u>Better cognitive performance</u> High score 'healthy pattern' (Q4 vs Q1) **+** P trend 0.001 (Executive fn) High score 'traditional pattern' (Q4 vs Q1) P trend 0.06 (Global cog fn) —	-/+
Nooyens (2011) Doetinchem Cohort Study	Netherlands	2613	43-70 years	10 years	Fruit and vegetables Self-reported FFQ.	Cognitive decline	Neuropsychological test battery	<u>Change in cognitive function</u> <u>Fruit and vegetables:</u> **0** <u>Fruit:</u> **0** <u>Vegetables:</u> **0**	+/+

								Legumes: **0** Juices: **0**	
Sabia (2009)	UK	5123	35-55 years	17 years	Fruit and veg intake Self-reported questionnaire (1 question about frequency)	Cognitive function	Executive function was derived from 3 measures: a measure of reasoning and 2 measures of verbal fluency. Memory was assessed by using a test of short-term verbal memory	Executive function: Fruit & veg(servings/d) >/= 2 vs <2: **+** Memory **0**	+/+

DIET – DEMENTIA OUTCOMES Note: a negative association (-) with diet is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Eskelinen (2009) CAIDE study	Finland	1409	SD: 50.4	21 years	Coffee and tea consumption *coffee drinking categorized as: 0-2 cups/day (low), 3-5 cups/day (moderate), >5 cups/day (high) *Tea consumption categorized as: none (0 cups/day), drinking tea (>=1 cups/day) Self-reported validated semi-quantitative food-frequency questionnaire	Dementia	*cognitive status assessing through screening, clinical and differential diagnosis *participants with score <=24 on MMSE referred for clinical examination for dementia diagnosis or not.	Dementia risk: Coffee: – lower for those consuming moderate amounts of coffee (3-5 cups/day) compared to low amounts (0-2 cups/day). Tea **0** (all associations) *for APOE4 carriers: Coffee: –	+/+
Elwood (2013)	UK (Caerphilly)	2235	45-59 years	30 years	3+ portions of fruit and veg/day Self-report, food-frequency questionnaire, cognitive function tests	Dementia	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	Dementia: **0**	+/++
Hughes (2010)	Sweden	3779 (3424 non-	Mean age 48	30 years	Diet questionnaire – single item on 4	Dementia	Cognitive screening by phone, full clinical evaluation using	Dementia No/small fruit& veg	+/+

		demented, 355 dementia cases)			point scale on fruit and veg intake ("great part", "medium part", "small part", or "no part")		standard diagnostic criteria	intake: 1.00 (ref) Medium or great Fruit & veg intake: —	
Laitala (2009) Finnish Twin cohort study	Finland	2606	Mean age 46-52	28 years	Coffee intake Self-reported questionnaire, telephone interviews (TELE, TICS, MMSE)	Dementia	TELE screening and the Telephone Interview for Cognitive Status (TICS) *TELE and TICS are sensitive and specific and correlate well with the MMSE	<u>Dementia</u> <u>Coffee (cups/d)</u> 0-3 (ref) 1.00 3.5-8 **0** >8 **0**	++/+
Laitinen (2006)	Finland	1449	SD: 50.4	21 years	Dietary fat (Sat fat and polyunsat fat from spreads) Self-reported questionnaire. (Qualitative or frequency based)	Dementia	Cognitive status assessed using MMSE; if score <=24, invited to clinical phase for dementia diagnosis	<u>Dementia</u> <u>Polyunsat fat (PUFA)</u> Moderate amounts PUFA vs Low amounts PUFA: — Moderate amounts sat fat vs Low amounts sat fat: **+** <u>APOE4 carriers</u> Moderate amounts PUFA vs Low amounts PUFA: — Moderate amounts sat fat vs Low amounts sat fat: **+**	++/+

Laurin (2004)	US (Hawaii)	2459	45-68 years (Mean: 51.2)	30.2 years	Dietary antioxidants 24-hour dietary recall interviews, clinical examinations, self-reported FFQ questionnaire	Dementia (and subtypes)	Cognitive Abilities Screening Instrument and then evaluated through a neurologic examination, neuropsychological testing, and an informant interview	<u>Dementia</u> <u>β-carotene</u> **<u>0</u>** <u>vitamin C</u> **<u>0</u>** <u>flavonoids</u> **<u>0</u>** <u>vitamin E</u> Q1 1.00 ref Q2 **+** Q3 0 Q4 0 <u>Alzheimer's disease</u> <u>β-carotene</u> **<u>0</u>** <u>vitamin C</u> **<u>0</u>** <u>flavonoids</u> **<u>0</u>** <u>vitamin E</u> Q1 1.00 ref Q2 **+** Q3 0 Q4 0 <u>Alzheimer's disease w/w'out cerebrovascular disease</u> <u>β-carotene</u> **<u>0</u>** <u>vitamin C</u> **<u>0</u>**	+/+

								<u>flavonoids **0**</u> <u>vitamin E</u> Q1 1.00 ref Q2 **+** Q3 0 Q4 **+** <u>Vascular dementia:</u> **0**	

DIET – TOTAL MORTALITY Note: a negative association (-) with diet is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Osler (2003)	Denmark	7540	30-70 years	36 years	Fish intake Self-reported questionnaires	Data on all-cause mortality, CHD mortality, incident CHD	National Board of Health Register of Cause of Death and the National Patient Register	<u>All cause mortality</u> <u>Men (times)</u> <1/month vs once/wk: — <u>Men and women</u> 2/month vs once/wk: — *among males and females combined, as well s 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)	+/+
Seccareccia (2003)	Italy	1536	45-65 years	30 years	Veg intake Home visits. Interviews using a dietary history interview sheet. Self-reported 7-day food-use diaries.	Total mortality	Official death certificates, hospital physicians, interviews with relatives of the deceased and other witnesses.	<u>Total mortality</u> <u>Vegetable intake (for each increase of 20g/day):</u> —	+/+
Akbaraly (2013)	UK	8815	35-55 years	18 years	Dietary patterns and adherence to the	Total and CVD mortality	Hospital data, register linkage, and screenings every 5 years	<u>Ideal aging</u>	+/++

					Alternative Healthy Eating Index (AHEI) Clinical examination, self-reported questionnaire, food-frequency questionnaire			<u>Western-type diet</u> (high intakes of fried and sweet food, processed food and red meat, refined grains, and high-fat dairy products) Top tertile compared to the bottom tertile: ─ <u>CVD and non-CVD deaths</u> <u>Healthy eating</u> High adherence to the AEHI: ─	
Strandhagen (2000)	Sweden	792	Age 54	26 years	Fruit and vegetable intake Self-reported FFQs	Total mortality,	Complete medical and physical health examinations. Telephone interviews. Info from autopsy reports, cancer registry and medical records	<u>Total mortality</u> Fruit: ─ Veg: **0**	++/+
Elwood (2013)	UK (Caerphilly)	2235	45-59 years	30 years	3+ portions of fruit and veg/day Self-report, food-frequency questionnaire, cognitive function tests	Total mortality	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	<u>Death:</u> **0**	+/++

DIET – CVD OUTCOMES

Note: a positive association (+) with diet is the worst outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Leosdottir (2007) Malmo Diet and Cancer Study	Sweden	28000	45-70 years	8.4 years	Dietary fat intake Self-reported 7 day menu diary, FFQ and interviews	Cardiovascular events	Information on prevalent and incident fatal or nonfatal CVD events was gathered from local and national registries.	Cardiovascular events Total fat: Women: **0** Men: **0** Sat fat: Women: **0** Men: **0** Monounsat fat**:** Women: **0** Men: **0** Polyunsat fat**:** Women: **0** Men: **0**	+/+
Beulens (2007)	Netherlands	1417	49-70	8-12 years	Glycemic index and glycemic load in the previous year Food frequency questionnaire (validated)	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 *vital status information obtained from municipal administration registries; cause of death obtained from GPs	CVD risk Glycemic load (GL) Highest vs lowest quartile: **+** (The higher the quartile of energy-adjusted glycemic load, the greater the risk for CVD)	++/+

								(p-value for trend: 0.033) <u>Glycemic index (GI)</u> Highest vs lowest quartile: **+** (p-value for trend: 0.02)	
Levitan (2007) Cohort of Swedish men	Sweden	36246	45-79 years	6 years	Glycaemic index (GI) and glycaemic load (GL) Self-reported FFQ questionnaire	CVD events CVD mortality All cause mortality	Hospital discharge and cause of death registries	<u>Myocardial infarction:</u> GI or GL **0** <u>Ischemic stroke:</u> GI or GL **0** <u>Hemorrhagic stroke</u>: GI or GL **0** <u>Cardiovascular mortality:</u> GI or GL **0** <u>All cause mortality</u>: GI or GL **0**	+/+
Levitan (2009) Cohort of Swedish men	Sweden	39367	45-79 years	7 years	Dietary fatty fish consumption, marine omega-3 fatty acids Food frequency questionnaires	Heart failure Hospitalisation for and death from heart failure	Swedish inpatient and cause-of-death registers	<u>Heart failure</u> <u>Fatty fish (servings):</u> Never 1.00 <1/wk 0 1/wk 0	+/+

					with 5 questions on fish intake			2/wk 0 >/=3/wk 0 <u>Marine omega-3 fatty acids:</u> Never 1.00 <1/wk 0 1/wk — 2/wk 0 >/=3/wk 0	
Levitan (2010) Swedish mammography cohort	Sweden	36019	48-83 years	9 years	Glycaemic index (GI) and glycaemic load (GL) Self-reported FFQ questionnaire	Heart failure Hospitalisation for and death from heart failure	Swedish inpatient and cause-of-death registers	<u>Heart failure events:</u> GI or GL **0**	+/+
Guallar-Castillon (2012)	Spain	40757	29-69	5 years	Dietary patterns Interviews, self-reported food diaries, questionnaire	CHD events and mortality	Hospital discharge registers CHD events were classified on the basis of symptoms, signs, biomarkers, and electrocardiogram	<u>Definite CHD events Westernized Diet Pattern</u> Quintile 1: 1 Ref. Quintile 2: 0 Quintile 3: 0 Quintile 4: 0 Quintile 5: 0 P for trend 0.51 <u>Evolved Mediterranean Pattern</u> Quintile 1) 1 Ref. Quintile 2) — Quintile 3) — Quintile 4) — Quintile 5) — P for trend 0.0013	+/+

Happonen (2004)	Finland	2005	42-60 years	14 years	Coffee Interview - checked 4-d food diary 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.	CHD events and mortality	National hospital discharge registry; diagnostic information was collected from the hospitals and classified using identical diagnostic criteria	<u>CHD events or mortality</u> Coffee intake category None **0** Light **0** Moderate 1.00 (ref) Heavy **+**	+/+
Lajous (2013) Health Professionals Follow-up Study/ Nurses Health Study	United States	79569 (25797 men, 53772 women)	40-75 years (men) Mean age 56.5 (SD 9.3) 30-55 (women) Mean age 52.1 (SD7.1)	22 years	Fish consumption Food frequency questionnaire, self-reported surveys	CHD (total, nonfatal, and fatal CHD)	Medical records, relatives, postal authorities, or the National Death Index (medical records, death certificates, autopsies used to identify cause of death)	<u>CHD HPFU Study</u> Males: all associations: **0** Females: 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 – *the lowest risk for *fatal coronary heart*	++/+

								disease was reported when: meat was replaced with fish to attain >=5 servings/week: — and when >=5 fish servings/week were consumed: —	
Menotti (2012)	Italy	1139	45-64 years	40 years	Mediterranean diet pattern measured by the Mediterranean Adequacy Index (MAI). Weighed food records and dietary recall with experienced dietitians.	CHD fatal events	Hospital and medical records. Interviews with physicians and relatives of deceased	<u>CHD mortality</u> MAI(1 unit): — *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	-/+
Mostofsky (2010) Swedish Mammography Cohort	Sweden	31823	48-83 years	9 years	Chocolate intake Self-reported questionnaire. FFQ.	Heart failure	Link to inpatient and cause-of-death registers	<u>Heart failure</u> <u>Chocolate (servings):</u> None (ref) 1-3/month — 1-2/wk 0 3-6/wk 0 1 or >1/d 0 (p for quadratic trend = 0.0005).	++/+
Mursu (2008)	Finland	1950	42-60 years	15.2 years	Dietary flavonoid intake Self-reported	Ischaemic stroke and CVD mortality	Regional coronary and stroke register teams collected data on strokes from hospitals	<u>Ischemic stroke</u> <u>Total flavonoids:0</u> <u>Flavonols:</u> —	+/+

					questionnaire, later checked by interviewer.		and wards of health centres and classified the events, as explained in detail previously. Data on strokes from the beginning of 1993 were obtained from national hospital discharge and death registers.	(Highest vs lowest quintile) <u>CVD mortality</u> Total flavonoids:**0**	
Preis (2010)	United States	43960	40-75	18 years	Dietary protein Food frequency questionnaire (every 4 yrs).	Ischemic heart disease	A review of medical or hospital records. Examination of National Death Index, medical records and autopsy reports.	<u>Ischemic heart disease</u> <u>Q5 vs Q1</u> Total protein: **0** Animal protein **:0** Veg protein: **0**	++/+
Qiu (2003)	China	50,252	40+ (SD: 55.3)	6 years	Frequency of food intake Door to door survey about lifestyle and health conducted by trained physicians.	Cerebrovascular disease mortality	Follow-up reports completed by village physicians	<u>Cerebrovascular disease mortality</u> <u>Meat (times):</u> Never/seldom: 1.00 (ref) 1/2 a month: — >1/wk: **0**	+/+
Strandhagen (2000)	Sweden	792	Age 54	26 years	Fruit and vegetable intake Self-reported FFQs	Mortality, cardiovascular disease, cardiovascular death, cancer morbidity and cancer death	Complete medical and physical health examinations. Telephone interviews. Info from autopsy reports, cancer registry and medical records	<u>Total mortality</u> Fruit: — Veg: **0** <u>CVD mortality</u> Fruit: — Veg: **0**	++/+

								CVD Fruit: **0** Veg: **0** Cancer Fruit: **0** Veg: **0** Cancer mortality Fruit: **0** Veg: **0**	
Elwood (2013)	UK (Caerphilly)	2235	45-59 years	30 years	3+ portions of fruit and veg/day Self-report, food-frequency questionnaire, cognitive function tests	Vascular disease	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	Vascular disease**: 0**	+/++

DIET – METABOLIC SYNDROME

Note: a negative association (-) with diet is the better outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Kato (2009)	Japan	55826	40-69	10 years	Coffee consumption Self-reported FFQ questionnaire	Diabetes	94% of the self-report cases of diagnosed diabetes were confirmed by medical records	<u>Diabetes</u> <u>Coffee consumption</u> <u>Men</u> almost never 1.00 (ref) 1-2 days per week **0** 3-4 days per week **0** 1-2 cups/day – 3-4 cups/day **0** >5 cup/day **0** p for trend 0.006 <u>Women</u> almost never 1.00 (ref) 1-2 days per week **0** 3-4 days per week **0** 1-2 cups/day **0** 3-4 cups/day – >5 cup/day – (p for trend <0.001	+/+

Song (2004) Nurses Health Study	United States	37309	45+ years	8.8 years	Red meat intake FFQs. Annual self-reported questionnaire. Contact with some primary care physicians.	Diabetes	Self-reported diagnosis of diabetes followed by telephone interview.	<u>Diabetes</u> <u>Highest vs lowest quintile</u> Red meat: **+** P trend<0.001 Processed meat: **+** P trend 0.001	+/+
Elwood (2013)	UK (Caerphilly)	2235	45-59 years	30 years	3+ portions of fruit and veg/day Self-report, food-frequency questionnaire, cognitive function tests	Diabetes	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	<u>Diabetes:</u> **0**	+/++
Tuomilehto (2004)	Finland	16670	35-65 years	12 years	Self-reported questionnaire.	Diabetes	National Hospital Discharge Register and the Drug Register of the National Social Insurance Institution	<u>Diabetes</u> <u>Coffee cups/d</u> <u>Women</u> </=2: 1.00 3-4: **0** 5-6: — 7-9: — >/=10: — P trend <0.001 <u>Men</u> </=2: 1.00 3-4: **0** 5-6: **0** 7-9: **0** >/=10: —	+/+

								P trend 0.12 <u>Men and women</u> </=2: 1.00 3-4: **0** 5-6: — 7-9: — >/=10: — P trend <0.001	
Villegas (2010)	China	64191	40-70 years	6.9 years	Dietary patterns Dietary intake, in-person interviews. Dietary patterns were assessed using K-means cluster analysis. Cox regression model for T2D.	Diabetes	Self report of diabetes and at least one of the following criteria as recommended by American Diabetes Association: fasting glucose level 57 mmol/l on at least two separate occasions, or an oral glucose tolerance test (OGTT) with a value 511.1 mmol/l, and/or use of hypoglycaemic medication (i.e. insulin or oral hypoglycaemic drugs).	<u>Diabetes</u> Dietary pattern low in staples and highest in dairy milk: — Dietary pattern with highest energy intake: **0** (Reference was dietary pattern highest in staples)	++/+
Villegas (2011)	China	116156 (51963 men, 64193 women)	40-74 years	12 years	Fish, shellfish, long chain n-3 fatty acids Detailed in-person interviews. Questionnaires.	Diabetes	Biennial in person surveys via Shanghai statistic registry	<u>Diabetes</u> <u>Women</u> <u>Fish intake</u> Q1 ref 1.00 Q2 **0** Q3 — Q4 — Q5 **0** Ptrend 0.006	++/+

								<u>Shellfish</u> Q1 ref 1.00 Q2 **0** Q3 — Q4 — Q5 — Ptrend 0.003 <u>Men</u> <u>Shellfish</u> Q1 ref 1.00 Q2 **0** Q3 — Q4 — Q5 **0** Ptrend 0.003	
Riserus (2007)	Sweden	770 (plus sub-sample of 440)	50	20 years	Saturated fat intake (using fatty acid composition as a biomarker of saturated fat intake ("saturated fat index")	Insulin sensitivity	Direct assessment using euglycemic clamp.	<u>Insulin sensitivity</u> <u>Saturated fat index:</u> — *Increasing sat fat, lower insulin sensitivity* (in all subjects and normal weight subjects only)	+/+

DIET – CANCER

Note: a positive association (+) with diet is the worst outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Wang (2009)	United States	38408	45+ years	11.5 years	Dietary flavonoids Semi-quantitative FFQ .	Cancer	Questionnaires, deaths ascertained through family member reports, postal authorities, National Death index; cancer was identified through pathology or cytology reports.	Total cancer Total or individual flavonoids: **0** **Other cancers:-** breast cancer, colorectal cancer, lung cancer, endometrial cancer, ovarian cancer: **0** stomach, pancreatic, bladder, brain, thyroid, cervical cancer, lymphoma/leukemia): **0**	+/+
Tsugane (2004)	Japan	39065	40-59 years	11 years	Salt and salted food intake Self-reported questionnaires:	Gastric cancer	Link to cancer registry	Gastric cancer Salt intake Men: **+** Highest vs lowest P trend<0.001 Women: **0**	+/+
Masaki (2003)	Japan	5644	40-69	10 years	Dietary patterns Self-reported FFQ. questionnaire	Stomach cancer	Medical examinations, detailed statements of medical care (performed for insured persons) by medical care facilities.	Stomach Cancer Vegetable and fruit pattern Low 1.00 Middle 0 High 0 P trend 0.56	+/+

