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ScHARR School of Health and Related Research
Public Health Collaborating Centre

Preventing the progression of pre-diabetes to type 2 diabetes in adults.

Systematic review and meta-analysis of lifestyle, pharmacological and surgical interventions

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About the *ScHARR Public Health Collaborating Centre*

The School of Health and Related Research (ScHARR), in the Faculty of Medicine, Dentistry and Health, University of Sheffield, is a multidisciplinary research-led academic department with established strengths in health technology assessment, health services research, public health, medical statistics, information science, health economics, operational research and mathematical modelling, and qualitative research methods. It has close links with the NHS locally and nationally and an extensive programme of undergraduate and postgraduate teaching, with Masters courses in public health, health services research, health economics and decision modelling.

ScHARR is one of the two Public Health Collaborating Centres for the Centre for Public Health Excellence (CPHE) in the National Institute for Health and Clinical Excellence (NICE) established in May 2008. The Public Health Collaborating Centres work closely with colleagues in the Centre for Public Health Excellence to produce evidence reviews, economic appraisals, systematic reviews and other evidence based products to support the development of guidance by the public health advisory committees of NICE (the Public Health Interventions Advisory Committee (PHIAC) and Programme Development Groups (PDG).

Contribution of Authors

Roy Jones was the systematic review lead. Crystal Freeman and Maxine Johnson were reviewers on the project. Helen Buckley Woods and Louise Guillaume developed and undertook literature searches. John Stevens undertook the network meta-analysis. Clare Gillies provided data from the original review. Nick Payne and Jim Chilcott were the senior leads. Elizabeth Goyder was the topic expert.

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1. LIST OF ABBREVIATIONS

BMI	Body Mass Index (kg / m^2)
CDQDPS	China Da Qing Diabetes Prevention Study
CI	Confidence Interval
CON	Control
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcomes Study
DPS	Diabetes Prevention Study
FFA	Free Fatty Acid
HDL	High-density Lipoprotein
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
INT	Intervention
ITT	Intention to Treat
LDL	Low-density Lipoprotein
MET	Metformin
NICE	National Institute for Health and Clinical Excellence
OGTT	Oral Glucose Tolerance Test
PDG	Programme Development Group
RCT	Randomised Controlled Trial
T2DM	Type 2 Diabetes
t.i.d	Ter in die, Latin for three times a day
WHO	World Health Organization
VIP	Vasterbotten Intervention Program

2. EXECUTIVE SUMMARY

2.1 Background

Type 2 diabetes is associated with significant clinical and social consequences. The National Institute for Health and Clinical Excellence has been asked by the Department of Health to develop public health guidance on the prevention of type 2 diabetes among high-risk groups. The referral is divided into two separate pieces of guidance. The first addresses the prevention of pre-diabetes (raised and impaired glucose levels) in populations and communities of high risk adults using community based interventions. The second piece of guidance will address how to prevent the progression from pre-diabetes to type 2 diabetes. To inform development of this second piece of guidance, four reviews of international evidence will be carried out that address the prevention of progression to type 2 diabetes as well as a health economic / modelling review. The aim of this review was to update a previous systematic review and meta-analysis of published randomised controlled trials (RCTs) by investigating the effects of lifestyle, pharmacological and surgical (weight reduction) interventions to prevent or delay type 2 diabetes mellitus (T2DM) in people with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). Since that initial review (Gillies et al. 2007), further additional randomised controlled studies and longer term follow up data from these earlier trials have been published. The current systematic review by ScHARR was designed to include these new studies along with the previously included data and include any studies missed by the initial review (Gillies et al. 2007). The effect of adding new data to the meta-analyses was examined, comparing our results with the results in the initial review (Gillies et al. 2007).

Type 2 diabetes has a long preclinical phase, with the condition remaining undiagnosed for many years in a significant number of cases (Woolthius et al. 2007). A group of conditions defined by blood glucose levels that fall between normal and those defining type 2 diabetes are typically known as Impaired Fasting Glucose (IFG) and Impaired Glucose tolerance (IGT) or collectively as ‘pre-diabetes’. It is recognised that the term ‘pre-diabetes’ is not ideal, as not everyone with raised or impaired blood glucose levels will go on to develop type 2 diabetes. However, the term ‘pre-diabetes’ has been chosen because of its widespread use and recognition by a broad range of stakeholder groups and because of the lack of consensus on a suitable alternative.