								Western breakfast Low 1.00 Middle 0 High 0 P trend 0.20 Meat Low 1.00 Middle 0 High 0 P trend 0.07 Rice/snacks Low 1.00 Middle 0 High 0 P trend 0 .05 There were no clear associations between the four major dietary patterns and stomach cancer risk	
Ruder (2011)	United States	292797	40-61 years	10 years	FFQ questionnaire (self-reported) assessed retrospectively	Colorectal cancer	Primary diagnoses of adenocarcinoma identified through state cancer registries	Risk of colorectal cancer Calcium: — Vitamin A: — Vitamin C: — Fruit: — Milk: — (lower risk of colon cancer) Total fat: **+** Red meat **+** Processed meat: **+** Rectal cancer Fibre **0** Milk —	++/+

Strandhagen (2000)	Sweden	792	Age 54	26 years	Fruit and vegetable intake Self-reported FFQs	Cancer morbidity and cancer death	Complete medical and physical health examinations. Telephone interviews. Info from autopsy reports, cancer registry and medical records	<u>Cancer</u> Fruit: **0** Veg: **0** <u>Cancer mortality</u> Fruit: **0** Veg: **0**	++/+
Elwood (2013)	UK (Caerphilly)	2235	45-59 years	30 years	3+ portions of fruit and veg/day Self-report, food-frequency questionnaire, cognitive function tests	Cancer	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	<u>Cancer:</u> **0**	+/++

DIET – OTHER CHRONIC DISEASES Note: a negative association (-) with diet is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Walda (2002)	Finland, Italy and The Netherlands	2917	50-69 years	20 years	Antioxidant, fruit, vegetable and fish intake . Cross-check dietary history method. FFQ. Interviews.	Chronic obstructive pulmonary disease (COPD) mortality	Access to clinical records	COPD mortality Fruit: – Vit C: **0** Vit E: **0** B-carotene **0** Veg: **0** Fish: –	+/+
Hu (2007)	Finland	29335	25-64 years	18.9 years	Tea and coffee consumption Self-reported questionnaire.	Parkinson's disease	National Social Insurance Institution's Register on special reimbursement for drug costs	Risk of Parkinson's Disease <u>Volume of coffee consumption (cups/d)</u> Men 0 1 1–4 **0** 5 or > – P-trend 0.063 Women 0 1 1–4 **0** 5 or > – P-trend 0.073 Men and Women 0 1 1–4 – 5 – P-trend 0.005	+/+

								<u>Volume of tea consumption</u> Men 0 1 1–4 **0** 5 **0** P-trend 0.31 Women 0 1 1–4 **0** 5 – P-trend 0.11 Men and Women 0 1 1–4 **0** 5 – 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	
Ross (2000)	US Hawaii	8004	45-68 years	30 years	Coffee, dietary caffeine 24 h recall dietary intake by a dietitian	Parkinson's Disease	Hospital records, ongoing review of death certificates, cross-check of records of local neurologists with cohort	<u>Parkinson's Disease</u> <u>Coffee (drinkers vs non-drinkers):</u> – <u>Caffeine:</u> –	+/+

DIET – MENTAL HEATH Note: a negative association (-) with diet is the worst outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Xu (2010)	Australia	564	45-60 years	5 years	Caffeine consumption Self-report questionnaire Only 1 question on caffeine dichotomized (yes/no)	Mental health (mental wellbeing, depression, anxiety)	SF-36 and the self-reported Greene Climacteric Scale (GCS) questionnaire,	<u>Anxiety</u> Caffeine drinkers vs non-caffeine: **0** <u>Depression</u> Caffeine drinkers vs non-caffeine: **0** <u>Psychological symptoms</u> Caffeine drinkers vs non-caffeine: **0** <u>SF-36 Mental Health</u> Caffeine drinkers vs non-caffeine: — (lower mental health in caffeine drinkers)	-/+
Hodge (2013)	Australia	8660	50-69 years	12 years	Dietary patterns [defined by factor analysis or the Mediterranean Diet Score (MDS)] The "Australian" diet:(negative loadings for olive oil and	Psychological distress	Kessler Psychological Distress Scale (K10).	Highest vs lowest adherence to Mediterranean Diet (MDS). — Highest vs lowest adherence to traditional Australian Diet: —	+/+

					feta cheese, and positive loadings for breakfast cereal, wholemeal bread, cheddar cheese, vegetables Food frequency questionnaire				
Lehto (2013)	Finland	2600	42-61 years	20.1 years	Energy-adjusted dietary zinc intake 4-day food record	Depressive symptoms	Depression was defined as having received a hospital discharge diagnosis of unipolar depressive disorder	<u>Depression</u> <u>Energy adjusted zinc intake:</u> **0**	+/+
Ruusanen (2010)	Finland	2232	42-60 years	17.5 years	Coffee, tea, caffeine 4day food recording, self-reported, checked by nutritionists	Severe depression	National hospital discharge register	<u>Coffee (ml/d)</u> None 1 Light (<375): — Moderate(375-813): **0** Heavy: — <u>Tea (ml/d)</u> None 1 Light (<375): **0** <u>Caffeine</u> All categories: **0**	+/+

DIET – PRECONDITIONS (FOR DEMENTIA, DISABILITY, FRAILTY)

Note: a positive association (+) with diet is the better outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association (-/+/0)	Quality/ Applicability
Wang (2012)	United States	28082	39+	12.9 years	Fruit and vegetable consumption Semi-quantitative FFQs.	Hypertension	Incident hypertension was identified from annual follow-up questionnaires.	Fruit & veg: **0** Fruit: **0** Vegetables: **0**	+/+
Wang (2008)	United States	28766	45+ years (SD 53.8)	10 years	Dairy products Self-reported questionnaire	Incidence of hypertension	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	Low fat dairy Q1 ref 1.00 Q2 **0** Q3 **0** Q4 **0** Q5 — Ptrend 0.001 High fat dairy Q1 ref 1.00 Q2 **0** Q3 **0** Q4 **0** Q5 **0** Ptrend 0.17 Total dairy Q1 ref 1.00 Q2 **0** Q3 — Q4 — Q5 — Ptrend 0.003	+/+

Song (2006)	United States	28349	45+ years	9.8 years	Dietary magnesium Self-reported FFQ.	Hypertension	Hypertension based on self-reported BP, treatment, and/or physician diagnosis	Hypertension Highest vs lowest quintile Magnesium: **0**	+/+
Miura (2004)	United States	1710	40-55 years (Mean 48.5)	39 years	Fruit and vegetables Standardised interviews and questionnaires, by two nutritionists	Systolic or diastolic blood pressure	Standard mercury sphygmomanometers	*Systolic blood pressure* (men) Vegetables (cups/month) <14 ref 14–42 **0** >42 **0** Fruits (cups/month) <14 ref 14–42 >42 **0** 14–42 — >42 **0** Fish (120-g units/month) None (ref) <4 **0** 4–8 **0** >8 **0** Beef-veal-lamb (120-g units/month) 8–20 **+** >20 + Pork (120-g units/month) 4–8 **+** >8 **0**	+/+

								Poultry (120-g units/month) 4–8 **0** >8 **0** *Diastolic blood pressure* Vegetables (cups/month) 14–42 **0** >42 **0** Fruits (cups/month) 14–42 **0** >42 **0** Fish (120-g units/month) <4 **0** 4–8 **0** >8 **0** Beef-veal-lamb (120-g units/month) 8–20 **0** >20 **+** Pork (120-g units/month) 4–8 **0** >8 **0** Poultry (120-g units/month) 4–8 + >8 +	

DIET – PRECONDITIONS (OBESITY) Note: a negative association (-) with diet is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association (-/+/0)**	**Quality/ Applicability**
Liu (2003)	United States	74091	38-63 years	12 years	Changes in intakes of dietary fibre and grain products Self-reported Food frequency questionnaires.	Changes in weight and development of obesity	Self-reported height and body weight at 2-4 year intervals (when self-reported and measured weights were compared in a sample of participants, correlation was 0.96)	Obesity (BMI >/=30) Wholegrains (change in intake) Q1 (ref) 1.00 Q2 – **Q3** – **Q4** – **Q5 (high intake)** – P trend 0.0002 Refined grains (change in intake) Q1 (ref) 1.00 Q2 **0** **Q3** **0** **Q4** **0** **Q5 (high. intake)** **0** Dietary fibre (change in intake) Q1 (ref) 1.00 Q2 – **Q3** – **Q4** – **Q5 (highest intake)** – P trend <0.0001 Weight gain >/= 25 kg Wholegrains (change in intake) Q1 (ref) 1.00	+/+

								Q2 **0** **Q3 0** **Q4 0** **Q5 (highest intake) 0** <u>Refined grains (change in intake)</u> Q1 (ref) 1.00 Q2 **0** **Q3 0** **Q4 0** **Q5 (highest intake) 0** <u>Dietary fibre (change in intake)</u> Q1 (ref) 1.00 Q2 — **Q3** — **Q4** — **Q5 (highest intake)** — P trend <0.0001	
He (2004)	United States	74063	38-63 years	12 years	Fruit and vegetables Self-reported semi quantitative food frequency questionnaire	Obesity defined as BMI >=30 kg/m2 and major weight gain as weight gain of 25 kg or more during follow-up	Self-reported body Weight captured through questionnaire every other year; when self-reported weight was compared with measured weight, correlation was 0.96	<u>Obesity</u> <u>Change in fruit and veg (servings/day):</u> -2.36 1.00 (ref) -0.49 — +0.64 — +1.83 — +3.99 — P trend <0.0001 <u>Weight gain >/+25kg:</u> <u>Change in fruit and</u>	+/+

								<u>veg (servings/day):</u> -2.36 1.00 (ref) -0.49 **0** +0.64 **0** +1.83 – +3.99 – P trend 0.01 Similar trends also reported for fruits or vegetables separately	

Footnotes:

I. Data is from multivariate models.
II. Where multiple models have been reported data from the most adjusted (or most relevant) model has been used.
III. + = significant positive association, – = significant inverse association, 0 = no significant association

Table 12. Overview of included studies – Smoking

SMOKING – SUCCESSFUL AGEING / QUALITY OF LIFE / WELL-BEING Note: A positive association (+) with smoking is the better outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results Association**	**Quality/Applicability**
Britton 2008	England	5823 (civil servant)	35-55	17yrs	Self-report • Never, former, current smoker	Successful aging, i.e. free from major disease and good physical & mental health	Walking speed, lung function, Alice Heim 4-I cognitive test, physical component SF36, self-report, medication use, clinical examinations,	Current smoker: 1 • Non-smoker: **+** Less exposure: **+** (in men & women)	+/++
Strandberg 2008	Finland	1658	40-55	26yrs	Self-report • 5 categories from never >20)	Bodily pain, general health, Mental health/emotional wellbeing, role limitations owing to mental problems or to physical health, Social functioning, Energy vitality, Physical functioning	RAND-36/SF-36	*All dimensions:* • Never smoker: **+** • Smoking: **–** *Except Role limitations owing to physical fx:* • Never smokers: **+** • Smoking: **0**	+/+
Wilcox 2006	USA	5820 Japanese American men	Mean 54yrs (45-68)	Up to 40yrs	Self-report • Ever or never	Overall survival • Non survivors: before age 75, 80, 85, 90 • Usual survivors + disabled • Usual survivors: wt major chronic diseases no disability • Exceptional survivors	Obituaries in local newspapers (English and Japanese) and through surveillance of hospital discharge records	Nonsurvival vs survival at 85yr • Ever smoker: + Usual survival vs Except. survival • Ever smoker: + *(borderline association)*	++/-

SMOKING – FRAILTY/DISABILITY (including fractures)

Note: A positive association (+) with smoking is a **worst** outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association	Quality/Applicability
Agahi 2013	Sweden	1060	30-50	Up to 34yrs	Interview: • None, light, heavy smoker (>10 cig/day) • Current, persistent & former smoker	Mobility impairment (rate of increase / progression) Musculoskeletal pain (rate of increased / progression) Psychological distress	**Mobility impairment:** Index measuring ability to walk, run go up stairs (0=no problem; 3=problem all 3 domains) **Musculoskeletal pain:** Pain index in past 12 months ranging from 0 (no pain) to 6 points (severe pain) **Psychological distress** 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)	**Mobility impairment:** Non Smoker: 1 • Persist heavy: + • Former heavy: + • Former light: + Persist non-smoker: 1 • All categories: + **Musculoskeletal pain:** 0 **Psychological distress:** Persist non-smoker: 1 • Heavy smoker: +	-/++
Ostbye 2002	US	7,845	51-61 years	HRS: 6yrs	Self-report Heavy smokers (1+ pack cig./day), light (<1 pack/day), former smokers (quit < 3 years, quit 3-15 years, quit 15+ years ago), never smokers	Disability • ADL Impaired mobility • difficulty walking • climbing stairs • Self-reported health Hospitalisation	Participant interviews	Never smoked = 1 ***FOR all specific outcomes:*** • Heavy: + • Light: + • Former <3yrs: + • Former 3-15yrs: + • Former 15+yrs: 0	-/+

Englund 2013	Sweden	778	54±5.9	11.2±2.6	Self-report Never, former, current smoker	Wrist fracture	Injury-fracture database	<u>Never smoker</u>: 1 • Former: 0 • Current: 0	+/++
Holmberg 2006	Sweden	22444 (M) 10902(W)	Men: 27-61 yrs Women: 28-58 yrs	19yrs (M) 15yrs (W)	Self-report • Smoke or not	Incident low-energy fractures (those resulting from falling from standing height or less) • Any fracture, vertebral, forearm, hip, humerus, ankle	Data linkage with hospital medical, radiological files	<u>Non-smoker</u>: 1 (vs smoker) **Women:** • Vert fracture: + • All other types: 0 **Men:** • Any fract: + • Forearm fract: 0 • Vert fracture: + • Prox humerus: + • Ankle: 0 • Hip: +	+/++
Moayyeri 2009	UK	25,311	W: 64.7 (8.4) M: 61.9 (9.7) (40-75yrs)	11.3yrs (SD = 1.5; range 9.2–14.1)	Self-report • Never; former, i.e. as much as one cig/day for more than 1 yr; current	Osteoporotic fractures	Hospital records & ICD 9-10 diagnostic codes	<u>Never smoker:</u> 1 • WomenCurrent: 0 • Men current: 0	+/++
Szoeke 2006	Australia	438	46-52	11 years	Self-report (Y/N)	Osteoarthritis	X-ray	<u>Never smokers</u>: 1 Smoking: +	+/-

SMOKING – DEMENTIA

Note: A positive association (+) with smoking is a **worst** outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association	Quality/Applicability
Sabia 2008	England	5388	35-55	85-88 to 97-99	Self-report • Never, long-term ex-smoker; recent ex-smoker, current Current smoker: pack-years based on g/day with 1 cig.=1g and 1 cigar=3g	Memory, reasoning, vocabulary, semantic and phonemic fluency	Cognitive function battery of tests (e.g., 20-word free recall test, Alice Heim AH4 Group Test of General Intelligence, Mill Hill Vocabulary Test, verbal fluency tests)	**(OR of being in the lowest quintile of cognitive function)** Never smoker: 1 *Memory* • LT ex-sm.: – • Recent ex.: 0 • Current sm.: + *Reasoning* • LT ex-sm.: 0 • Recent ex-sm.: 0 • Current sm.: 0 *Vocabulary* • LT ex-sm.: – • Recent ex-sm.: – • Current sm.: 0 *Phonemic fluency* • LT ex-sm.: – • Recent ex-sm.: 0 • Current sm.: 0 *Semantic fluency* • LT ex-sm.: – • Recent ex-sm.: – • Current sm.: 0	+/++
Sabia 2009	England	5123	Mean 56yrs	5yrs	Self-report current smoking	Cognitive function Short-term assoc. with poor executive function & memory	Cognitive tests to measure executive function (reasoning, verbal fluency measures)	Current smoking No: 1 Yes: +	+/++

Nooyens 2008	Netherlands	1964	56.0 (7.0)	5yrs	Self-report Never, former, current, recent quitter, resumed smoking	Cognitive decline	Neuropsychological test battery,15-Word Verbal Learning Test, Stroop Color–Word Test Animal Naming Verbal Fluency Tes	<u>Never Smoker:</u> 1 • Mem function: + • Speed of cog processing: + • Cog Flexibility: + Global cog Fx: 0	+/+
Alonso 2009	USA	11,151	45-64	Up to 10yrs	Self-report Never, former, current smoker	Incident dementia	Participant & proxy report; chart abstraction; 3 cognitive tests	<u>Never smoker</u>: 1 • Current: +	+/+
Whitmer 2005	USA	8,845	40-44	27yrs ('64-'03)	Self-report never or ever smoked	Dementia	Electronic medical records	Never smoker: 1 Smoking: +	+/-
Rusanen 2011	USA	21,123	50-60	17yrs	Self-report Never; former; current smoker: less than 0.5 pack/day, 0.5-1 pack/day, 1-2 packs/day, 2+ packs/day	Dementia, Alzheimer's disease AD), vascular dementia (VD)	Electronic health records with ICD codes	<u>Never smoker</u>: 1 ***Dementia*** Current-pack/d: • <0.5: 0 • 0.5-1: + • 1-2: + • >=2: + ***AD*** • Former: 0 Current, pack/d: • <0.5: 0 • 0.5-1: 0 • 1-2: 0 • >=2: + ***VD*** • Former: 0 Current, pack/d: • <0.5: 0 • 0.5-1: 0 • 1-2: + >=2: 0	+/+

Kimm 2011	Korea	3252	Men 51.9 ±8.7 Women 53.6 ±9.9	14yrs	Self-report Never, former, current smoker	Dementia Alzheimer's disease AD, vascular dementia VD, unspecified	ICD-10; medical history, physical, neuro. lab and imaging evaluation	Never smoker: 1 **AD & VD - Men** • Former: 0 • Current: 0 **AD & VD - Women** • Former: 0 • Current: + **Unspec – both sex** • Former: 0 • Current: + **All – both sex** • Former: 0 Current: +	+/+
Tyas 2003	Hawaii	3734	(mid-life)	('65–'71) and ('91–'96)	Self-report Never, former, current smoker	Vascular dementia	DSM-III-R	Smoking: +	+/-
Debette 2011	USA	1352	61±9	10yrs	Self-report Smoke or not	White matter, total brain, and LV temporal horn volume Verbal memory, visuospatial memory and exec. function	Brain MRI techniques Validated cognitive tests	White matter vol.: 0 Total brain vol.: - Temp. horn vol + Verbal memory: 0 Visual memory: 0 Exec function: 0	+/+
Knopman 2001	USA	10,963	47-70	6yrs	Self-report Never, former, current smoker	Cognitive change	Change in follow-up scores minus baseline scores for cognitive testing using: Delayed Word Recall test, the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised, First Letter	Never: 0 Former: 0 Current: 0	+/+

							World Fluency test		
Strand 2013	Norway	48,793	35–50	35yrs	Self-report	Dementia death	Death with ICD codes	Non-smokers: 0 Current <15: 0 Current 15+: 0	++/-

SMOKING – OVERALL MORTALITY

Note: A positive association (+) with smoking is a **worst** outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association	Quality/Applicability
Shaper 2003	Britain	7735	40–59	22yrs ('78-'00)	Self-report 8 categories; none to current	Total mortality	National Health Service register	Never smoker: 1 • Pipe/cigar (primary & secondary): + • Former: 0 Current: +	++/++
Strandberg 2008	Finland	1658	40-55	26yrs ('74-'00)	Self-report (5 categories from never >20)	Mortality	National Population Information System of the Finnish Population Register Centre	Never smoker: - Smoking: +	+/+
Qiao 2000	Finland	1673	Not reported	35yrs	Self-report Never, former, current smoker	Mortality (range of specific outcomes)	Death certificate	Men smoking persistently were most at risk, while those who persisted in quitting had no increased risk of death compared with non-smokers	+/+
Pelkonen 2000	Finland	1582	Not reported	30yrs	Self-report Never, former, current smoker Exp: Smoking cessation	Mortality	Death certificate	Smokers across the entire range of pulmonary function may increase their expectation of lifespan by giving up smoking	++/+
Lim 2013	Singapore	48,251	45-74	93-98 to 2009	Self-reported • Never, • Long-term quitters (quitter at baseline and f/u interview), • New quitters	Mortality: all-cause, lung cancer, other cancers, coronary heart disease, stroke, chronic obstructive	Nationwide death registry with ICD code	Current smoker: 1 *All-cause* • New quitters: - • LT quitters: - • Never: - *Other than lung*	-/+

					(baseline smoking and quitter at f/u interview), • Current smokers (smoking at baseline and f/u interview)	pulmonary disease		*cancer mortality* • New quitters: 0 • LT quitters: - • Never: -	
Gerber 2012	Israel	4633	50.1±6.5	Median 26yrs (quartiles 1–3: 16–35)	Self-report • Never, former; current 1–10, current 11–20, current more than 20 cigarettes per day Exposure: change in smoking intensity	All cause mortality	Mortality register	<u>Maintained</u>: 1 *All cause mortality* • Increased: 0 • Reduced: - • Quit: -	++/+
Hara 2002	Japan	41,484	40-59	Never: 64,986 PA Former: 42,798 PA Current: 103,537 PA	Self-report Never, former, current smoker	All cause mortality	Death certificates	<u>Never smoked</u>: 1 Former (M & F): 0 Current (M & F): +	+/+

SMOKING – CARDIOVASCULAR MORTALITY Note: A positive association (+) with smoking is a **worst** outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results Association**	**Quality/Applicability**
Blanco-Cedres 2002	USA	8,816	40-59yrs	25yrs	Self-report Past/current status	CHD death, CVD death, all-cause mortality (per strata cholesterol levels)	Social Security Administration and National Death Index records	Non-smoker: 1 • CHD Current: + • CVD Current: + • All cause mort. current: + *Across all choles. levels*	+/+
Boudik 2006	Prague	926 men	Mean 46.1 (Middle aged men)	21yrs	Self-report non-smokers; <15cig/d; >=15cig/day (heavy); ex heavy smokers <1yr	Atherosclerotic CVD mortality	Outpatient departments, postal questionnaires, and registry offices	<15cig/d = 1 >=15cig/d: +	-/+
Baba 2006	Japan	41,307	40-59yrs	11yrs	Self-report: • Never, ex, current smoker • Additional categories for male 'current smokers': 1-14, 15-34, >35/day	Acute coronary events [MI, sudden cardiac death, other fatal coronary events]	MI (Monica criteria) Death certificates	Never smoker: 1 • Current: + • Past smoker: + • Men: + (increase with increase # of cig/day • Women: +	+/+
Hara 2002	Japan	41,484	40-59	Never: 64,986 PA Former: 42,798 PA Current: 103,537 PA	Self-report Never, former, current smoker	Circulatory death	Death certificates	Never smoked: 1 • Former (M & F): 0 • Current (M): - • Current (F): +	+/+
Gerber 2012	Israel	4633	50.1±6.5	Median 26yrs (quartiles 1–3:	Self-report • Never, former;	CVD death Non-CVD death	Mortality register	Maintained: 1	++/+

				16–35)	current 1–10, current 11–20, current more than 20 cigarettes per day			*CVD mortality* • Increased: 0 • Reduced: - • Quit: -	
Lim 2013	Singapore	48,251	45-74	93-98 to 2009	Self-reported • Never, • Long-term quitters (quitter at baseline and f/u interview), • New quitters (baseline smoking and quitter at f/u interview), • Current smokers (smoking at baseline and f/u interview)	Mortality from coronary heart disease, stroke, chronic obstructive pulmonary disease	Nationwide death registry with ICD code	<u>Current smoker</u>: 1 *CHD mortality* • New quitters: 0 • LT quitters: - • Never: - *Stroke mortality* • New quitters: 0 • LT quitters: 0 • Never: - *COPD mortality* • New quitters: 0 • LT quitters: - Never: -	-/+
Qiu 2003	China	50,069	55.3±11.8	6yrs	Self-report • Never, former, current smoker	CVD death	Physician report to township hospital	<u>Non-smoker:</u> 1 • Former: 0 • Current: 0	+/-
Gerber 2012	Israel	4633	50.1±6.5	Median 26yrs (quartiles 1–3: 16–35)	Self-report • Never, former; current 1–10, current 11–20, current more than 20 cigarettes per day	CVD death Non-CVD death	Mortality register	<u>Maintained</u>: 1 *CVD mortality* • Increased: 0 • Reduced: - • Quit: -	++/+
Lim 2013	Singapore	48,251	45-74	93-98 to 2009	Self-reported • Never,	Mortality from coronary heart	Nationwide death registry with ICD code	<u>Current smoker</u>: 1	-/+

					• Long-term quitters (quitter at baseline and f/u interview), • New quitters (baseline smoking and quitter at f/u interview), • Current smokers (smoking at baseline and f/u interview)	disease, stroke, chronic obstructive pulmonary disease		*CHD mortality* • New quitters: 0 • LT quitters: - • Never: - *Stroke mortality* • New quitters: 0 • LT quitters: 0 • Never: - *COPD mortality* • New quitters: 0 • LT quitters: - Never: -	
Qiu 2003	China	50,069	55.3±11.8	6yrs	Self-report • Never, former, current smoker	CVD death	Physician report to township hospital	<u>Non-smoker:</u> 1 • Former: 0 • Current: 0	+/-

SMOKING – CARDIOVASCULAR OUTCOMES Note: A positive association (+) with smoking is a **worst** outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results Association**	**Quality/Applicability**
Shaper 2003	Britain	7735	40–59	22yrs	Self-report 8 categories; none to current	Cardiovascular events	Questionnaires on recall of doctor	Never smokers: 1 • Pipe/cigar (primary and secondary): + • Former: 0 • Current: +	++/+
Humphries 2001	UK	3052 men	55.7±3.2	11yrs	Self-report • Never; former, i.e. as much as one cig/day for more than 1 yr; current	Coronary hearth disease (according to APOE genotype)	ECG	Never smoked: 1 Ex-smokers • E3/E3 : 0 • E2+ : 0 • E4+ : 0 Smokers • E3/E3 : 0 • E2+ : 0 • E4+ : ++	+/+
Satoh 2006	Japan	2,764	35-44	10yrs	Self-report	Coronary Artery Disease	Subject's clinical chart	Non-smoker: 1 Smokers: 0	+/-
Mannami 2004	Japan	19,782 men and 21,500 women	40-59	90-92 to 01 (total of 461,761 person-year follow-up)	Self-reported smoking (never-smokers, ex-smokers, and current smokers; current smokers: number of cigarettes 1 to 19/d, 20 to 39/d, • and >= 40/d)	Total stroke, Intraparenchyma hemorrhage, Subarachnoid hemorrhage, Ischemic stroke	Medical records, death certificates with ICD codes	Never smoked: 1 Former - Men or Women: • Range of CV outcomes: 0 Current – Men: • Total stroke: + • Intraparenchymal haemorrhage: 0 • Subarachnoid haemorrhage: + • Ischemic stroke +	++/+

								• Lacunar infarct: + • Large-artery occlusive infart: + • Embolic infarct: 0 <u>Current – Women</u>: • Total stroke: + • Intraparenchymal haemorrhage: 0 • Subarachnoid haemorrhage: na • Ischemic stroke 0 • Lacunar infarct: + • Large-artery occlu. Infart: na • Embolic infarct: 0 *Details on smoking intensity available*	
Harmsen 2006	Sweden	7457	Middle-age men	28yrs	Self-report • never smokers & former smokers coded non-smoker; current smokers	Stroke	First ever stroke from multiple sources	<u>Non-smoker</u>: 1 Smoking: +	+/+
Nakayama 2000	Japan	998	40-64yrs	20yrs	Not reported	Stroke	Laboratory and diagnostic imaging examined by clinicians	Smoking : + PAF: 14.9 (+)	+/-
Janzon 2004	Sweden	10619	49 yrs (28.3-57.6)	14.0±4.5yrs (range 0.5–21.9 years)	Self-report • Never, former, low smoker <10cig/day, medium smoker>10 <20 cig/day; heavy smoker >20cig/day	Myocardial infarction (according to other risk factors)	Malmo Myocardial Infarction register and from the Swedish Myocardial Infarction register	<u>Never smoker</u> • Normotension 0 • Hypertension + • Norm Chol 0 • High Chol: + • No diabetes 0 • Diabetes + <u>Ex-smoker</u> • Normotension 0	+/+

								• Hypertension + • Norm Chol 0 • High chol: + • No diabetes + • Diabetes + <u>Current smoker</u> • Normotension + • Hypertension + • Norm Chol + • High chol: + • No diabetes + Diabetes +	
Dubas 2007	Sweden	7388	47-55	28yrs ('70-'98)	Self report (5 point scale; 1 cig=1g tobacco)	All AMI	At discharge or death with ICD codes	<u>Never smoker</u>: 1 Former: + 1–14 g/day: + 15–24 g/day: + >25 g/day: + Smoking (1–5): +	++/+
						Coronary bypass	At discharge or death with ICD codes	<u>Never smoker</u>: 1 Former: 0 1–14 g/day: 0 15–24 g/day: 0 >25 g/day: + Smoking (1–5): +	
Halperin 2008	USA	13,529	52.4±8.9	Med 14.5yrs Max 20.5yrs	Self-report • never, former, current, #cig /day	Hypertension	Self-reported BP and/or the initiation of antihypertensive	<u>Never smoker</u>: 1 • Past: + • <20cig/day: + • ≥20cig/day: - • Current: +	+/+

Räikkönen 2001	USA	541	48.0±1.5	9.2yrs; SD, 3.4 years	Self-report • Number of cig/day	Hypertension	Use of BP medication and/or had elevated systolic BP or diastolic BP on 2 consecutive	• Smoking (no/yes) 0	+/-
Khalili 2002	Sweden	22 444 – (not clear)	Mean 42.2	17yrs	Self-report	Relationship between systolic BP Cardiovascular	Registers (local & national)	Non-smoker: 1 • CVD Morbidity: + • CVD Morbidity (in BP drugs): + • Mortality: + • Mortality (in BP drugs): +	+/+

SMOKING - DIABETES/METABOLIC SYNDROME Note: A positive association (+) with smoking is a **worst** outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results Association**	**Quality/Applicability**
Wannamethe 2001	UK	7735	40-59	16.8 yrs	Self-report 8 categories; none to current	Type 2 diabetes	Self-report postal questionnaires and review of all death certificates	Never smoker: 1 Smoking: +	+/+
Patja 2005	Finland	41 372	25–64	Mean follow-up 21 years	Self-report • Never, former, current smoker - smokers); Current smokers: <20 vs. >20 cig.	Type 2 diabetes	Hospital discharge register, social insurance drug register	Never smoker: 1 **Men:** • Former: 0 • Current <20cig/day: + • Current >=20cig/day: + **Women:** • Former: 0 • Current <20cig/day: + • Current >=20cig/day: + **Men and women combined:** • Former: 0 • Current <20cig/day: + • Current >=20cig/day: +	-/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association	Quality/Applicability
Sairenchi 2004	Japan	39,528 men and 88,613 women	40-79 (sub group: 40-59)	93-02	Self report • Never, former, current smoker For smoker: number of cigarettes smoked per day)	Type 2 diabetes mellitus	Annual follow-up examinations with measurement of plasma glucose levels and interview on diabetes medications	Never smoker: 1 *Men:* • Former: + • Current: + • < 20 cig/day: + • >=20 cig/day: + *Women:* • Former: 0 • Current: + • <20 cig/day: + • >=20 cig/day: +	+/+
Fogelholm 2000	Finland	1143	36-88	10 yrs (’85-‘95)	Self-reported smoking (smoker vs. non-smoker) •	Weight change	Self-report	Never smoker: 1 Smoking: +	+/+
Holme 2007	Norway	6382(M)	40-49	28yrs	Self-report • Never, former, current smoker	Metabolic syndrome	3 out of 5 clinical criteria	Never smoker: 1 • Current: +	+/++
						Diabetes	Clinical assessment	Never smoker: 1 Current: 0	
Riserus 2007	Sweden	770	50	20 yrs (70-73 to 91-95)	Self-report • Smoke vs not	Insulin sensitivity	Hyperinsulinemic – euglycemic clamp used to calculate glucose infusion rate	Never smoker: 1 • Smoking: 0	+/+

SMOKING – CANCERS

Note: A positive association (+) with smoking is a **worst** outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association	Quality/Applicability
Shaper 2003	Britain	7735	40–59	21.8yrs (20 – 22.5)	Self-report 8 categories; none to current	Cancer	The cancer registry	• Never smokers: 1 • Pipe/cigar (primary and secondary): + • Former: + • Current: +	++/++
Stevens 2009	England Scotland	1.3 million	50-60 (women)	5-9yrs	Self-report Never, former, current smoker	Pancreatic cancer	NHS central register	• Never smoker: 0 • Former: - • Current (<15): +	++/++
Otani 2003	Japan	19,862 (cohort 1) 10,212 (cohort 2)	48.9 (6.0) (cohort 1) 53.4 (8.2) (cohort 2)	10yrs (cohort 1) 7yrs (cohort 2)	Self-report • Never, former, current smoker Smoker: Pack-years <20, 20–29, 30–39, 40+	Colorectal cancer Invasive colorectal cancer Colon cancer Rectal cancer	JPHC cancer registry based on site codes	<u>Never smoker</u>: 1 *Colorectal* • Former: 0 • Current: + Pack-years • <20: 0 • 20–29: 0 • 30–39: + • 40+: 0 *Invasive Colorectal* • Former: + • Current: + Pack-years • <20: 0 • 20–29: 0 • 30–39: 0 • 40+: + *Colon / rectal* • Former: 0 • Current: 0	+/+

								Pack-years • <20: 0 • 20–29: 0 • 30–39: + • 40+: 0	
Sobue 2002	Japan	91,738	40–69	9yrs	Self report Never, former, current smoker	Squamous cell small cell carcinoma	Histologic examination of specimens from surgery or autopsy, biopsy or cytology	• Non-smoker: 0 • Former: + Current: +	++/+
						Adenocarcinoma	Histologic examination of specimens from surgery or autopsy, biopsy or cytology	• Non-smoker: 0 • Former: - Current: +	
Lim 2013	Singapore	48,251	45-74	93-98 to 2009	Self-reported • Never, • Long-term quitters (quitter at baseline and f/u interview), • New quitters (baseline smoking and quitter at f/u interview), • Current smokers (smoking at baseline and f/u interview)	Lung cancer, mortality from other cancers, coronary heart	Nationwide death registry with ICD code	Current smoker: 1 *Lung cancer* • New quitters: - • LT quitters: - • Never: - *Other than lung cancer mortality* • New quitters: 0 • LT quitters: - • Never: -	-/+

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association	Quality/Applicability
Inoue 2004	Japan	92,792	40-69 (mean 53)	10 yrs	Self report Never, former, current smoker	Cancers Death (due to cancer)	Active patients' notification from local major hospitals; data linkage with population-based cancer registries; death certificate	Never smoker: 1 (M & W) • Former: + • Current: + # daily cig (dose): • Men: + • Women: - Pack/year (dose): • Men: + • Women: - Age started smoke: • Men: + • Women: -	+/+
						Total cancer death	Death certificate	Never smoker: 1 (M&W) • Men former: + • Men Current: + • Women former: - • Women current: + # daily cig (dose): - Pack/year (dose): - Age started smoke: • Men: + • Women: -	

SMOKING – OTHER OUTCOMES Note: A positive association (+) with smoking is a **worst** outcome									
Noborisaka 2013	Japan	6998	Men 84.3% bt 30-59yrs Women 86.3% bt 30-59yrs	6 yrs	Self-report • Never, former, current up to one pack/day, current smokers > one pack/day	Chronic kidney condition	Categorisation in subjects based on single measurements of proteinuria and eGFR	Non-smoker: 1 • Former: 0 • Smoking: +	+/-

Table 13. Overview of included studies – Smokeless tobacco (snus)*

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association (–/+/0)*	Quality/ Applicability
Nafziger (2007)	Sweden	82927	30-60	10 years	Health surveys, medical examinations	Maintaining weight	BMI	User: - Non-user: +	++/+/-
Östenson 2012	Sweden	2382	47.2 (46.9–47.4)	10 years	Self-report Never, former, current smoker **of SNUS**	Type 2 diabetes	Oral glucose tolerance test	Never use SNUS: 1 • Former: 0 • 1-5 boxes/w: 0 • >5 boxes/w: + • Consistent smo.: 0 • Former : 0 Never smoker: 1 • 1–15 cig/day: 0 • >15 cig/day +	+/-

*Note: A positive association (+) with smoking is a **worst** outcome

Table 14. Overview of included studies – Alcohol

ALCOHOL – DISABILTY/FRAILTY Note: a positive association (+) with alcohol is the worst outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association[c] (-/+/0)**	**Quality/ Applicability**
Ostbye 2002	US	HRS study: 7,845 people	HRS study: ages 51-61 yrs	HRS: 92-98	Self-reported alcohol intake and history of drinking problems	Disability, impaired mobility, self-reported health, and health care utilization	Participant interviews	**HRS study:** *1) ADL dependence; 2) difficulty climbing stairs; 3) difficulty walking; 4) poor health; 5) hospitalized, respectively* Up to 2 drinks/day (ref: never drinking): 1)- 2)- 3)- 4)- 5)- 2+ drinks/day (ref: never drink.): 1)0 2)0 3)0 4)- 5) 0 Past drinking problem (ref: never drink.): 1)+ 2)+ 3)+ 4)+ 5)+	-/+
Englund 2013	Sweden	778	49-61	85-08	Self-report (coded as “teetotaller” or “alcohol user”)	Wrist fracture	Prospective injury-fracture database	**Alcohol level** None 1.00 User: 0	+/-
Moayyeri 2009	UK	25311	40-75 years	1993–1997 to 2007	Self-report (‘How many alcoholic drinks do you have each week?)	Osteoporotic fractures	Death certificates and linkage of the National Health Service number with the East Norfolk Health Authority	**Alcohol level** Men None 1.00 User: + Women None 1.00 User: 0	+/+