The increase in obesity and type 2 diabetes may be attributed to changes in lifestyle over the past few decades that will likely continue in the foreseeable future. The loss

of traditional dietary habits and the increasing consumption of unhealthy diets and increasing portion sizes, together with less physical activity at work, home, and during leisure time, are strongly associated with an increase in diabetes. Lifestyle factors such as diet and physical activity are modifiable, and disease manifestation from these factors can be preventable. The World Health Organization describes obesity as one of the most blatantly visible, yet most neglected, public health problems and it threatens to overwhelm both developed and developing countries.

Risk factors for the development of diabetes include obesity, a family history of diabetes, physical inactivity, insulin resistance, hypertension, dyslipidemia, vascular disease, and polycystic ovary syndrome. Body Mass Index (BMI), expressed as weight (kilograms) divided by height (metres) squared, is often used to classify overweight (BMI>25) and obesity (BMI>30).

2.2 Aims and Objectives

The aims of this review were to undertake an update of the initial review (Gillies et al. 2007) and where possible, conduct sub-group analysis.

The objectives of this current review are:

1. To update the searches carried out in the initial review and identify any relevant studies not included in the initial review;
2. To identify any additional effectiveness evidence from these studies;
3. To update the meta-analysis including additional data now available;
4. To explore the effect of study duration on risk reduction;
5. To conduct sub-group analysis, where data are available, for population subgroups for example, baseline age, ethnicity, socio-economic status or risk factors.

Following on from the searches undertaken by the initial review (Gillies et al. 2007) a search strategy which was based upon the initial review (Gillies et al. 2007), with some modifications, was adopted to identify additional papers to those identified in the searches of the initial review (Gillies et al. 2007). These revised searches by ScHARR used a wider number of databases for relevant evidence.

2.3 Methods

The ScHARR review largely adopted the methods, including the inclusion criteria and meta-analysis methods used in the initial review (Gillies et al. 2007). As in that review, study selection was restricted to randomised controlled trials, to ensure only high quality evidence was included. Studies were selected where an intervention had been applied with the aim of delaying or preventing T2DM in a sample or sub-sample of individuals with IGT or IFG. Development of T2DM was the required outcome measure. Trials that were selected for inclusion in the current review were included in the meta-analysis if they supplied sufficient data.

The standard NICE Methods, as outlined in the Methods for the Development of NICE Public Health Guidance (2009) were used to guide the development of the search strategy. The aim of the search strategy was to retrieve the best available evidence to inform the effectiveness review and meta analysis.

The search strategy developed by Gillies et al. (2007) was used as a starting point in the development of the search strategy for this review. The Gillies search strategy was modified to meet the need for a more sensitive search strategy (henceforth referred to as the ScHARR search strategy). The terms used in the ScHARR search strategy for diabetes and Type 2 diabetes were the terms that were tested and used successfully in the searches for Review One (identification of adults with pre-diabetes).

References were scrutinised at title and abstract stage for inclusion / exclusion (see Section 4). Papers were included if the study included adults at risk of, but with no diagnosis of type 2 diabetes. Papers were retrieved at full title if, from the abstract it was clear that they met the criteria (progression/development of diabetes was an outcome).

Data were extracted from included studies using a piloted template, and all papers were assessed for quality using a tool adopted by NICE (NICE 2009), as well as by the Jadad quality scoring method (Jadad et al. 1996).

Data that related to secondary outcomes, such as BMI, weight etc. were extracted where available. Some secondary outcomes, such as cholesterol, lipids and physical activity were not examined as the data for these outcomes were rarely or never provided in the published studies. Data extraction was done when the data allowed.

2.4 Results

Searches and Quality assessment

From an initial total of 5,601 references, 48 were examined at full paper stage with 37 being excluded, leaving a total of 12 papers of varying quality that met the inclusion criteria for the current review. There were six additional papers published after the initial review and three papers detailing additional follow-up data. A further three papers were identified by PDG members, along with the included papers from the initial review (14), there were 26 papers identified for the current review.