ALCOHOL – DEMENTIA

Note: a positive association (+) with alcohol is the worst outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association[c] (-/+/0)	Quality/ Applicability
Virta 2010	Finland	1,486	Mean age in 1981: 51.7 yrs (SD: 6.1)	1975-81 to 1999-07 (mean follow-up: 22.8 yrs.)	Self-reported total weekly (for beer, wine) or monthly (for spirits) alcohol intake: *1 drink=12 g ethanol; 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) *# of pass-outs *binge drinking at least monthly	Cognitive function	TELE, a self-report telephone interview	Abstainer: + Light drinker: 1.00 Moderate: 0 Heavy: + Binge drinking: no: 1.00 Yes: + Number of pass-outs: 0: 1.00 1: 0 >2: +	++/++
Elwood 2013	Caerphilly, UK	1,320 men	45–59	1979-04	self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include	Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia	Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological	Diabetes: 0 Vascular disease: 0 Cancer: 0 Any impairment: 0 Dementia: 0 Death: 0	+/++

					abstinence)		examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score)		
Sabia 2009	England	5,123	Mean age 56 yrs	97-99 to 02-04	Self-reported alcohol units in last 7 days; 1unit=8 g ethanol	Cognitive function	Cognitive tests to measure executive function (reasoning, verbal fluency measures)	**Alcohol consumption (units/week):** 0: + 1-14: 1.00 >=15: 0	+/++
Sabia 2011	France	4073 men	Ages 40–50 for men and 35–50 for women	10 yrs (1992 to 2002-04)	Self-reported units of alcoholic drinks (beer, wine, aperitif, spirits) consumed (1 unit: 10–12 g of alcohol) in a week *mean alcohol consumption over 10 yrs	Cognitive performance (psychomotor speed, attention and reasoning) measured	Digit Symbol Substitution Test (DSST)	**Drinks/week by occupational position (Low/ intermediate/ high position):** 0 drinks/wk: 0/0/0 1-3 d/wk: 0/0/0 4-14 d/wk: 1.00 15-21 d/wk: 0/0/0 >21 d/wk: -/0/0	+/++
Anttila 2004	Finland	632 women and 386 men	Mean age 48.3 yrs	1972-77 to 1998	Self-reported frequency of alcohol intake: never drank, drank infrequently (less than once a month), drank frequently (several times a month)	Cognitive function	MMSE; DSM-IV dementia diagnosis	**Dementia:** Never: 0 Infrequent: 1.00 Frequent: 0 **Mild cognitive impairment:** Never: + Infrequent: 1.00 Frequent: +	+/++

ALCOHOL – CARDIOVASCULAR OUTCOMES

Note: a positive association (+) with alcohol is the worst outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association[c] (-/+/0)	Quality/ Applicability
Beulens 2007	Netherlands	1,417	49-70 yrs	1993-97 to 2005	Self-reported alcohol intake (<=10, 11-25, 26-50, >50 g/day)	cardiovascular disease (coronary heart disease, cerebrovascular accidents, cardiovascular disease)	hospital discharge diagnoses with ICD codes (CVD); municipal administration registries (vital status); GP (cause of death)	U-shaped relationship between alcohol-intake and CVD risk	++/-
Wannamethee 2002	England, Wales, and Scotland	7157	40-59yrs	('78–'80)-(2000)	Self-report (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)	Major coronary heart disease events	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-report questionnaires	**Alcohol level** non-drinkers: 1.0 occasional drinkers who took up regular drinking: + continuing regular drinkers: + stable occasional drinkers: 0	+/+
Emberson	England,	7,735	40–59	1978/1980 to	Self-report (A	cardiovascular	Established ''tagging''	**Alcohol level**	++/+

2005	Wales, and Scotland		years	1998/2000	five-point scale from zero (none) to four (heavy))	morbidity	procedures provided by the National Health Service central register	None 1.00 Occasional 1.00 Light : - Moderate *0* Heavy +	
						all-cause mortality	Established ‘‘tagging’’ procedures provided by the National Health Service central register	**Alcohol level** None: 0 Occasional 1.00 Light: - Moderate: 0 Heavy: +	
Qiu 2003	China	50069	40-80+	1994/1996-2000	Self-report	CVD death	Clinical visit by practitioner to town	**Alcohol level** Non-drinker 1.00 Ex-drinker: 0 Current drinker: 0	+/ -
Iso 2004	Japan	19 544	40-59	1990-2000	Self-report (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)	Stroke	computer tomographic scan and/or magnetic resonance images	**Alcohol level** **<450g ethanol pw:** 0 **>450 g ethanol pw:** +	+/ -
Elwood 2013	Caerphilly, UK	1,320 men	45–59	1979-04	self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include abstinence)	Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia	Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score)	Diabetes: 0 Vascular disease: 0 Cancer: 0 Any impairment: 0 Dementia: 0 Death: 0	+/++

ALCOHOL – DIABETES/METABOLIC SYNDROME

Note: a positive association (+) with alcohol is the worst outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association[c] (-/+/0)	Quality/ Applicability
Elwood 2013	Caerphilly, UK	1,320 men	45–59	1979-04	Self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include abstinence)	Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia	Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score)	Diabetes: 0 Vascular disease: 0 Cancer: 0 Any impairment: 0 Dementia: 0 Death: 0	+/++
Waki 2005	Japan	28,893	40-59 yrs	10 yrs (baseline: 1990)	Self-reported total daily alcohol intake based on type, freq., quantity of alcohol and alc. content: e.g., 180 ml sake has 23g ethanol, 180 ml sochu has 36g ethanol	Incident type 2 diabetes	Self-report	**Alcohol intake in g/day (men/women):** Non-drinkers and eth. intake on <=3 days/month: 1.00, 1.00 0 <ethanol <=4.9: 0, 0 4.9 < ethanol <=11.5: +, 0 ethanol >11.5: 0, 0	+/+
Wannameth ee 2003	England, Wales, Scotland	7,608 men	40-59 yrs	1978-80 to 1983-85	Self-reported freq., quantity and type of alcohol (1 unit UK alc.= about 10 g alcohol) *occasional drinkers (e.g. <1 unit/week); light-moderate (e.g.	BMI	Weight gain using height and weight measurements	**Baseline - f/u changes in alcohol intake (5 yrs):** Stable intake: None-occasional: 1.00 Light-moderate: 0 Heavy: + Changed intake: Light-moderate (*at*	+/++

					1-20 units/week), heavy (e.g. 21-42 units/week), very heavy (e.g. >42 units/week – used for 'ex-heavy'/'new heavy')			*baseline*) to none-occasional (*at f/u*): 0 None-occasional to light-moderate: 0 Ex-heavy: 0 New heavy: +	
Wang 2010	US	19,220	38-89 yrs	12.9 yrs. follow-up (baseline: 1992-95)	Self-reported freq. of alcohol intake over the past year ('never' to '6+ per day') *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	Overweight or obesity	Self-reported f/u weight and baseline height used for BMI: **overweight:** 25 to 30 kg/m2 **obese:** >=30 kg/m2	Total alcohol intake (g/day) (association with **overweight or obese; obese)**: 0: 1.00, 1.00 >0- <5: 0, - 5- <15: -, - 15- <30: -, - >= 30: -, -	+/+

ALCOHOL – CANCER Note: a positive association (+) with alcohol is the worst outcome									
Study	**Country**	**n**	**Age at baseline**	**Length of follow-up**	**Exposure measurement**	**Outcome**	**Outcome measure**	**Results association[c] (-/+/0)**	**Quality/ Applicability**
Stevens 2009	England and Scotland	1.29 million women		96-01 to 2005-07 Mean yrs of follow-up: 7.2 for cancer incidence; 8.9 for mortality	Self-reported alcohol intake	Incident and fatal pancreatic cancer	National Health Service Central Register (deaths, cancer registrations with ICD codes)	**Alcohol units per week and RR for incidence/mortality):** None: + / + 1-2: 0 / 0 3-6: - / - 7-13: 0 / 0 14+: 0 / 0	+/++
Flood 2008	USA	49238	older than 50 y	1995–1996 to 2000	Self-report (question not detailed)	Colorectal cancer	probabilistic linkage between cancer registry databases	**Alcohol level** None 1.00 User: 0	++/ -
Otani 2003	Japan	90004	40–59 Cohort 1 40–69 Cohort 2	Cohort I After January 1, 1990-1999 Cohort II January 1, 1993–1994-1999	Self-report (less than 1 day/month, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week, and everyday)	Colorectal cancer	Cancer registry	**Alcohol level** Men None 1.00 User: + Women None 1.00 User: 0	+/ -
Elwood 2013	Caerphilly, UK	1,320 men	45–59	1979-04	Self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include abstinence)	Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia	Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score)	Diabetes: 0 Vascular disease: 0 Cancer: 0 Any impairment: 0 Dementia: 0 Death: 0	+/++

ALCOHOL – OTHER

Note: a positive association (+) with alcohol is the worst outcome

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results association[c] (-/+/0)	Quality/ Applicability
Xu 2010	South East Queensland, Australia	564	45-60 yrs	2001-06	Self-reported alcohol use: >never >drank in past >occasionally >regularly	General mental well-being, and psychological symptoms	SF-36 and the self-reported Greene Climacteric Scale (GCS) questionnaire	**Correlations between alcohol and 1) anxiety, 2) depression, 3) psychological symptoms, 4) SF-36 mental health:** *Alcohol* Never: ref Past drinker: 1)- 2)0 3)0 4)0 Occasionally: 1)0, 2)0, 3)0, 4)0 Regularly: 1)0, 2)0, 3)0, 4)0	-/+
Sun 2011	US	13,894	70+	84-00	Self-report (avg. alcohol intake in g/day over 1 year) Portion size: 13.2 g alcohol of beer; 10.8 g of wine, 15.1 g of liquor	Successful ageing (free of major chronic diseases, no major cognitive impairment, physical impairment, or mental health limitations)	**Chronic diseases:** Questionnaire, medical record review, pathology report review, telephone interview **Cognitive function:** Telephone Interview for Cognitive Status (TICS) **Physical function and mental status** Medical Outcomes Study Short-Form Health Survey (SF-36)	**Days of alcohol use/week:** Nondrinker: 1.00 1-2: 0 3-4: + 5-7: +	++/+
Willcox 2006	island of Oahu	5820	45-68yrs	Not reported	Self-report (High alcohol intake was dichotomized as 3 or + drinks/d)	Overall survival	Survival	**Alcohol level** <3 1.00 >3 -	++/-

Lin 2005	Japan	110,792	40 to 79 years	1988–1990 to 1999	Self-report (‘nondrinkers’ reported no alcohol drinking in the past; ‘never or almost never”; “exdrinkers”; “current drinkers”)	All-cause mortality	Death certificates	**Alcohol level** <23 g/d 0 >23 g/d +	++/ -
Emberson 2005	England, Wales, and Scotland	7,735	40–59 years	1978/1980 to 1998/2000	Self-report (A five-point scale from zero (none) to four (heavy))	cardiovascular morbidity	Established ‘‘tagging’’ procedures provided by the National Health Service central register	**Alcohol level** None 1.00 Occasional 1.00 Light : - Moderate 0 Heavy +	++/+
						all-cause mortality	Established ‘‘tagging’’ procedures provided by the National Health Service central register	**Alcohol level** None: 0 Occasional 1.00 Light: - Moderate: 0 Heavy: +	
Tabak 2001	Finland, Italy, Nether-lands	2,953 men (Finland: 1,186 men; Italy: 1,183; Netherlands: 667)	40-59	20 yrs (1965-70 to 1990)	Self-reported drinks: none, <=1 per week (occasional); <=1 drink/week, >1 and <=3 drinks /day (light); >3 and <=9 /day; >9 /day	chronic obstructive pulmonary disease mortality	clinical records, from family doctors, specialists, relatives, with ICD codes	Nondrinkers: 1.00 Light drinkers: 0 Higher alcohol consumption: 0 e.g., >9 drinks /day: 0	-/+

Table 15. Overview of included studies – Weight change/weight cycling*

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association (-/+/0)	Quality/ Applicability
Field (2009)	United States	44842	30-55	16 years	Weight cycling: Postal questionnaire	Mortality	Next of kin, the postal service, or ascertained by the National Death Index	Mild: 0 Severe: 0	+/-
Langlois (2001)	United States	2180	50-74	22 years	Weight loss of >10% from max: Self-report	Hip Fracture	Hospital records and death certificates	50–64 years: + 65–74 years: +	++/+
Ravona-Springer (2013)	Israel	10000	40-70	36 years	Weight variability (independent of direction of weight change): Interviews, clinical assessments	Dementia	Interview and Hebrew version of the Modified Telephone Interview for Cognitive Status	Wt change I: 0 Wt change II: 0 Wt change III: + Wt change IV: +	+/-
Waring (2010)	United States	1577	40-50	11 years	Weight loss/gain/cycling: Interviews, clinical examinations, laboratory tests	Diabetes	Nonfasting plasma glucose level and/or reported treatment with insulin or an oral hypoglycemic agent	Weight loss: 0 Weight gain: 0 Weight cycling: 0	++/-

*Note: a positive association (+) with alcohol is the worst outcome

Table 16. Overview of included studies – Combined lifestyles

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association (–/+/0)	Quality/ Applicability
King (2007)	United States	15708	45-64	11-13 years	Interviews, questionnaire, medical examination	Cardiovascular disease	A single variable in the ARIC dataset (PRVCHD05)	Switched from Unhealthy to Healthy Lifestyle 1 healthy behaviour: 0 *(nsig)* 2 healthy behaviours: 0 *(nsig)* 3 healthy behaviours: - *(sig)* 4 healthy behaviours: - *(sig)*	++/+/-
						Mortality	State death certificates	Switched from Unhealthy to Healthy Lifestyle 1 healthy behaviour: 0 *(nsig)* 2 healthy behaviours: - *(sig)* 3 healthy behaviours: - *(sig)* 4 healthy behaviours: - *(sig)*	
Agrigoroaei (2011)	United States	4995	33-84	9-10 years	Telephone interviews	Episodic memory Executive functioning	Brief Test of Adult Cognition Brief Test of Adult Cognition	behavioural protective factors + *(sig)* behavioural protective factors + *(sig)*	++/+/-

Elwood (2013)	Caerphilly, UK	1,320 men	45–59	1979-04	Self-reported drinking: three or fewer units alcohol per day treated as healthy behaviour (does not include abstinence)	Type 2 diabetes, vascular events, cancer, cognitive impairment and dementia	Self-report, primary care and hospital records, CT scans, Office of National Statistics, cognitive impairment screening and assessment (e.g., CAMCOG, CAMDEX, neurological examination, informant questionnaire, Clinical Dementia Rating, Hachinski Ischaemic Score)	Diabetes: 0 Vascular disease: 0 Cancer: 0 Any impairment: 0 Dementia: 0 Death: 0	+/++
					Self-reported (method?) Regular exercise: walking two or more miles to work each day, or cycling ten or more miles to work each day, or 'vigorous' exercise described as a regular habit	Diabetes Vascular disease Cancer Cognitive impairment Dementia Death	Interview, examination, primary care and hospital records. Deaths and cancer from ONS.	Diabetes: – Vascular disease: **0** Cancer: **0** Cog impairment: – Dementia: – Death: –	/++

Table 17. Overview of included studies – Leisure/cognitive activity/social networks

Study	Country	n	Age at baseline	Length of follow-up	Exposure measurement	Outcome	Outcome measure	Results Association (–/+/0)	Quality/ Applicability
Bielak (2012)	Australia	7152	20-24: 2404 40-44: 2530 60:64: 2551	7 years	Activity engagement Self-reported survey	Perceptual speed	Symbol Digit Modalities Test	Activity Engagement 20: + 40: + 60: +	++/+
						Short-term memory	California Verbal Learning Test	Activity Engagement 20: + 40: + 60: +	
						Working memory	Wechsler Memory Scale	Activity Engagement 20: + 40: + 60: +	
						Episodic memory	CVLT-Delayed	Activity Engagement 20: + 40: + 60: +	
						Vocabulary	Spot-the-Word Test	Activity Engagement 20: + 40: + 60: +	
Britton (2008)	UK (England)	5823	35-55	17 years	Social network Self-reported questionnaire Frequency and number of hours per week.	Successful aging: free from major disease (coronary heart disease, stroke, cancer, diabetes mellitus, depression, metabolic syndrome and with good physical and mental functioning.	Self-reported questionnaires, medication use, clinical examinations, evidence from GPs and hospitals.	<u>Successful aging</u> <u>Men and women</u> Low: 1 Medium 0 High 0	+/++

Friedland (2001)	United States	193 cases/358 controls (for total study, not reported for 40-59 year olds)	40-59	>12 (not fully reported)	Diversity and intensity of participation in intellectual, passive and physical activities Self-reported or surrogate reported (for cases) Questionnaire Physical intensity (total hours per month – sports, gardening, walking)	Alzheimer's Disease	Neuropsychological, laboratory, and neurological exams and all had x-ray computed tomography or MRI scans of the brain.	Intellectual activity: - Physical activity: - **Passive activity: -**	-/+
Holtzman (2004)	United States	354	50+	12.4 years	Larger social networks Interviews	Cognition	MMSE	Risk of low MMSE score: -	++/+
Kareholt (2011)	Sweden	1643	57.4	20+ years	Baseline leisure activity (political, mental, socio-cultural, social, physical, and organizational activities. Interviews	Cognition	MMSE	Association of type of activity with cognition Political: + Mental: + Socio-cultural: + Social: 0 Organisational: 0 Physical: 0	++/+
Raikkonen (2001)	United States	541	42-50	9.2 years	Social support Questionnaires plus clinical examinations	Hypertension	Random-zero muddler sphygmomanometer	Women: 0	++/+

3.2.1 Quality and applicability of studies

Appendix C summarises the quality of included studies. These scores are also integrated in the summary statements and in the evidence tables. An applicability statement is provided for each evidence statement.

Overall, the evidence cited in the review is good (or very good) and the applicability directly or partially applicable.

3.2.2 Structure of evidence statements

Evidence statements are organised in the same way as the summary tables presented in the previous section: for each risk factors, the evidence is reported by individual outcome category.

To facilitate cross-reference to the PH guideline, the first digit of the evidence statements refers to the review (i.e. here always 2 for Review 2), the other digits follow the numbering system for this report (3.1, 3.2, etc.), and the letters refer to risk factors.

3.3 Evidence statements for PHYSICAL ACTIVITY (PA)

Summary data for PA studies is reported in Table 9.

2.3.1PA Healthy Ageing / Quality of Life / Well-being

There is consistent evidence from good quality studies that PA in mid-life is related to healthy and successful ageing outcomes from studies followed up from eight to 17 years.

Three prospective cohort studies [+][1], [++][2], [++][3] reported longitudinal associations between mid-life physical activity and dementia or Alzheimer's disease. All three studies reported a significant positive and beneficial association between mid-life PA and healthy ageing outcomes. Healthy ageing or successful survival was defined in all three studies as having no history of major chronic diseases and no cognitive impairment, physical impairment, or mental health limitations.

[1]Britton 2008; [2]Hamer 2013; [3]Sun 2010

- **Applicability**: Directly applicable. Two studies that reported beneficial association between PA in mid-life and healthy ageing were conducted in the UK and one in the US. One UK study and one US study were high quality and the other study conducted in the

UK was of good quality. One study reported outcomes separately for men and women and in both groups PA was related to more successful ageing.

2.3.2PA Disability / Frailty

There is consistent evidence that PA in mid-life is related to more positive outcomes in terms of disability and frailty in later life from studies followed up from five to 26 years. Studies were found relating to physical mobility, physical functioning, bone health.

Physical mobility/functioning

Six prospective cohort studies reported on longitudinal associations between mid-life PA and physical mobility or physical functioning, gait speed or disability [+][1], [+][2], [-][3], [+][4], [+][5], [-][6]. Five of the six studies found that mid-life PA was significantly related to better mobility and functioning outcomes in later life. One study was conducted in the UK [+][1], one in Italy [+][2] , one in Iceland [-][3], one in Finland [+][4] and one in the US[-][6]. A different study from Finland reported no significant associations [+][5].

Fractures and bone health

Three studies reported on the association between mid-life PA and bone fractures or bone health. One study reported less risk of hip or wrist fractures 11 years later in two papers [-][8], [-][9]. One study that used accelerometry to measure PA reported improved bone mineral density in those who took part in PA in mid-life [+][10]. One study reported no significant association between mid-life physical activity and risk of osteoarthritis [+][11].

[1]Lang 2007; [2]Patel 2006; [3]Chang 2013; [4]Malmberg 2006; [5]Lahti 2010; [6]Ostbye 2002; [7]Chang 2010; [8]Englund 2011; [9]Englund 2013; [10]Nokes 2012; [11]Szoeke 2006

- **Applicability**: Partially applicable. One study that reported beneficial associations between PA in mid-life and disability/frailty was conducted in the UK, the others were conducted in in developed European countries or the US.

2.3.3PA Dementia & Cognition

There is consistent evidence that PA in mid-life is related to less risk of dementia in later life from studies followed up from 12 to 40 years.

Six prospective studies (eight papers [++][1], [+][2], [+][3], [+][4], [+][5], [+][6], [-][7], [-][8]) reported longitudinal associations between mid-life physical activity and dementia or Alzheimer's

disease. Four of the six studies reported a significant beneficial association between mid-life PA and dementia in later life and in two studies associations were non-significant.

One study (two papers [+][3], [+][4]) conducted in the UK found an inverse association between regular or vigorous PA and dementia over 30 years. The three other studies that found an inverse association between PA and dementia were conducted in Sweden (two papers) and Iceland. The two studies that reported no significant association were conducted in the US [++][1], [-][8].

Two Swedish studies found a significant inverse association between light or regular PA but not for heavy PA [+][2], [-][7].

Cognitive function

Two studies were found that examined associations between mid-life PA and later life cognitive function [-][9], [+][10]. Both studies found a positive relationship between mid-life PA and improved cognitive function in later life.

[1]Carlson 2008; [2]Andel 2008; [3]Elwood 2013; [4]Morgan 2012; [5]Rovio 2005; [6]Rovio 2007; [7]Chang 2010; [8]Friedland 2001; [9]Chang 2013; [10]Sabia 2009

- **Applicability**: Directly applicable. One study that reported beneficial association between PA in mid-life and dementia was conducted in the UK. The other studies that found a similar relationship were conducted in developed European countries (Sweden and Iceland). For cognitive function, both studies were conducted in the UK.

2.3.4PA Overall mortality

There is consistent evidence that PA in mid-life is related to lower mortality in later life from studies followed up from five to 30 years.

Four prospective studies (five papers [+][1], [+][2], [+][3], [+][4], [+][5]) reported longitudinal associations between mid-life physical activity and dementia or Alzheimer's disease. All four of the studies report lower mortality in those that participate in PA in mid-life.

One study (two papers, [+][4], [+][5]) from the UK reports all cause mortality data followed up at 10 years and 30 years. Mid-life PA was associated with lower mortality at both timepoints. The other three studies were conducted in Finland [+][1], Denmark [+][2] and Germany [+][3].

Both high and moderate levels of PA compared to low levels of PA were related to lower mortality rates in two studies [+][1], [+][2]. In one study regular or vigorous exercise was associated with lower mortality and in the other study, heavy PA intensity was related to lower overall mortality rates.

[1]Hu 2005; [2]Holtermann 2009; [3]Menotti 2006; [4]Yu 2003; [5]Elwood 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between PA in mid-life and dementia was conducted in the UK. The three other studies that found a similar relationship were conducted in developed European countries (Finland, Denmark and Germany).

2.3.5PA Cardiovascular (CVD) Outcomes

There is strong evidence from six prospective studies (in nine papers, [+][1], [+][2], [+][3], [+][4], [+][5], [+][6], [+][7], [++][8], [+][9]) reported longitudinal associations between mid-life physical activity and CVD events or CVD mortality followed up between nine and 40 years.

Six papers reported a significant beneficial association between mid-life PA and CVD risk or events in later life (stroke [+][1], CVD risk [+][2], coronary heart disease (CHD) events [+][4], myocardial infarction, ischaemic heart disease, vascular disease) and three papers reported lower CVD related mortality from stroke [++][8] , CHD [+][5] and CVD [+][3] related to PA in mid-life.

One study (two papers [+][5] ,[+][6]) that reported 10 and 30 year follow-up was conducted in the UK. One study (three papers reporting at different timepoints and for different outcomes) was conducted in Finland [+][2], [+][3], [+][4,] and one in each from Sweden, Germany, Greece (Corfu) and Denmark.

[1]Harmsen 2006; [2]Hu 2006; [3]Hu 2005; [4]Hu 2007; [5]Yu 2003; [6]Elwood 2013; [7]Meisinger 2007; [8]Pitsavos 2004; [9]Holterman 2009

- **Applicability**: Directly applicable. One study that reported beneficial associations between PA in mid-life and CVD outcomes was conducted in the UK, the other five studies were conducted in in developed European countries.

2.3.6PA Diabetes / Metabolic Syndrome

There is some consistent evidence that PA in mid-life is related to lower incidence of diabetes in later life from two prospective cohort studies followed up for 28 [+][4] and 30 years [+][2]. The two studies were conducted in the UK [+][2] and Norway [+][4].

Three prospective cohort studies also reported on relationships between mid-life PA and pre-conditions for diabetes. Two reported metabolic syndrome as an outcome [+][3], [+][4] and one reported insulin sensitivity as an outcome [+][5]. All three studies reported a beneficial association between mid-life PA and the diabetes preconditions. The two studies with metabolic syndrome as an outcome were conducted in the UK [+][3] and Norway [+][4] and the study that reported insulin sensitivity was conducted in Sweden.

[1]Hu 2003; [2]Elwood 2013; [3]Ekelund 2005; [4]Holme 2007; [5]Riserus 2007

- **Applicability**: Directly applicable. Two studies that reported beneficial associations between PA in mid-life and metabolic syndrome outcomes was conducted in the UK, the other 5 study was from Norway. Two studies with metabolic syndrome as an outcome were conducted in the UK.

2.3.7PA Cancer

The evidence relating to the associations between PA and cancer is mixed.

Four prospective cohort studies [+][1], [+][2], [+][3], [+][4] reported longitudinal associations between mid-life physical activity and cancer or cancer mortality followed up between seven and 30 years.

One study in the UK reported no significant relationship between mid-life PA and incident and fatal pancreatic cancer [+][1], A different UK study [+][2] examined associations between total PA and a range of different cancers and found lower rates of total cancer, upper digestive tract cancers (oral, oesophagus, stomach cancer) in those who participated in moderate or vigorous PA at mid-life compared to those who did not. No significant associations were found for lung, stomach, colorectal, lymphatic/haematopoetic cancers. However, the same study [+][2] reported that vigorous exercise at mid-life was associated with a significantly *increased* risk of bladder cancer.

A third UK study found no significant relationship between mid-life PA and cancer [+][3].

Total cancer mortality was lower in those who took part in moderate or high levels of PA [+][4] in a study from Finland.

[1]Stevens 2009; [2]Wannamethee 2001; [3]Hu 2005; [4]Elwood 2013

- **Applicability**: Directly applicable. Three studies that reported beneficial associations between PA in mid-life and diabetes outcomes were conducted in the UK, the other study was from Finland. One study that reported increased risk of bladder cancer was conducted in the UK.

2.3.8PA Mental health

The evidence for an association between mid-life PA and mental health is inconclusive.

One prospective cohort study [++][1] in the UK reported less risk of anxiety and/or depression for heavy PA at five-year follow-up but not at 10 years.

One prospective cohort study [-][2] in Australia found no significant association between mental wellbeing, including anxiety and depression and mid-life PA at five years follow-up.

[1]Wiles 2007; [2]Xu 2010

- **Applicability**: Directly applicable. One study was conducted in the UK, the other study was from Australia.

3.4 Evidence statements for PHYSICAL INACTIVITY/SEDENTARY BEHAVIOUR (IN)

Summary of data from studies is reported in Table 10. Two studies use self-reported PA data.

2.4.1IN Healthy Ageing / Quality of Life / Well-being

No study found.

2.4.2IN Disability / Frailty

One study examined associations between mid-life inactivity disability at age 75 [-][1]. No significant association was found between inactivity in leisure time and disability at age 75.

[1]Christenson 2006

- **Applicability**: Partially applicable. The study was conducted in Denmark.

2.4.3IN Dementia

No study found.

2.4.4IN Overall mortality

One study from Finland followed up for 16 years [+][1] found no significant relationship between leisure time inactivity in mid-life and all cause mortality.

[1]Haapanen-Niemi 2000

- **Applicability**: Partially applicable. The study was conducted in Finland.

2.4.5IN Cardiovascular (CVD) Outcomes

One study from Finland followed up for 16 years [+][1] found a significant positive relationship between a single item measure of leisure time inactivity in mid-life and CVD mortality. However using an index measure of LTPA no significant association was found.

[1]Haapanen-Niemi 2000

- **Applicability**: Partially applicable. The study was conducted in Finland.

2.4.6IN Diabetes / Metabolic Syndrome

No study found.

2.4.7IN Cancer

No study found.

2.4.8IN Mental health

No study found.

3.5 Evidence statements for DIET (DI)

2.5.1DI Overall diet / dietary patterns

Summary of data from studies is reported in Table 11. All studies reported below are observational longitudinal cohort studies that report mid-life diet or components of diet and dementia, disability, frailty outcomes in later life.

2.5.1.1DI Overall diet – Healthy Ageing outcomes

'Healthy' diet

There is consistent evidence from three longitudinal cohort studies [+][1], [+][2], [+][3] that a healthy diet in mid-life is related to healthy and successful ageing. In these studies healthy ageing is defined as no major chronic diseases or major impairments in cognitive or physical function or mental health.

Two studies reported a significant positive and beneficial association between mid-life 'healthy' dietary patterns and successful ageing outcomes. In the other study, a Western dietary pattern characterised by high intakes of fried and sweet food, processed food and red meat, refined grains, and high-fat dairy products was associated with less successful ageing.

Mediterranean diet

There is evidence from one study that a Mediterranean type diet is associated with more successful ageing [+][3].

[1]Akbaraly 2013; [2]Britton 2008; [3]Semieri 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between healthy diet in mid-life and healthy ageing was conducted in the UK and one in the US. The UK study and US study were of moderate quality. The third study, also conducted in the UK, reporting inverse relationship with Western dietary pattern was of moderate quality also.

2.5.1.2DI Overall diet – Disability / Frailty outcomes

There is some limited evidence from one study conducted in France that 'healthy' diet or dietary patterns in mid-life is related to more positive outcomes in later life, in relation to cognitive functioning. The study reported better cognitive outcomes for those consuming a 'healthy pattern' diet [-][1], characterised as consumption of fruit (fresh and dried), whole grains, fresh dairy products, vegetables, breakfast cereal, tea, vegetable fat, nuts, and fish

and negatively correlated with meat and poultry, refined grains, animal fat, and processed meat.

[1]Kesse-Guyot 2012

- **Applicability**: Partially applicable. The study that reported beneficial associations between a healthy diet or components of diet in mid-life and cognitive function was conducted in France.

2.5.1.3DI Overall diet – Dementia outcomes

No study found.

2.5.1.4DI Overall diet – Total mortality

No study found.

2.5.1.5DI Overall diet – Cardiovascular (CVD) Outcomes

Dietary pattern – two studies conducted in Spain and Italy reported beneficial effects of a Mediterranean diet pattern with lower risk of CHD events and mortality [+][1], [-][2].

[1]Guallar-Castillon 2012; [2]Menotti 2012

- **Applicability**: Partially applicable. Both studies were conducted in developed European (Mediterranean) countries.

2.5.1.6DI Overall diet – Diabetes / Metabolic Syndrome

One study conducted in China reported that a dietary pattern low in staples and high in milk was associated with less risk of diabetes [++][1].

[1]Villegas 2010

- **Applicability**: Partially applicable. The Chinese diet studies may be different from a UK diet.

2.5.1.7DI Overall diet – Cancer

One study conducted in Japan [+][1] found no clear associations between the four major dietary patterns studied (fruit and vegetable pattern, western breakfast, meat pattern, rice/snacks pattern) and cancer.

[1]Masaki 2003

- **Applicability**: Partially applicable. Study conducted in Japan, Japanese diet different from UK diet but a Western breakfast pattern was studied.

2.5.1.8DI Overall diet – Other chronic diseases

No study found.

2.5.1.9DI Overall diet – Mental health

Mediterranean diet

One study from Australia [+][1] reported less psychological distress in those with the highest compared to lowest adherence to the Mediterranean diet.

Traditional Australian diet

The same Australian study [+][1] also reported those with the highest compared to lowest adherence to a traditional Australian diet (positive loadings for breakfast cereal, wholemeal bread, cheddar cheese, vegetables – carrot, pumpkin, beetroot, green beans, peas, and cauliflower; some fruit, tea, margarine, pudding, cake, cream, jam, vegemite, and roast lamb), a generally healthy diet apart from some cake and puddings.

[1]Hodge 2013

- **Applicability**: Partially applicable. The study was from Australia.

2.5.2DI – FRUIT AND VEGETABLES

2.5.2.1DI Fruit and vegetables – Healthy ageing outcomes

No study found.

2.5.2.2DI Fruit and vegetables – Disability / Frailty outcomes

One study from the UK reported that more than two portions of fruit and vegetables a day was associated with better cognitive performance [+][1].

However, two studies reported no significant association between higher levels of fruit and vegetables and cognitive function [+][2], [+][3]. One study was conducted in the UK and one was from the Netherlands.

[1]Sabia 2009; [2]Elwood 2013; [3]Nooyens 2009

- **Applicability**: Partially applicable. Two studies were conducted in the UK, one reported a positive relationship and in one the association was not significant. The other study was conducted in the Netherlands.

2.5.2.3DI Fruit and vegetables – Dementia outcomes

Two studies reported relationships between fruit and vegetable intake in mid-life and dementia [+][1], [+][2]. One study conducted in Sweden found that medium or great amounts of fruit and vegetables compared to lower amounts were associated with less risk of dementia. One study from the UK found no significant association between three or greater portions of fruit and veg per day compared to lower intakes and dementia.

[1]Hughes 2010; [2]Elwood 2013

- **Applicability**: Partially applicable. One study from Sweden reported a positive relationship and in one study from the UK the association was not significant.

2.5.2.4DI Fruit and vegetables – Total mortality outcome

Three studies reported associations between fruit and/or vegetable intake and total mortality. One study from Sweden reported significantly lower risk of death in people consuming higher levels of fruit and vegetables at mid-life [+][1]. One study from Italy reported significantly lower overall mortality for each increase of 20g/day in vegetable intake [+][2]. In one UK study associations between >3 portions fruit and vegetables/day were not significant [+][3].

[1]Strandhagen 2000; [2]Seccareccia 2003; [3]Elwood 2013

- **Applicability**: Partially applicable. One study from Sweden reported a positive relationship and in one study from the UK and one from Italy the association was not significant.

2.5.2.5DI Fruit and vegetables – CVD outcomes

Two studies reported relationships between fruit and vegetables and CVD outcomes and/or mortality. In one study fruit and vegetable intake was associated with lower CVD mortality [+][1] and in the other study [+][2] associations between fruit and veg intake (>3/day) and CVD outcomes were not significant.

[1]Strandhagen 2000: [2]Elwood 2013

- **Applicability**: Partially applicable. One study from Sweden reported a positive relationship and in one study from the UK the association was not significant.

2.5.2.6DI Fruit and vegetables – Diabetes/metabolic syndrome outcomes

One study conducted in the UK reported association between fruit and vegetables and diabetes. No statistically significant association between fruit and veg intake (>3/day) and diabetes [+][1] was found.

[1]Elwood 2013

- **Applicability**: Directly applicable. The study was conducted in the UK.

2.5.2.7DI Fruit and vegetables – Cancer outcomes

One study from the US reported lower risk of colorectal cancer with consumption of fruit [++][1].

Two studies, from the UK and Sweden reported no significant associations between fruit and vegetables and cancer incidence or mortality [+][2], [++][3].

[1]Ruder 2011; [2]Elwood 2013; [3]Strandhagen 2000

- **Applicability**: Partially applicable. The one study that found a significant lower risk of cancer with fruit intake at mid-life was conducted in the US. The other studies were from the UK and Sweden.

2.5.2.8DI Fruit and vegetables – Other chronic disease outcomes

Fruit intake was significantly associated with lower risk of chronic obstructive pulmonary disease mortality in one study conducted across Finland, Italy and the Netherlands [+][1].

[1]Walda 2002

- **Applicability**: Partially applicable. The study was conducted in developed, western European countries.

2.5.2.9DI Fruit and vegetables – Mental health outcomes

No study found.

2.5.3DI – DIETARY FAT (Total, saturated, polyunsaturated (PUFA), monounsaturated (MUFA)

2.5.3.1DI Fat – Healthy ageing outcomes

No study found.

2.5.3.2DI Fat – Disability / Frailty outcomes

One Finnish study reported that higher levels of total or saturated fat were associated with greater cognitive impairment in later life [+][1].

[1]Eskelinen 2008

- **Applicability**: Partially applicable. One study from Finland.

2.5.3.3DI Fat – Dementia outcomes

One study in Finland reported greater risk of dementia in those consuming moderate compared to low amounts of saturated fat but lower rates of dementia in those consuming moderate compared to low amounts of polyunsaturated fat (PUFA) [++][1].

[1]Laitinen 2006

- **Applicability**: Partially applicable. One study from Finland.

2.5.3.4DI Fat – Total mortality outcomes

No study found.

2.5.3.5DI Fat – CVD outcomes

One study from Sweden reported no significant associations between either total, saturated, monounsaturated or polyunsaturated fat and fatal or non-fatal cardiovascular events [++][1].

[1]Leosdottir

- **Applicability**: Partially applicable. One study from Sweden

2.5.3.6DI Fat – Diabetes/metabolic syndrome outcomes

One study conducted in Sweden reported that higher saturated fat intake at mid-life was associated with lower insulin sensitivity [+][1].

[1]Riserus 2007

- **Applicability**: Partially applicable. One study from Finland.

2.5.3.7DI Fat – Cancer outcomes

No study found.

2.5.3.8DI Fat – Other chronic disease outcomes

No study found.

2.5.3.9DI Fat - Mental health outcomes

No study found.

2.5.4DI – FISH

2.5.4.1DI Fish – Healthy ageing outcomes

No study found.

2.5.4.2DI Fish – Disability / Frailty outcomes

No study found.

2.5.4.3DI Fish – Dementia outcomes

No study found.

2.5.4.4DI Fish – Total mortality outcomes

One Danish study that measured fish intake using a self-reported food frequency questionnaire reported some limited evidence for increased mortality with greater fish consumption [+][1] in a population sample and also in those at high risk of CHD.

[1]Osler 2003

- **Applicability**: Partially applicable. One study from Denmark.