The quality of papers was on the whole very good, with 21 papers were rated as very good (++), three as good (+) and two as poor (-) using the NICE quality assessment criteria checklist. Of the papers in the initial review (Gillies et al.), 11 were rated as very good (++), two as good (+) and one as poor (-) using the NICE checklist.

When using the Jadad quality score (Jadad et al. 1996), which allocates randomised controlled trials a score of between zero (very poor) and five (rigorous) points, two studies scored 4 points, eight studies scored 3 points, 12 studies scored 2 points and four studies scored 1 point. Of the papers in the initial review (Gillies et al. 2007), one study scored 4 points, five studies scored 3 points, seven studies scored 2 points and one study scored 1 point.

Lifestyle interventions

For lifestyle interventions, there were 14 studies in total (eight from the initial review, three updated studies from the initial review, and three new studies. The three studies with longer-term follow-up reported were, the Da Qing study (Li et al. 2008 -) with data on a 20 year follow-up, the DPS (Lindstrom et al. 2006 ++) with data on a seven year follow-up and the DPP (Diabetes Prevention Programme Research Group 2009) with data on a ten year follow-up.

After replacing the studies that had more recent data, the studies on lifestyle interventions published after the initial review (Gillies et al. 2007), were included in the meta-analysis. Three studies examined a diet only intervention, one study examined an exercise only intervention, and nine studies examined a combination of diet and exercise. The addition of the new studies slightly altered the overall pooled hazard ratio for the prevention of type 2 diabetes, from 0.53 (95%CI 0.43 – 0.66) reported in the initial review in to 0.51 (95% CI 0.43 – 0.62). There was a slight change in the pooled effect estimate for diet and exercise studies, from 0.49 (95%CI 0.36 – 0.65) to 0.47 (95%CI 0.37 – 0.59). For diet alone, there was no change with

both meta-analyses having an overall effect estimate of 0.67 (95%CI 0.49 – 0.92). For exercise alone, again there was no change, both meta-analyses had an overall effect estimate of 0.53 (95%CI 0.34 – 0.83).

From the meta-analysis, the combination of diet and exercise appears to have more effect in the delaying or preventing the progression from IGT or pre-diabetes to a diagnosis of diabetes, than diet alone and exercise alone. In all of the studies, the intervention group had lower rates of progression to diabetes than the control group, although not every individual study had a statistically significant result.

Pharmacological interventions

There were 14 studies (eight from the initial review, one updated study from the initial review and five new studies) looking at pharmacological interventions. When the data from studies published after the initial review were added the overall pooled effect was 0.64 (95% CI 0.53 – 0.76) compared to 0.69 (95% CI 0.61 – 0.78) in the initial review. Three studies examined the effect of metformin, two studies examined acarbose, one study examined glipizide, two studies examined pioglitazone, one study examined voglibose, one study examined ramipril, one study examined valsartan, one study examined nateglinide and two studies examined the anti-obesity drug orlistat. From the meta-analysis, the anti-obesity drug appears to have slightly more effect in the delaying or preventing the progression from IGT to a diagnosis of diabetes than the combined results of the oral diabetes drugs. In all studies, the intervention group had lower rates of progress to diabetes than the control group.

Network analysis

The only interventions that were evaluated over both the short-term and medium-term were Diet and Diet + Exercise. In both cases the hazard ratios for the intervention effects relative to Placebo were bigger in short-term trials compared to medium-term trials, 0.63 and 0.73 for Diet, and 0.43 and 0.56 for Diet + Exercise, respectively. Although there was reasonable uncertainty as to the true effects, these results are consistent with the opinion *a priori* that the hazard ratio varies over time and is shrinking back to unity. There may be various reasons for this including the possibility that the patients randomised to Placebo switch to alternative strategies to delay their onset of type 2 diabetes rather than continuing with their previous lifestyle, and the possibility that patients randomised to an active intervention may not be as compliant with their intervention over the medium term as they were at the start of their intervention.

The only interventions that were evaluated in at least three RCTs were Diet + Exercise (5 short-term RCTs, 3 medium-term RCTs) and Metformin (3 short-term RCTs). Thus, there was very little information with which to conduct a meta-regression adjusting for mean age and mean BMI in each trial. The meta-regression models are over-specified in terms of the number of parameters to be estimated given the number of observations available. A more informative meta-regression would require more replication of interventions in different RCTs and in patients whose mean ages and BMIs were sufficiently different to enable the identification of these as potential intervention effect modifiers.

Sub group analysis

Although, none of the trials reported to date have separate data on sub-groups such as those in socio-economic or ethnic groups, a number of trials included in this review, recruited the whole trial population only from a south Asian population, enabling a meta-analysis of trials with a south Asian population.

South Asian populations

For south Asian populations, in the short-term, it would appear both a lifestyle intervention of diet combined with exercise and pharmacological interventions have an effect in delaying or preventing the progression from IGT to a diagnosis of diabetes. The diet and exercise lifestyle intervention seems to have more effect on the progression from IGT to diabetes (overall pooled effect of 0.58, 95% CI 0.47 – 0.73), than pharmacological interventions (overall pooled effect of 0.72, 95% CI 0.52 – 0.99).

Secondary outcomes

As well as the primary outcome of progression to diabetes, analysis by other outcomes was also of interest, particularly changes in BMI, weight, blood pressure, blood glucose, waist circumference and cholesterol. Not all studies reported follow-up data on these variables, even when baseline measurements were reported. Where authors reported secondary outcome variables at baseline and at the end of follow-up, but did not report on the change, the mean change was calculated by the authors of this review.

BMI

For lifestyle interventions, the mean changes in BMI in the intervention groups ranged from -1.3 to 0.8, while mean changes in the control groups ranged from -0.3 to 0.6. The follow-up periods ranged from two years to five years, with the most BMI reductions happening within three years, although at a 5-year follow-up the intervention group had maintained a reduction in BMI while the control group had not. In the pharmacological interventions, the mean changes in BMI in the intervention groups ranged from -1.6 to +1.4, while mean changes in the control groups ranged from -0.1 to 0.5. The follow-up periods in the pharmacological interventions were shorter than the lifestyle interventions, ranging from one year to three years. For both lifestyle and pharmacological interventions, the intervention groups had a greater reduction in BMI than control groups, -1.3 in lifestyle intervention compared to -0.3 in lifestyle control and -1.6 in pharmacological interventions compared to -0.1 in pharmacological control.

Weight Change

As with BMI, not every study reported and commented on the changes in weight in the intervention and control groups at the end of the follow-up periods. Where changes were reported these have been included, where changes were not reported or commented on, but weight measurements for baseline and at the end of follow-up were provided in tables of characteristics, the change has been calculated.

For lifestyle interventions, the mean change in weight in the intervention groups ranged from -5.6 kg to +0.16 kg, while mean changes in the control groups ranged from -3.5 kg to +0.7 kg. The follow-up periods ranged from two years to five years, with the best reductions in weight happening within three years, although at a 5-year follow-up the intervention group had maintained a small weight loss while the control group had not. In the pharmacological interventions, the mean weight change in the intervention groups ranged from -2.9 kg to +0.8 kg, while mean changes in the control groups ranged from -1.6 kg to +0.3 kg. The follow-up periods in the pharmacological interventions were shorter than the lifestyle interventions, ranging from 16 weeks to four years. For both lifestyle and pharmacological interventions, the intervention groups had a greater weight loss than control groups.

Blood pressure

For lifestyle interventions, the mean change in systolic blood pressure in the intervention groups ranged from -10.0 to 11.0 mmHg, while mean changes in the control groups ranged from -4.3 to 13.0 mmHg. The mean change in diastolic blood pressure in the intervention groups ranged from -7.0 to 2.0 mmHg, while mean changes in the control groups ranged from -5.0 to 3.6 mmHg. Most of the studies had a short-term follow-up period (range 1-year to 4-years). Looking only at studies with a short-term follow-up, the mean change in systolic blood pressure in the intervention groups ranged from -10.0 to 4.4 mmHg, while mean changes in the control groups ranged from -4.3 to 5.5 mmHg, and the mean change in diastolic blood pressure in the intervention groups ranged from -6.2 to 2.0 mmHg, while mean changes in the control groups ranged from -4.0 to 3.6 mmHg.