2.5.4.5DI Fish – CVD outcomes

One study from the US found lower risk of CHD events and mortality in women when meat was replaced with fish so that >/= 3 servings wk were consumed [++][1]. Another study from Sweden reported no significant association between fatty fish consumption and heart failure but lower risk of heart failure in those consuming marine omega 3 fatty acids once a week [+][2]. Higher intakes of marine omega 3 fatty acids were not significantly associated with heart failure.

[1]Lajous 2013; [2]Levitan 2009

- **Applicability**: Partially applicable. One study from Sweden, one from the US.

2.5.4.6DI Fish – Diabetes/metabolic syndrome outcomes

One study conducted in China [++][1] reported lower risk of diabetes in women eating moderate and high amounts of fish and shellfish with a significant trend with greater fish and shellfish intake. In men associations between fish intake and diabetes were not significant but lower risk of diabetes was reported for shellfish with a significant trend with greater shellfish intake.

[1]Villegas 2011

- **Applicability**: Partially applicable. One study from China.

2.5.4.7DI Fish – Cancer outcomes

No study found.

2.5.4.8DI Fish – Other chronic disease outcomes

Fish intake was associated with less risk of chronic obstructive pulmonary disease (COPD) in one study conducted across Finland, Italy and the Netherlands [+][1].

[1]Walda 2002

- **Applicability**: Partially applicable. One European study.

2.5.4.9DI Fish – Mental health outcomes

No study found.

2.5.5DI – MEAT

2.5.5.1DI Meat – Healthy ageing outcomes

No study found.

2.5.5.2DI Meat – Disability / Frailty outcomes

One prospective cohort study conducted in Japan reported on longitudinal associations between mid-life diet and activities of daily living [+][1]. Men who ate meat at least once every two days or more were less likely to have impairment in activities of daily living (ADL) [+][1] .

[1]Nakamura 2009

- **Applicability**: Partially applicable. One Japanese study.

2.5.5.3DI Meat – Dementia outcomes

No study found.

2.5.5.4DI Meat – Total mortality outcomes

No study found.

2.5.5.5DI Meat – CVD outcomes

One study conducted in China [+][1] reported lower risk of cerebrovascular disease in those consuming meat 1-2 times a month compared to those consuming no meat or those who ate meat more than once a week.

[1]Qiu 2003

- **Applicability**: Partially applicable. One study from China.

2.5.5.6DI Meat – Diabetes/metabolic syndrome outcomes

One study conducted in the US found increased risk of diabetes in those consuming higher versus lower levels of red and processed meat [+][1] with a significant trend from lower to higher intake.

[1]Song 2004

- **Applicability**: Partially applicable. One study from the US.

2.5.5.7DI Meat – Cancer outcomes

One study from the US [++][1] reported higher risk of colorectal cancer with consumption of red and processed meat.

[1]Ruder 2011

- **Applicability**: Partially applicable. One study from the US.

2.5.5.8DI Meat – Other chronic disease outcomes

No study found.

2.5.5.9DI Meat – Mental health outcomes

No study found.

2.5.6DI – COFFEE

2.5.6.1 Coffee – Healthy ageing outcomes

No study found.

2.5.6.2DI Coffee – Disability / Frailty outcomes

One study reported no association of later life cognitive function with mid-life coffee intake [++][1].

[1]Laitala 2007

- **Applicability**: Partially applicable. One study from Finland.

2.5.6.3DI Coffee – Dementia outcomes

Two studies examined relationships between coffee consumption in mid-life and dementia [+][1], [++][2]. One study from Finland [+][1] reported that moderate coffee consumption (3-5 cups/day) was associated with lower risk of dementia, but not tea drinking. A different study conducted in Finland in twins found no significant association between coffee consumption and dementia [++][2].

[1]Eskelinen 2009; [2]Laitala 2007

- **Applicability**: Partially applicable. Two studies from Finland.

2.5.6.4DI Coffee – Total mortality outcomes

No study found.

2.5.6.5DI Coffee – CVD outcomes

One study from Finland reported a higher risk of CHD events and mortality with heavy coffee intake (>814 ml/d) compared to moderate coffee drinking (376-813 ml/d) [+][1]. Associations were not significant for light or no coffee drinking (0-375 ml/d) compared to moderate intake.

[1]Happonen 2004

- **Applicability:** Partially applicable. One study from Finland.

2.5.6.6DI Coffee – Diabetes/metabolic syndrome outcomes

Two studies reported lower risk of diabetes with coffee intake. One study from Finland reported significantly lower risk of diabetes with coffee intake in men and women [+][1]. For both men and women combined, and for women only, there was a significant trend towards lower risk for diabetes with increasing coffee consumption. In men the trend was not significant but there was a significant relationship between higher levels of coffee intake (>/= 10 cups/d) and less risk of diabetes. The other study from Japan [+][2] reported a significant inverse relationship for women consuming 3 or more cups of coffee a day with a significant trend. In men only 1-2 cups/day was significantly associated with lower risk of diabetes but there was also a significant inverse trend between coffee consumption and diabetes.

[1]Tuomilehto 2004; [2]Kato 2009

- **Applicability**: Partially applicable. One study from Finland, one from Japan.

2.5.6.7DI Coffee – Cancer outcomes

No study found.

2.5.6.8DI Coffee – Other chronic disease outcomes

Lower risk of Parkinson's disease with coffee consumption was consistently reported in two studies from Finland [+][1] and the US respectively [+][2]. In men and women combined, 1-4 cups/day or 5 cups/day compared to none were both significantly related to less risk of Parkinson's disease [+][1] .Tea drinking was also associated with less risk of Parkinson's disease at the level of 5 cups/d [+][1]. In the US study [+][2], there were lower rates of Parkinson's disease in coffee drinkers compared to non-coffee consumers. An inverse association between caffeine intake and Parkinson's disease was also reported.

[1]Hu 2007; [2]Ross 2000

- **Applicability**: Partially applicable. One study from Finland, one from US.

2.5.6.9DI Coffee – Mental health outcomes

One study from Australia [+][1] found no significant association between coffee drinking and anxiety, depression or psychological symptoms, but reported lower scores on the mental health scale on the SF-36 general health questionnaire.

In one study from Finland[+][2], light (<315 ml/d) or heavy (>813 ml/d) coffee consumption was associated with lower risk of severe depression. There was no association with tea or caffeine intake, although the study reported fewer tea drinkers and less tea drinking.

[1]Xu 2010; [2]Ruusanen 2010

- **Applicability**: Partially applicable. One study from Finland, one from Australia.

There were fewer relevant studies from this point onwards, and only the outcomes and available data are reported. For all other outcomes, no studies were found.

2.5.7DI – MILK

2.5.7.1DI Milk – Cancer outcomes

One study from the US reported lower incidence of colorectal and rectal cancer in those in the highest versus the lowest quintile of consumption of milk [++][1].

[1]Ruder 2011

- **Applicability**: Partially applicable. One study from the US.

2.5.8DI – SALT

2.5.8.1DI Salt – Cancer outcomes

One study from Japan [+][1] found a significant association between salt intake and higher risk of gastric cancer in highest versus lowest in male consumers with a significant trend with higher intake but in women the association was not significant.

[1]Tsugane 2004

- **Applicability**: Partially applicable. One study from Japan.

2.5.9DI – GLYCAEMIC INDEX/GLYCAEMIC LOAD (GI/GL)

2.5.9.1DI GI/GL – CVD outcomes

One study conducted in the Netherlands reported higher risk of CVD for those consuming diets with the highest compared to the lowest dietary glycaemic index (GI) and glycaemic load (GL) [++][1]. In another from Finland, study associations between GI/ GL and CVD events were not significant [+][2].

[1]Beulens 2007; [2]Levitan 2009

- **Applicability**: Partially applicable. One study from Finland, one from the Netherlands.

2.5.10DI – PROTEIN

2.5.10.1DI Protein – CVD outcomes

One study found no sig associations between mid-life protein intake and ischemic heart disease [++][1].

[1]Preis 2010

- **Applicability**: Partially applicable. One study from the US.

2.5.10.2DI Protein – Cancer outcomes

One study found no sig associations between protein and colorectal cancer [++][1].

[1]Ruder 2011

- **Applicability**: Partially applicable. One study from the US.

2.5.11DI – CHOCOLATE

2.5.11.1DI Chocolate – CVD outcomes

One study conducted in Sweden [+][1] reported lower risk of heart failure when chocolate was consumed 1-3 times month compared to no chocolate consumption. Associations at higher chocolate intakes were not significant although there was a significant trend with higher intakes of chocolate towards lower risk of heart failure [++][1].

[1]Mostofsky 2010

- **Applicability**: Partially applicable. One study from Sweden.

2.5.12DI – DIETARY FIBRE

2.5.12.1DI Fibre – Cancer outcomes

One study from the US reported no association between mid-life fibre intake and colorectal cancer [++][1].

[1]Ruder 2011

- **Applicability**: Partially applicable. One study from the US.

2.5.13DI – MICRONUTRIENTS / ANTIOXIDANTS / FLAVONOIDS

2.5.13.1DI Micronutrients – Dementia outcomes

One US study reported a non-significant relationship between mid-life dietary antioxidant intake and dementia [+][2].

2.5.13.2DI Micronutrients – Cancer outcomes

One study from the US [++][1] reported lower risk of colorectal cancer with consumption of dietary calcium, vitamin A and vitamin C.

2.5.13.3DI Micronutrients – Mental health outcomes

One study from Finland [+][3] found no association between dietary zinc intake and depression.

2.5.13.4DI Flavonoids – CVD outcomes

One study from Finland [+][4] found no association between total flavonoid intake and ischemic stroke but did find lower ischemic stroke risk in highest flavonol vs lowest flavonol intake.

2.5.13.5DI Flavonoids – Cancer outcomes

One US study found no significant relationship between flavonoids and total cancer or site-specific cancers [+][5].

2.5.13.6DI Flavonoids – Dementia outcomes

One US study found no significant relationship between flavonoids and dementia [+][2].

[1]Ruder 2011; [2]Laurin 2004; [3]Lehto 2013; [4]Mursu 2008; [5]Wang 2009

- **Applicability**: Partially applicable. All studies from the US or Western European countries.

Evidence statements for diet (and components of diet) - associations between mid-life diet and PRECONDITIONS for dementia, disability, frailty

2.5.14DI Preconditions

2.5.14.1DI Blood pressure outcomes

Two studies reported relationships between fruit and vegetable intake and blood pressure. One study conducted in the US reported less risk of hypertension with mid-life fruit intake [+][1]. In another study conducted in the US associations between fruit and vegetable intake and blood pressure were not significant [+][2].

One study from the US reported lower incidence of hypertension with increased levels of dairy intake [+][3] and another US study reported no relationship between dietary magnesium intake and hypertension [+][4].

[1]Miura 2004; [2]Wang 2012; [3]Wang 2008; [4]Song 2006

- **Applicability**: Partially applicable. All four studies from the US.

2.5.14.2DI Obesity outcomes

Two different papers from the same US study [+][1], [+][2] reported that increase in fruit and vegetable intake or wholegrains and dietary fibre between mid-life and later life was significantly associated with less risk of obesity or major weight gain (>/= 25kg).

[1]He 2004; [2]Liu 2003

Applicability: Partially applicable. Both papers were from the same US study (Nurses Health Study)

3.6 Evidence statement for SMOKING (SM)

Summary of data from smoking studies is reported in Table 12.

2.6.1SM Healthy Ageing / Quality of Life / Well-being

There is consistent evidence from three studies demonstrating an association between smoking and healthy ageing, quality of life or well-being outcomes. A UK study [++][1] using data from Whitehall II showed that not smoking was related to a favorable

older life (i.e. entering older age without disease and with good functioning) after adjustment for age and socioeconomic position. A study [+][2] in a socioeconomically homogeneous cohort of older Finnish men found that never-smokers lived longer than heavy smokers, and their extra years were of better quality. Health-related quality of life deteriorated with an increase in daily cigarettes smoked in a dose-dependent manner. The third study [++] looking at Japanese American men suggests that ever smoking is associated with overall survival and a borderline association with exceptional survival (i.e. free of a set of major diseases and impairments).

[1]Britton 2008 [+]; [2]Strandberg 2008 [+]; [3]Willcox 2006 [++]

- **Applicability:** Partially applicable; the UK study is highly applicable but the other two are conducted in men only, including a cohort of Japanese American.

2.6.2SM Disability / Frailty

2.6.2.1SM There is consistent evidence from two studies demonstrating the dose-response relationship between smoking and impaired mobility. A Swedish study [+][1] suggests that a history of smoking, especially heavy smoking, with or without quitting, is associated with an earlier onset, and a faster elevation, of mobility problems during the transition from middle age to old age. All smoking groups reported more pain symptoms than the non-smokers, at baseline and over time, but most of these differences did not reach statistical significance. Persistent heavy smokers reported elevated levels of psychological distress at baseline and over time. A USA study [-][2] showed a consistent adverse dose-response relationships between smoking and ill health defined in a multidimensional fashion (i.e. disability, impaired mobility, health care utilisation, self-reported health).

[1]Agahi 2013 [-]; [2]Ostbye 2002 [-]

- **Applicability:** Partially applicable; populations from Sweden and USA, but most importantly, quality of studies is [-].

2.6.2.2SM There is inconsistent evidence from three studies demonstrating the association between smoking and low energy fractures. A Swedish study [+][1] looking at active commuting showed no association between smoking and wrist fractures. A second Swedish [+][2] study looking at a wider range of low energy fractures showed that among women, smokers had a higher risk for vertebral fractures than non-smokers. Among men, smokers had a greater risk for low energy fractures, vertebral fractures, proximal humerus fractures, and hip fractures than non-smokers. A large UK study [+][3] showed no association between smoking and osteoporotic fractures. Although not focused on fracture, another

study [+][4], conducted in Australia, found a positive association between smoking and risk of osteoarthritis.

[1]Englund 2013; [2]Homberg 2006; [3]Moayyeri 2009; [4]Szoeke 2006

- **Applicability:** Directly applicable; but would interpret findings from UK study [+][3] with caution as osteoporotic fractures were documented using death certificates, which are not reliable as a sole source of information to document fractures (except maybe hip fractures).

2.6.3SM Dementia

There is strong evidence consistent evidence demonstrating the association between smoking in mid-life and dementia or cognitive decline in later life. The association between smoking and specific types of dementia is less clear.

Eleven cohort studies reported on the association between smoking and dementia or cognitive outcomes. In most studies, smoking was considered a cardiovascular risk factor for dementia/cognitive decline. Two UK studies [+][1,2] based on Whitehall II data showed an association between smoking and cognition. The longest follow-up (17-year) [+][1] showed that smoking in middle age is associated with memory deficit and decline in reasoning abilities; long-term ex-smokers (compared to current smokers and recent ex-smokers) are less likely to have cognitive deficits in memory, vocabulary, and verbal fluency. In a 5-year follow-up in a Dutch study [+][3], decline among smokers was greater for memory function, cognitive flexibility, and cognitive function than among never smokers. Among ever smokers, the declines in all cognitive domains were larger with increasing number of pack-years smoked.

In two USA study [+][4,5] smoking was strongly associated with subsequent risk of hospitalisation with dementia (proxy for incident dementia) in caucasians and African-Americans [+][4], and with being diagnosed with dementia in a diverse population [+][5]. In another large USA multi-ethnic cohort study with long follow-up [+][6], heavy smoking in mid-life was associated with a greater than 100% risk of dementia, AD, and VaD. A Korean study [+][7] showed an increased risk of unspecified dementia or any type of dementia in men and women who smoke compared to the never-smoker; the increased risk of Alzheimer's disease and vascular dementia was observed in women who smoke but not in men. However, a study conducted in Hawaiian men [+][8] showed an association between smoking in mid-life and a diagnostic of vascular dementia later on. In another USA study based on the Framingham offspring cohort [+][9], mid-life smoking was associated with an increased rate of progression of vascular brain injury, global and hippocampal atrophy.

Only Knopman [+][10] found that smoking at baseline was not associated with change in cognitive decline (six years follow-up). Also, a study [+][11] looking at dementia death (based on ICD codes failed to demonstrate an association with smoking.

[1]Sabia 2008; [2]Sabia 2009; [3]Nooyens 2008; [4]Alonso 2009; [5]Whitmer 2005; [6]Rusanen 2011; [7]Kimm 2011; [8]Tyas 2003; [9]Debette 2011; [10]Knopman 2001; [11] Strand 2013

- **Applicability:** Directly applicable; mostly European and US studies, good quality and mostly reliable outcome measurements.

2.6.4SM Overall mortality

There is strong evidence from seven studies demonstrating a dose-response relationship between smoking in mid-life and total mortality. Compared to never smokers, smokers are at increased risk of mortality. Compared to those who maintain their smoking habit, those who reduce or quit smoking have a decreased risk of mortality.

A UK study [+][1] showed that current smokers showed the highest RR of total mortality with a dose-response relationship with increasing number of cigarettes smoked. Compared to never smokers, primary pipe/cigar smokers showed a marginally significant increased risk of total mortality, but secondary pipe/cigar smokers showed a significantly increased risk of total mortality. Ex-cigarette smokers showed similar risk to never smokers after full adjustment.

Three related Finnish studies [+][2,3,4] and one Japanese studies [+][7] showed the corroborating results. Qiao et al. [+][3] showed that men smoking persistently were most at risk, while those who persisted in quitting had no increased risk of death compared with non-smokers. Pelkonen [+][4] concluded that smokers across the entire range of pulmonary function may increase their expectation of lifespan by giving up smoking. Finally, Lim [+][5] showed that compared to current smokers, never smokers, long-term quitters and new quitters had a decreased risk of all-cause mortality; the same association was observed for never smokers and long-term quitters for other non-lung cancer mortality. Gerber et al (Israeal) [+][6] found that compared to those who maintained their smoking habit, individuals reduced or quit smoking had a decrease risk of all cause mortality.

[1]Shaper 2003; [2]Strandberg 2008; [3]Qiao 2000; [4]Pelkonen 2000; [5]Lim 2013; [6]Gerber 2012; [7]Hara 2002

- **Applicability:** Directly applicable; mostly European and US studies, good quality and reliable outcome measurements.

2.6.5SM Cardiovascular (CVD) Outcomes

Smoking or having smoked is consistently associated with increased risk of cardiovascular mortality and cardiovascular diseases.

Cardiovascular Mortality – Six studies provide evidence of a strong association between smoking and cardiovascular mortality; only one didn't. Overall, current smokers are more likely to die from cardiovascular events compared to non-smokers. Lim [+][6] showed that compared to current smokers, never smokers and long-term quitters had a decreased risk of CHD mortality and COPD mortality; the same association was observed for never smokers for stroke mortality. The relationship with former smoking status varies across studies (probably owing to great heterogeneity across studies re follow-up, outcome measurements, etc.). Only Qui [+][7], a study from China did not find an association between smoking and cardiovascular mortality.

[1]Blanco-Cedres 2002; [2]Boudik 2006; [3]Baba 2006; [4]Hara 2002; [5]Gerber 2012; [6]Lim 2013; [7]Qui 2003

- **Applicability**: Partially applicable; no studies from the UK or Europe.