Blood glucose

For lifestyle interventions, the mean change in fasting blood glucose in the diet only and exercise only intervention groups was 0.38 and 1.27 mmol/L respectively, and 2.07 mmol/L in the control groups. The mean change in fasting blood glucose in the diet combined with exercise intervention groups ranged from 0.0 to 2.3 mmol/L, while mean changes in the control groups ranged from 0.1 to 3.18 mmol/L. For pharmacological interventions, the mean change in two hour glucose ranged from -1.9 to 0.24 mmol/L, while mean changes in the control groups ranged from -1.1 to 0.5 mmol/L.

A change in two hour glucose in the diet only and exercise only intervention groups was 1.51 and in the control groups it was 2.07 mmol/L. The mean change in two hour glucose in the diet combined with exercise intervention groups ranged from -0.5 to 2.53 mmol/L, while mean changes in the control groups ranged from -0.1 to 4.78 mmol/L. For pharmacological interventions, the mean change in two hour glucose ranged from -3.1 to 0.59 mmol/L, while mean changes in the control groups ranged from -1.6 to 0.68 mmol/L.

Waist circumference

Based on the limited evidence available, for lifestyle and pharmacological interventions, the mean reduction in waist circumference in the intervention groups was very slightly greater than the mean changes in the control groups.

Cholesterol

Based on the limited evidence available, for lifestyle and pharmacological interventions, there was mixed evidence on the change in cholesterol in the intervention groups and the control groups.

Phenformin

As phenformin was withdrawn from most markets in the late 1970s due to a high risk of lactic acidosis, the data from the study (Jarrett et al. 1979 +) on phenformin has not been included in any of the updated pharmacological interventions meta-analyses, although the information on the diet arms have been included. Of the remaining papers, there were six additional papers published after the initial review and three papers detailing additional follow-up data; updated data from these studies have been used to replace the data originally used. A further three papers were identified by PDG members, along with the included papers from the initial review, in total there were 26 papers identified for the current review.; 14 of these papers were included in the initial review (Gillies et al. 2007) and nine were new studies. For each of these papers, a calculated hazard ratio was used in the production of further meta-analyses.

Conclusion

The data derived from the trials show that an intervention can reduce the risk of type 2 diabetes in people with IGT, and lifestyle interventions seem to be at least as effective as pharmacological interventions. Lifestyle interventions, which aim to reduce obesity and increase physical activity, help in addressing directly these risk factors, and incur fewer and less serious side effects than drug treatment. As in pharmacological interventions, lifestyle interventions may not be permanent, so advice on diet and exercise needs to be regularly reinforced in order to maintain behavioural changes. For pharmacological interventions, adverse effects need to be fully taken into account to enable the overall harms and benefits to be assessed.

Surgical interventions

Although studies on surgical interventions were searched for, none where found that fully met the inclusion criteria for inclusion in this review. However, recent searching identified one non-randomised longitudinal study (Long et al. 1994), a brief outline of

the findings is presented here for information. The population consisted of clinically severe obese individuals with IGT (109 in Intervention group, 27 in Control group). The intervention was a gastric bypass operation compared to no surgery. The individuals were followed for an average of 5.8 years (range 2 to 10 years), and the progression to diabetes was 0.15 cases per 100 patient-years in the intervention group (1/109), and 4.72 cases per 100 patient-years in the control group (6/27), this was statistically significant ($p<0.0001$).

2.5 Evidence statements

The following evidence statements are the result of the synthesis of available evidence and are intended to show the effect of lifestyle and pharmacological interventions on the progress to type 2 diabetes for people with pre-diabetes and on secondary outcomes, where these have been reported in sufficient detail.

Evidence statement 1:

Lifestyle interventions

The meta-analysis of hazard ratios shows that lifestyle interventions (pooled HR 0.51 95% CI 0.43-0.62) can reduce the progress to diabetes for people with IGT. Each type of lifestyle intervention, whether diet (HR 0.67 95% CI 0.49-0.92), exercise (0.53 95% CI 0.34-0.83), or a combination of diet and exercise (HR 0.47 95% CI 0.37-0.59) had a beneficial effect, although a combination of diet and exercise appeared to have more effect that either diet or exercise alone.