Other cardiac outcomes – Twelve studies provide evidence of a strong association between smoking and cardiovascular events and outcomes. In a UK study [++][1], the highest risks for both CHD events and stroke were seen in heavy current smokers. Ex-cigarette smokers showed similar risk of major CHD and stroke events to never smokers. Pipe/cigar smokers (primary and secondary combined) also showed significantly higher risk compared with never smokers and non-smokers, and similar to light cigarette smokers. The other UK study [+][2] showed that smoking increases the risk of coronary heart disease in men of all *APOE* genotype genotypes but particularly in men carrying the e*4* allele. Apart from Satoh [+][3] who showed not association between smoking (vs non-smoker) and CHD, all other studies have shown an association between smoking and stroke [++][4], [+][3,5] and MI [+][6].

[1]Shaper 2003; [2]Humphries 2001; [3]Satoh 2006; [4]Mannami 2004; [5]Harmsen 2006; [6]Nakayama 2000; [7]Janzon 2004; [8]Dubas 2007; [9]Halperin 2008; [10]Raikkonen 2001; [11]Khalili 2002

2.6.6SM Diabetes / Metabolic Syndrome

Cigarette smoking is an independent and modifiable risk factor for type II diabetes; the evidence for insulin sensitivity and metabolic syndrome is not sufficient to conclude.

Three studies, one conducted in the UK men [+][1], one in Finland [+][2] and one in Japan [+][3], demonstrated cigarette smoking is an independent and modifiable risk factor for type 2 diabetes; and one conducted in Norway didn't. The UK study [+][1] examined the effects of cigarette smoking, giving up smoking, and primary or secondary pipe or cigar smoking on the risk of type 2 diabetes. The benefit of giving up smoking was only apparent after 5 years of smoking cessation, and risk reverted to that of never-smokers only after 20 years. The risk of diabetes in those who switched from smoking cigarettes to pipe or cigars remained equal to the risk in continuing cigarette smokers. Smoking cessation is associated with weight gain and a subsequent increase in risk of diabetes, but in the long term, the benefits of giving up smoking outweigh the adverse effects of early weight gain. The Finish study [+][2] also showed that smoking of a risk factor for type 2 diabetes independently of BMI and physical activity. And another study [+][4] demonstrated that being a smoker was associated with weight loss. The longest follow-up was in a Norwegian study [+][5], which found that smoking was associated with the metabolic syndrome but not diabetes – (potential confounding and methodological may explain the later findings).

Finally, a Swedish study [+][6] looking at long-term predictors of insulin sensitivity in men found no significant association with smoking.

[1]Wannamethee 2001; [2]Patja 2005; [3]Sairenchi 2004; [4]Fogelholm 2000; [5]Holme 2007; [6]Riserus 2007.

- **Applicability**: Directly applicable. Mostly UK, European studies with long-term follow-up and good quality.

2.6.7SM Cancer

Evidence from six studies showed a consistent association between smoking and cancer with a dose-response effect. The dose-response and exposure association seems to depend on the type of cancer considered.

In a UK study [+][1] current cigarette smokers showed the highest risk of total cancer with a strong dose-response effect. Ex-cigarette smokers showed a significant increase in smoking-related cancers, particularly affecting 'other' smoking-related cancers rather than lung cancer. Compared with never smokers, pipe/cigar smokers (primary and secondary

combined) also showed a significantly higher incidence of smoking-related cancers largely due to lung cancer. Overall, the effects in pipe/cigar smokers were intermediate between never-smokers and light cigarette smokers, although risks for lung cancer were similar to light cigarette smokers. In a second UK study [+][2] looking specifically at pancreatic cancer in women, pancreatic cancer incidence was greater in current than never smokers, the risk increasing with the number of cigarettes smoked. Current smokers were at two-fold or higher risk than never smokers across all categories of height, BMI, alcohol and physical activity.

Three Japanese studies also demonstrated significant associations [+][3], [+][4]. One [+][3] showed that smoking was significantly associated with colorectal cancer in men and not significantly in women. Furthermore, long-term smoking significantly elevated the risk compared with never-smoking but a non-significant linear trend was obtained according to smoking intensity except for rectal cancer. The relative risk in smokers who also drink was also increased compared to non-drinkers – non-smokers men. Looking at lung cancer by histological types, Sobue et al [+][4] findings indicated that current cigarette smoking is associated with an elevated lung cancer risk approximately 10- to 20-fold higher for squamous cell and small cell carcinoma and 2- to 3-fold higher for adenocarcinoma in both men and women. When all histologic types were combined, the relative risk was approximately 4 in both men and women. They also showed that the 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. Using the same cohort, another study [+][5] confirmed the strong association between smoking and cancer, and cancer related mortality in the Japanese population.

Lim [+][6] showed that compared to current smokers, never smokers, long-term quitters and new quitters had a decreased risk of lung cancer, mortality; the same association was observed for never smokers and long-term quitters for other non-lung cancer mortality.

[1]Shaper 2003; [2]Steven 2009; [3]Otani 2003; [4]Sobue 2002; [5]Inoue 2004; [6]Lim 2013

- **Applicability**: Directly applicable, two studies conducted in the UK; overall good quality studies. Note that although Japanese studies are relevant effect sizes would differ in UK population.

2.6.8SM Mental health

No study found.

2.6.9SM Others

One Japanese study [+][1] found that smoking increases the risk of chronic kidney condition.

[1]Noborisaka 2013 [+]

- **Applicability**: Limited; Japanese study and outcome measurement not optimal.

3.7 Evidence statements for ALCOHOL (AL)

Summary of data from Alcohol studies is presented in Table 14. We included 24 prospective cohort studies on alcohol intake between 40 and 64 years of age (midlife). These were conducted in the UK (n=7); USA (n=5); Sweden (n=1); Finland (n=2); France (n=1); the Netherlands (n=1); China (n=1); Japan (n=4); and Australia (n=1). A multi-site study (n=1) was conducted in Italy, Finland, and the Netherlands. Follow-up ranged from 4 years (Qiu 2003, Flood 2008) to 26 years (Virta 2010). There was heterogeneity in the categorisation of self-reported alcohol intake levels. Five articles (n=5) assessed the number of drinks consumed per week, one (n=1) differentiated teetotallers from alcohol users, five (n=5) documented the number of drinks per day, one (n=1) assessed the number of drinks per month, while the rest of the studies (n=12) used a combination of measurements examining alcohol intake over various time spans.

2.7.1AL Healthy Ageing / Quality of Life / Well-being

No study found.

2.7.2AL Disability / Frailty

Two studies reported higher odds for ill health and osteoporotic fractures among alcohol drinkers compared to non-drinkers, while one study found no link between ethanol use and wrist fractures.

A Swedish study [+][1] did not find a statistically significant association between alcohol intake and wrist fractures. Conversely, the risk for any incident osteoporotic fracture over 11 years was reported to be higher among male alcohol users compared to male teetotalers in Norfolk, UK [+][2]. A large study [-][3] of middle-aged American males and females followed from 1992 to 1998 showed that, compared to those who never drink, respondents with a past drinking problem had the highest odds for ill health in terms of ADL dependence, difficulty

climbing stairs, difficulty walking, poor health, and hospitalization (results were statistically significant).

[1]Englund 2013; [2]Moayyeri 2009; [3]Ostbye 2002

- **Applicability**: The studies are applicable, particularly the UK and Swedish studies. Generalizability may be limited as alcohol intake was measured using different categories across studies.

2.7.3AL Dementia

There is consistent evidence from four studies demonstrating an association between alcohol abstinence and/or heavy drinking and cognitive impairment. One study reported no association with impairment or dementia.

Five European longitudinal studies analysed the influence of mid-life alcohol intake and cognitive function in old age. One Finnish study [++][1] with a mean follow-up of 23 years showed an increased risk of cognitive impairment for both abstainers and heavy drinkers in comparison with light drinkers. Binge drinking and pass-outs were positively associated with cognitive impairment, as was abstaining from drinking among those without the apolipoprotein e4 allele. Similarly, alcohol abstinence among middle-aged participants in the Whitehall II study [+][2] had a higher risk of poor executive function and poor memory in comparison with those consuming moderate amounts (1-14 units/week). Conversely, a study [+][3] on men living in Caerphilly, UK did not find an association between alcohol intake and impairment or dementia. Among French people with a low occupational position, an inverse relationship was found between high alcohol intake (>21 drinks/week) and cognitive performance [+][4]. In a population-based sample [+][5] of Finnish participants, the risk for mild cognitive impairment was higher among those reporting abstinence or frequent alcohol consumption compared to people reporting infrequent drinking. Among carriers of the APOE4 allele, the risk of dementia was greater for frequent drinkers compared to non-drinkers.

[1]Virta 2010; [2]Sabia 2009; [3]Elwood 2013; [4]Sabia 2011; [5]Anttila 2004

- **Applicability:** Directly applicable. Generalizability may be limited as alcohol intake was measured using different categories across studies.

2.7.4AL Overall mortality

See below.

2.7.5AL Cardiovascular outcomes

The evidence regarding alcohol use and cardiovascular outcomes is inconsistent.

Three studies conducted in England, Wales, Scotland [+][1], [++][2] and Japan [+][3] showed a significant association between alcohol intake and cardiovascular outcomes. Among middle-aged men recruited from British general practices [+][1], regular drinkers had a significantly lower risk of major coronary heart disease events, coronary heart disease deaths, and cardiovascular disease deaths in comparison with occasional drinkers after full adjustment for lifestyle characteristics and pre-existing disease. In contrast, heavy drinkers (>6 drinks/day) had a higher risk of both major coronary heart disease and stroke compared to occasional drinkers (one-two times/month or on special occasions) in a cohort of middle-aged British men followed for 20 years [++][2]. The previous two studies were part of the British Regional Heart Study. A large population-based sample of Japanese men [+][3] showed a significantly higher risk for stroke (total stroke, hemorrhagic, and intraparenchymal hemorrhage) among those consuming over 450g ethanol per week compared to those drinking occasionally, one-three days per month. No significant associations were observed between alcohol intake and cardiovascular outcomes (e.g., disease development, death) in three studies conducted in Caerphilly [+][4], China [+][5], and the Netherlands [++][6]. Nevertheless, there appeared to be a U-shaped relationship between alcohol intake and cardiovascular disease risk in the latter study [++][6].

[1]Wannamethee 2002; [2]Emberson 2005; [3]Iso 2004; [4]Elwood 2013; [5]Qiu 2003; [6]Beulens 2007

- **Applicability:** The UK and Dutch studies are directly applicable; however, the inconsistency in alcohol intake measurements limits the generalizability of findings

2.7.6AL Diabetes/Metabolic syndrome

Findings were inconsistent with respect to the influence of alcohol intake on diabetes/metabolic syndrome. One study did not find a link with vascular disease, another found higher odds for type 2 diabetes, while two studies reported conflicting results with respect to weight change.

Three studies [+][1], [+][2], [+][3] found significant associations between alcohol intake levels and diabetes/metabolic syndrome, while one study[4] on men living in Caerphilly, UK did not find

an association (with vascular disease). Sex-stratified results of a Japanese study with a 10-year follow-up period [+][1] revealed significantly higher odds of type 2 diabetes mellitus among males consuming moderate or high amounts (over 4.9 g/day) of ethanol compared to male non-drinkers and infrequent occasional drinkers who consumed ethanol on three or fewer days per month. BMI-stratified findings further showed that underweight (BMI <=22kg/m^2) males who consumed over 23 g/day of ethanol also had a significantly higher risk for type 2 diabetes compared to those who consumed less than this amount.

A large UK study [+][2] of men selected from the registers of general practices showed that heavy drinkers had a significantly higher risk of weight gain over five years compared to non-drinkers or occasional drinkers. Also, the proportion of men with high BMI increased significantly with higher levels of alcohol intake at baseline. In contrast, a study [+][3] of predominantly white US female health professionals followed for an average of 13 years showed that increasing levels of self-reported alcohol intake were associated with decreasing incidence of overweight or obesity.

[1]Waki 2005; [2]Wannamethee 2003; [3]Wang 2010; [4]Elwood 2013

- **Applicability:** Partially applicable (particularly the UK and US studies). One UK study cannot be generalised to women. Another US study also had limited generalizability as the sample consisted predominantly of white US female health professionals. Studies also used different categories for alcohol intake, rendering the comparison of findings between studies difficult.

2.7.7AL Cancer

There is consistent evidence from three studies demonstrating the absence of an association between alcohol intake and cancer, while a fourth study reported a higher risk for colorectal cancer among alcohol drinkers.

Three studies conducted in England/Scotland [+][1], the Caerphilly region in the UK [+][2], and the US [++][3] did not find significant associations between alcohol intake and incident and fatal pancreatic cancer; cancer in general; and colorectal cancer, respectively. In contrast, sex-stratified results of a Japanese study [+][4] showed a significantly higher risk for colorectal cancer among men who drink alcohol compared to non-drinkers.

[1]Stevens 2009; [2]Elwood 2013; [3]Flood 2008; [4]Otani 2003

- **Applicability:** Directly applicable; however, self-reported alcohol consumption was derived and categorized differently across studies making comparison of findings difficult.

2.7.8AL Others (Mental health, survival, mortality, chronic obstructive pulmonary disease mortality)

Two studies showed the health benefits of alcohol consumption with respect to anxiety and survival; two studies revealed the link between intake and (all-cause) mortality; while a fifth study reported no association between ethanol consumption and chronic obstructive pulmonary disease mortality.

A study [-][1] of women from rural and urban areas of South East Queensland, Australia indicated that past alcohol drinkers had lower anxiety than non-drinkers. In a sample of Japanese-American men living in Hawaii [++][2], excessive alcohol consumption was associated with overall and exceptional survival at age 85 years (exception survival was defined as men without major chronic disease and without cognitive or physical impairment). A large Japanese prospective cohort study [++][3] showed that, compared to non-drinkers, the risk of all-cause mortality was lowest among males consuming 0.1-22.9 g/day of alcohol during 1990-99; excessive mortality was significantly associated with heavy drinking (more than 69 g/day) among men diagnosed with cancer and cardiovascular disease in this time period. A UK study [++][4] showed that alcohol intake was associated with a higher risk for all-cause mortality among middle-aged British men, while no association with alcohol was reported in relation to chronic obstructive pulmonary disease mortality among a European cohort of Finnish, Italian, and Dutch men [-][5] followed for 20 years. Finally, a large US study showed that higher levels of alcohol intake were associated with a greater likelihood of successful aging [++][6].

[1]Xu 2010; [2]Willcox 2006; [3]Lin 2005; [4]Emberson 2005; [5]Tabak 2001; [6]Sun 2011

- Applicability: Partially applicable – the UK study is directly applicable. Alcohol measurement may be imprecise.

3.8 Evidence statements for WEIGHT CHANGE, WEIGHT CYCLING (WC)

Summary of data from smoking studies is reported in Table 15.

2.8.1WC Healthy Ageing / Quality of Life / Well-being

No study found.

2.8.2WC Disability / Frailty

There is weak and limited evidence from one study from the US that weight loss of more than 10% of max body weight in mid-life is related to hip fracture in a study lasting 22 years.

One study ([++][1]) reported longitudinal associations between weight change and hip fracture. The impact was statistically significant for those in both age groups (50-64 and 65-74 years) who were weight-cycling in mid-life.

[1]Langlois 2001

- **Applicability**: Partially applicable. One study that reported an association between weight change/weight cycling and hip fracture was conducted in US.

2.8.3WC Dementia

There is weak and limited evidence from one study in Israel to suggest that weight change in mid-life is related to dementia in a study lasting 36 years.

One study [+][1] reported longitudinal associations between weight change and dementia. Those in the highest two quartiles of weight change had a significantly higher risk of dementia, independent of the direction of weight change.

[1]Ravona-Springer 2013

- **Applicability**: Partially applicable. One study reported an association between weight change/weight cycling and dementia was conducted in Israel.

2.8.4WC Overall mortality

There is weak and limited evidence from one study in the US that there is no association between weight cycling in mid-life and mortality in a study lasting 16 years.

One study [+][1] reported longitudinal relationships between weight change/weight cycling in midlife and death and reported no association.

[1]Field 2009

- **Applicability**: Partially applicable.The one study that reported an association between weight change/weight cycling and mortality was conducted in US.

2.8.5WC Cardiovascular (CVD) Outcomes

No study found.

2.8.6WC Diabetes / Metabolic Syndrome

There is weak and limited evidence from one study that weight change/weight cycling in mid-life is not related to type 2 diabetes in a study lasting 11 years.

One study [++][1] reported longitudinal associations between weight change/weight cycling and diabetes. The impact was not significant for weight change or weight cycling but but overall weight status was more important with those who were overweight or obese at increased risk of diabetes. In fully adjusted models, adjusted for BMI there was no effect of weight change.

[1]Waring 2010

- **Applicability**: Partially applicable. One study that reported an association between weight change/weight cycling and diabetes was conducted in US.

2.8.7WC Cancer

No study found.

2.8.8WC Mental health

No study found.

3.9 Evidence statements for LEISURE/COGNITIVE ACTIVITY/SOCIAL NETWORKS (LC)

Summary of data from smoking studies is reported in Table 17.

2.9.1LC Healthy Ageing / Quality of Life / Well-being

There is little available evidence to determine if leisure and cognitive activities, and an individual's social network in mid-life is related to successful aging in a study lasting 17 years.

One UK study [+][1] reported longitudinal associations between leisure, cognitive activities, social network and successful aging in both men and women. While there was a beneficial association these were non-significant.

[1]Britton 2008

- **Applicability**: Directly applicable. The study was conducted in the UK.

2.9.2LC Disability / Frailty

No study found.

2.9.3LC Dementia

There is some consistent evidence from three high quality studies that leisure and cognitive activities, and an individual's social network in mid-life is related to less risk of cognitive decline in later life from studies followed up seven to >12 years.

One study from the US [-][1] reported an association between diversity and intensity of participation in intellectual, physical and passive activities and lower risk of Alzheimer's disease. Three studies ([++][2], [++][3], [++][4]) reported longitudinal associations between leisure, cognitive activities, social network and dementia or cognitive impairment. All studies reported a beneficial association between mid-life factors and dementia or cognitive decline in later life however in one study the associations were non-significant for some activities including social, organisational and physical activities[4].

[1]Friedland 2001; [2]Bielak 2012; [3]Holtzman 2004; [4]Kareholt 2011

- **Applicability**: Partially applicable. No UK studies, but studies finding associations were conducted in developed non-European countries (US and Australia).

2.9.4LC Overall mortality

No study found.

2.9.5LC Cardiovascular (CVD) Outcomes

There is no evidence from any study that leisure, cognitive activity or social networks in mid-life is related to reduced hypertension. One study [++][1] was conducted and this found no correlation.

[1] Raikkonen 2001

- **Applicability**: Partially applicable. The one study reporting no association between activities in mid-life and hypertension was conducted in the US and was rated as high quality.

2.9.6LC Diabetes / Metabolic Syndrome

No study found.

2.9.7LC Cancer

No study found.

2.9.8LC Other chronic diseases

No study found.

2.9.9LC Mental health

No study found.

3.10 Evidence statements for COMBINED LIFESTYLE (CL)

Summary data for combined lifestyle studies is presented in Table 16.

2.10.1CL Healthy Ageing / Quality of Life / Well-being

No study found.

2.10.2CL Disability / Frailty

No study found.

2.10.3CL Dementia

There is consistent evidence that combined lifestyle in mid-life is related to less risk of dementia in later life from studies followed up 10 to 25 years.

Two studies [++][1], [+][2] reported longitudinal associations between lifestyle and dementia or cognitive impairment. Both studies reported a beneficial association between mid-life protective behaviours and dementia or cognitive decline in later life however in one study the associations were non-significant[2].

One study was conducted in the US and found a significant association between combined lifestyle and other episodic memory and executive functioning. The UK-based study found a non-significant association with dementia.

[1]Agrigoroaei 2011; [2]Elwood 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between PA in mid-life and dementia was conducted in the UK. The 3 other studies that found a similar relationship were conducted in developed European countries (Sweden and Iceland).

2.10.4CL Overall mortality

There is consistent evidence from high and good quality studies that reducing unhealthy behaviours or adopting a healthier lifestyle in mid-life is related to reduced death.

Two cohort studies [++][1], [+][2] reported longitudinal associations between combined lifestyle behaviours and mortality. Two high or good quality studies reported a significant negative association between number of unhealthy behaviours and mortality.

[1]King 2007; [2]Elwood 2013

- **Applicability**: Directly applicable. Two cohort studies report a beneficial association between combined lifestyle in mid-life and mortality. One study was conducted in the UK and the other USA. Both studies were rated as good or high quality.

2.10.5CL Cardiovascular (CVD) Outcomes

There is inconsistent evidence from high and good quality studies that reducing unhealthy behaviours or adopting a healthier lifestyle in mid-life is related to reduced CVD from studies followed up 13 to 25 years.

Two cohort studies [++][1], [+][2] reported longitudinal associations between combined lifestyle behaviours and Cardiovascular disease. One study reported a significant negative association between number of unhealthy behaviours and CVD[1] while the other[2] reported no association. Importantly the combined behaviours in these two studies vary.

[1] King 2007; [2] Elwood 2013

- **Applicability**: Partially applicable. The one study reporting a beneficial association between combined lifestyle in mid-life and CVD was conducted in the USA. The study reporting no association was conducted in the UK. Both studies were rated as good or high quality.

2.10.6CL Diabetes / Metabolic Syndrome

There is evidence that association exists between reducing unhealthy combined lifestyle behaviours in mid-life is related to diabetes from studies followed up 25 years.

One study [+][1] examined the impact of combined lifestyle on diabetes; while there was a negative correlation this was non-significant.

[1]Elwood 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between changing combined lifestyle and diabetes in mid-life was conducted in the UK.

2.10.7CL Cancer

There is no evidence that association exists between reducing unhealthy combined lifestyle behaviours in mid-life is related to cancer from studies followed up 25 years.

One study [+][1] examined the impact of combined lifestyle on cancer; there was no correlation.

[1]Elwood 2013

- **Applicability**: Directly applicable. One study that reported beneficial association between changing combined lifestyle and cancer in mid-life was conducted in the UK.

2.10.8CL Other chronic diseases

No study found.

2.10.9CL Mental health

No study found.

3.11 Evidence statements for SMOKELESS TOBACCO (ST)

2.11.1ST Diabetes

There is some evidence to suggest that the use of smokeless tobacco (snuff/snus) in mid-life is related to successful type two diabetes in a study lasting 10 years.

One study [+][1] reported longitudinal associations between smokeless tobacco use and diabetes. The use of smokeless tobacco was associated with low insulin response but not low insulin sensitivity.

[1]Ostenson 2012

- **Applicability**: Partially applicable. One study reported an association between smokeless tobacco and was conducted in Sweden.

2.11.2ST Weight

There is some evidence to suggest that smokeless tobacco use in mid-life is related to weight and weight maintenance later life from studies followed up 10 years.

One study [++][1] reported that those who did not use snuff were more likely to be those who did not gain weight; the lack of snuff use increased the chances of not gaining weight.

[1] Nafziger 2007

- **Applicability**: Partially applicable. One study reported an association between smokeless tobacco and was conducted in Sweden.

3.12 Evidence statements for DISADVANTAGED GROUPS

The definition used for this review is that 'disadvantaged populations' includes (but is not limited to) low socioeconomic status; ethnic minority groups; lesbian, gay, bisexual and transsexual (LGBT) community groups; travellers; and other groups with protected characteristics under the equality and diversity legislation.

Studies included in this evidence statement are those that examined differential risk factors (in midlife) within the same cohort for disadvantaged groups.

12.1 DG Dementia

Smoking - Ethnic minority groups

There is weak and limited evidence from one moderate quality study conducted in the US [+][1] that in midlife smokers there is no difference in risk of developing dementia by ethnicity.

The study [+][1] examined associations between midlife smoking and incidence of dementia over twelve years in Caucasian and African American groups and found no differences in development of dementia by ethnicity.

- **Applicability**: Partially applicable. The study was conducted in the US. The study was limited to comparison of African American and Caucasian groups. There may be cultural and ethnic differences between US ethnic groups and the UK and the results may not be relevant to other ethnic groups.

Smoking – Gender

There is weak and limited evidence from one moderate quality study conducted in the US [+][1] that in midlife smokers there is no difference in risk of developing dementia by gender.

One study conducted in the US [+][1] that examined associations between midlife smoking and incidence of dementia over twelve years in Caucasian and African American groups found no differences in development of dementia by gender.

- **Applicability**: Partially applicable. The study was conducted in the US. The study was limited to comparison of African American and Caucasian groups. There may be cultural and ethnic differences between US ethnic groups and the UK.

Alcohol - Low socioeconomic status (SES)

There is weak and limited evidence from one moderate quality study conducted in France [+][2] that for people in lower SES groups high alcohol intake (>21 drinks/week) at midlife is related to poorer cognitive performance at follow up.

One study conducted in France [+][2], found that for people with a lower SES based on occupational position, those with high alcohol intake (>21 drinks/week) had poorer cognitive performance than those consuming 4 -14 drinks per week over ten years follow up. Results were based on a test measuring psychomotor speed, attention and reasoning. The DSST test (digital symbol substitution test) score difference was - 2.1 points (95% CI -3.9, -0.3). No association between alcohol consumption and cognitive performance was found in those in intermediate or high socioeconomic groups.

- **Applicability**: Partially applicable. The study was conducted in France.

12.2 DG Cardiovascular (CVD) Outcomes

Smoking – Gender

There is weak and limited evidence from one moderate quality study conducted in Japan [+][3] of little difference between midlife male or female smokers in risk of cardiovascular disease.

One study conducted in Japan [+][3] found little difference in risk of total CHD or myocardial infarction (MI) between male and female smokers. For both men and women, current smoking was positively associated with the age-adjusted risk of total CHD or MI. The multivariate relative risk for current smokers versus never smokers in men was 2.85 (95%CI 1.98, 4.12) for total CHD and 3.64 (95%CI 2.27, 5.83) for MI. For women the results were 3.07 (95%CI 1.48, 6.40) for total CHD and 2.90 (95%CI 1.18, 7.18) for MI.

- **Applicability**: Partially applicable. The study was conducted in Japan.

Physical activity *– Gender*

There is very weak and limited evidence from one moderate quality study conducted in Germany [+][4] of less risk of myocardial infarction (MI) in women participating in moderate or high levels of leisure time sports at midlife.

The study [+][4] reported that moderate or high levels of sports in leisure time were associated with significantly reduced risk of MI in women but not men in most fully adjusted models (adjusted for other major coronary heart disease risk factors). However this result was based on only a small number of women who participated in moderate or high levels of PA.

- **Applicability**: Partially applicable. The study was conducted in Germany.

[1] Alonso 2009; [2] Sabia 2011; [3] Baba 2006; [4] Meisinger 2007

4. DISCUSSION

Findings into context & implications of findings

The DH has asked NICE to produce public health guidance on preventive approaches to be adopted in mid-life to delay the onset of disability, dementia and frailty in later life. Three evidence reviews and an economic model underpin the guidance. The reviews looked for evidence on a wide range of potential influences on well-being in later life and at the effectiveness and cost effectiveness of available interventions to act on these factors. This review (Review 2) aimed to identify if there were any specific issues or behavioural risk factors at midlife that should be considered by the PHAC team when designing the guidance. The specific objective was to synthesise the evidence for the association between modifiable behavioural risk factors in midlife (age 40-65 years) and dementia, disability and frailty in later life (DDF) (age >65 years).

A comprehensive search of the literature was conducted using a wide range of search terms to identify the range of likely behavioural risk factors (such as physical activity, diet, smoking, alcohol, overweight, social exposure and integration, and hearing and vision-related behaviours) and the broad range of potential outcomes (relating to successful or healthy ageing, quality of life or wellbeing, dementia, disability, frailty including chronic conditions such as cardiovascular outcomes, cancer, diabetes, mood disorders and mortality).

After a rigorous selection process, 164 observational longitudinal cohort studies that have measured behavioural risk factors in midlife and followed up outcomes for the same participants in later life were included in the review. The behavioural risk factors for which we found published data in midlife with relevant outcomes in later life were: physical activity and inactivity; diet and components of diet; smoking and smokeless tobacco (snuff/snus); alcohol; weight change or weight cycling; combinations of lifestyle components e.g. physical activity, diet and smoking; and leisure, cognitive activity or social networks. Studies of behaviour related to hearing or vision were sought but none were found that met the inclusion criteria for this review.

<u>Physical activity and inactivity</u>

Forty-five papers were found relating to PA, of which two specifically aimed to look at inactivity. Some studies reported multiple associations and different exposures relating to PA (an example would be a positive beneficial association with improved DDF outcomes for vigorous PA and null association for light activity) so where there are different associations

these have been reported in the tables. The available data covers different levels and intensity of PA and a few report specific types of activity (e.g. walking, active commuting).

Twelve of the PA papers were conducted in the UK. Some of these were different publications from the same study e.g. Caerphilly cohort study, but which reported different behavioural risk factors or outcomes. Other included studies were mainly from OECD countries and most were from Europe and the US.

Diet

For diet, 48 studies were included. Some studies reported more than one relevant outcome or different types of exposure (e.g. fruit or vegetables) or amounts of exposure (e.g. low, moderate or heavy coffee consumption). Three studies reported outcomes relevant to successful ageing, seven reported disability and frailty outcomes, six dementia or cognitive outcomes, five on total mortality, fifteen on CVD outcomes, seven on diabetes outcomes, six on cancer outcomes, three on mental health, and three on other communicable diseases. Six studies reported on the relationships between diet or components of diet and preconditions (as specified in Figure 1) for DDF or NCC.

Evidence was found covering midlife dietary patterns and consumption of dietary components, such as macronutrients and for specific foods. Included studies cover dietary patterns, fat (total, saturated, poly- and mono-unsaturated), protein, fibre, fruit and vegetables, fish, meat, red and processed meat, milk, salt, glycaemic index or glycaemic load, micronutrients, coffee, tea and caffeine.

There is some consistent evidence (but from a limited number of studies) that a healthy diet in general (studies included e.g. ADA diets) or Mediterranean diet, and fruit and vegetables has beneficial effects on DDF and NCC outcomes. There is also some consistent evidence (again from a limited number of studies) that higher consumption of saturated fat or processed and red meat (reported together) in midlife is associated with poorer ageing, DDF and NCC outcomes. There was some consistent evidence (from a limited number of studies) that coffee consumption in moderation may be beneficial. However, one study reported increased risk of coronary events with very heavy coffee consumption

Smoking

The review found a wealth of evidence from longitudinal cohort studies relating to the association between midlife smoking and dementia, disability, frailty outcomes (DDF). Fifty seven studies were included. Some studies reported more than one relevant outcome or different levels of exposure (e.g. heavy or light smoking and populations (e.g. current, former

and never smokers). Three studies reported healthy ageing outcomes, six with disability and/or frailty outcomes, seven reported total mortality, nineteen reported CVD outcomes, four on diabetes related outcomes, six with cancer outcomes, one on other chronic diseases (kidney disease).

There was a very consistent association across studies between midlife smoking and poorer DDF and NCC outcomes. All included studies either reported poorer outcomes for those who smoked at midlife or a very small number of studies reported a null association. No studies reported beneficial outcomes in later life for midlife smokers. The majority of studies were rated as moderate quality with a few studies of high or low quality. Studies were conducted in men and women. Only a few studies examined differential risk factors for dementia between men and women and across different ethnic groups. The limited available evidence suggests similar risks of smoking on later health outcomes by gender or ethnicity.

Smokeless tobacco

One study reported longitudinal associations between smokeless tobacco (snuff/snus) and improved diabetes related outcomes. The use of smokeless tobacco was associated with lower insulin response.

Alcohol

Twenty four prospective cohort studies were included on alcohol intake between 40 and 64 years of age (midlife), in relation to disability, dementia, cardiovascular outcomes, diabetes and metabolic syndrome, cancer and other outcomes assessed after 55 years of age (late-life). Seven studies were conducted in the UK and the rest were mainly conducted in developed OECD countries,

There was heterogeneity in the categorisation of self-reported alcohol intake levels. Five articles (n=5) assessed the number of drinks consumed per week, one (n=1) differentiated teetotallers from alcohol users, five (n=5) documented the number of drinks per day, one (n=1) assessed the number of drinks per month, while the rest of the studies (n=12) used a combination of measurements examining alcohol intake over various time spans.

Evidence specific to midlife alcohol consumption was mixed and inconsistent with smaller effect sizes than for smoking and physical activity. Some studies reported negative outcomes e.g. for dementia, mortality and cancer and some more positive outcomes e.g. for ageing and mental health. However studies found were sparsely distributed among different outcomes. Two studies reported moderate quality evidence of higher risk of dementia in non-drinkers

and heavy drinkers compared to moderate drinkers, but limited evidence was available specific to midlife.

There was limited evidence, from one study, that for people in lower SES groups high alcohol intake (>21 drinks/week) at midlife is related to poorer cognitive performance in later life.

Weight change, weight cycling

Four studies were included that reported an association between weight change patterns in midlife and later outcomes. One study reported increased risk of hip fracture in those losing greater than 10% of their body weight (as determined from maximum weight during follow up). Two studies reported null relationships with weight loss/gain or cycling, one with mortality as an outcome and one with diabetes as an outcome. One study reported increased risk of dementia with weight change in midlife (independent of the direction of weight change). However the study that reported diabetes as an outcome also examined overall weight status, being overweight or obese appeared to be a more important factor in the association with diabetes than weight change.

Combined lifestyles

Three studies reported data for combinations of lifestyle programmes. One reported relationship between uptake of number of healthy behaviours with CVD and mortality. One reported the relationship of a combination of behavioural protective factors with cognitive function and one combinations of healthy behaviours (not smoking, BMI, fruit and veg intake, regular exercise, moderate alcohol intake). In those practising at least four behaviours there was a significantly lower risk of diabetes, vascular disease, cancer, dementia and cognitive impairment and mortality.

Leisure, cognitive activity, social networks

Four studies were found that examined the relationship between midlife activities and DDF outcomes. One study reported a beneficial effect of diversity and intensity of intellectual, passive and physical activities on later risk of Alzheimer's disease. Three studies reported relationships with cognitive function, all found a beneficial association. The activities ranged from engagement with number of activities, social network size and political, mental or socio-cultural activities.

However one study examined both activity participation in relation to cognitive ability over time but also in relation to the baseline cognitive activity and the results suggested that while activity participation is related to cognitive ability across adulthood it may be intrinsically related to the baseline cognitive function (Bielak 2012).

Other health-related behaviours

Evidence was sought but not found within the inclusion criteria for other behaviours including vision and hearing related behaviours.

Disadvantaged groups/health inequalities

Data relating to disadvantaged groups was also limited with some sparse data on people with low SES, ethnic minority groups and gender in midlife with relevant outcomes. This data is summarised for each health behaviour. No relevant data was found for other groups covered by the equality and diversity legislation.

Limitations of the evidence, gaps

Most of the evidence found comes from Europe or the US or other developed OECD countries. There is a fairly good representation of studies from the UK.

Limited evidence was found specifically relating to midlife behaviours for leisure activities including cognitive activities and social networks, weight change and weight cycling and smokeless tobacco. While many diet-related studies were found they covered a broad range of diets and dietary components. There were some diets or dietary components for which studies specifically pertaining to midlife were not found. Data relating to disadvantaged groups was also limited. Some sparse data on people with low SES, ethnic minority groups and gender in midlife was found. No longitudinal data was found relevant to other groups covered by the equality and diversity legislation such as LGBT groups or travellers.

Much of the data used to assess behaviour was self-reported. For physical activity all studies used self-reports of activity except one which used accelerometry. For smoking many studies used self-reports with biochemical confirmation of smoking status. Most diet and alcohol behaviour was self-reported. However, in general outcome data was assessed objectively using clinical data and medical records or registers.

The review only includes longitudinal observational studies, which can show an association between midlife risk factors and later life outcomes. However associations from this type of study are not necessarily causal.

Limitations of the review

The remit of this review was specifically to identify midlife behavioural risk factors for DDF outcomes and common NCCs in later life. Determinants of dementia, disability, frailty over the whole lifecourse were not included. Pragmatically, due to the wide scope of the review,

the large amount of literature covering behavioural risk factors and the outcomes of interest, and the timescales for the review, the searches were focused on studies with midlife-related terms in the title, abstract or related MeSH indexing to identify those studies that specifically aimed to report on midlife exposure. The implication is that cohort studies that have followed individuals from mid- to late life and reported associations of interest without specifying midlife terms in the title or abstract were not identified by the searches. This might explain some of the gaps in evidence and further work is ongoing (though beyond the scope of this report) to address this limitation.

Because a very large amount of data was found for a wide range of risks and outcomes, the search limitations are unlikely to have an impact on the overall findings. In fact, it appears that a lot of what we know of the associations between behavioural risk factors and late life outcomes comes from studies conducted in people in mid-life. So, where caution should be exercised is in extrapolating the mid-life associations to older age groups – the direction and magnitude of these associations vary across the life cycle. This is the focus of several work packages undertaken by NIHR SPHR Ageing Well programme, which should complement the findings of this review with regards to identifying behavioural risk factors that are amenable to change for improved health outcomes in later life.

5. OVERALL SUMMARY AND RECOMMENDATIONS

Physical activity

There is consistent evidence that midlife physical activity has a beneficial effect on later life DDF and NCC outcomes. However, one report (from 45) reported increased risk of bladder cancer in men participating in vigorous activity at midlife.

- The promotion of physical activity in all midlife populations including men and women and different ethnic groups should be addressed by the guidance. All types of activity appear to have a positive relationship with outcomes.

Diet

- A healthy diet (standard guidelines) or Mediterranean-type diet could be recommended, also diets which minimise consumption of saturated fat, increase fruit and vegetable intake with moderate consumption of processed or red meat. Coffee consumption in moderation.

Smoking

There is consistent evidence that prevention, reduction and cessation of smoking behaviour in all midlife populations including men and women and different ethnic groups could lead to improved outcomes.

- Smoking prevention, reduction and cessation in midlife should be addressed by the guidance.

Alcohol

- Evidence specific to midlife alcohol consumption was mixed (across studies and across outcomes). It is not clear from the findings of this review whether there is a safe level of alcohol consumption, so caution should be exercised in making recommendations in that respect.

Combined healthy lifestyle programmes

- Consideration could be given to programmes which combine at least two or more aspects of healthy behaviour (from PA, healthy diet, non-smoking, alcohol in moderation, leisure activities)

Leisure activities/social activities

There is some evidence that those who participate in a diverse range of intellectual, passive, physical and leisure activities have better cognitive outcomes.

- Consideration could be given to improving social support and access to activities. This could be incorporated into healthy lifestyle programmes (with evaluation to build the evidence base).

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