The hazard ratio for diet only intervention was based on three studies, one UK (Jarrett et al. 1979 +), one Chinese (Da Qing, Pan et al. 1997 ++) and one Australian (Wein et al. 1999 -). The hazard ratio for exercise only intervention was based on one Chinese study (Da Qing, Pan et al. 1997 ++). The hazard ratio for the diet combined with exercise intervention was based on nine studies, one study in each of the following countries, UK (Penn et al. 2009 ++), Japan (Kosaka et al. 2005 ++), China (Li et al. 2008 -), India (Ramachandran et al. 2008 ++), Netherlands (Roumen et al. 2008 ++), Finland (Lindstrom et al. 2006 ++), Sweden (Lindahl et al. 2009 ++) and two US studies (Diabetes Prevention Program Research group 2009 ++; Liao et al. 2002 +).

Evidence statement 2:

Pharmacological interventions

The meta-analysis of hazard ratios shows that pharmacological interventions (pooled HR 0.64 95% CI 0.53-0.76) can reduce the progress to diabetes for people with IGT. Both types of intervention, oral diabetes drugs (HR 0.60 95% CI 0.44-0.82), and anti-obesity drugs (HR 0.67 95% CI 0.55-0.81) had a beneficial effect.

The hazard ratio for oral diabetes drugs was based on twelve studies, Three multi-country study (Dream Trial Investigators 2006 ++, NAVIGATOR Study Group[a] 2010 ++, NAVIGATOR Study Group[b] 2010 ++),one study in each of the following countries Canada/Europe (Chiasson et al. 2002 ++), Finland (Erkisson et al. 2006 ++), Japan (Kawamori et al. 2009 ++), two US (Diabetes Prevention Program Research Group 2009 ++, DeFronzo et al. 2011 +) , two Indian (Ramachandran et al. 2006 ++; Ramachandran et al. 2009 ++)` and two Chinese (Li et al. 1999 ++; Pan et al. 2003 ++).

For anti-obesity drugs, the hazard ratio was based two studies, one US/Europe (Heymsfiled et al. 2000 ++) and one Swedish (Torgerson et al. 2004 ++).

Evidence statement 3:

Network meta-analysis

Network meta-analysis

The network meta-analysis comparison of the effect of diet only and diet + exercise for short-term and medium-term interventions showed a greater effect in short-term studies (diet v placebo: population HR 0.63 95% CrI 0.29-1.34; diet + exercise v placebo : population HR 0.43 95% CrI 0.31-0.59) compared to medium-term studies (diet v placebo : population HR 0.73 95% CrI 0.37-1.79; diet + exercise v placebo : population HR 0.56 95% CrI 0.30-0.93)

The network meta-analysis comparison of diet versus placebo incorporates indirect evidence about the treatment effect from related studies as well as direct evidence from one short-term study (Wein et al. 1999 -) and two mid-term studies (Pan et al. 1997 ++, Jarrett et al. 1979 +). The network meta-analysis comparison of diet plus exercise versus placebo incorporates indirect evidence about the treatment effect from related studies as well as direct evidence from five short-term studies (Roumen et al. 2008 ++, Ramachandran et al. 2006 ++, Kosaka et al. 2005 ++, Knowler et al. 2002 ++, Liao et al. 2002 +) and three medium-term studies (Lindahl et al. 2009 ++, Penn et al. 2009 ++, Lindstrom et al. 2006 ++).

Evidence statement 4:

Probability of treatment ranking

Probability of treatment ranking

The network meta-analysis of the short-term trials showed that, of all 12 interventions being compared, diet + exercise + 0.6 mg voglibose (daily) had the greatest probability of being the most effective intervention (probability=0.589) followed by diet + exercise + 20 mg pioglitazone (daily) (probability=0.324). When considering the evidence in the network meta-analysis about lifestyle interventions, diet + exercise had the greatest probability of being the most effective intervention (probability=0.900).

For the mid-term trials, the network meta-analysis showed that, of all interventions being compared, diet + 50mg phenformin had the greatest probability of being the most effective intervention (probability=0.345), followed by diet + exercise + up to 60mg nateglinide (3 times daily) (probability=0.338) and 50mg phenformin (probability=0.153). When considering the evidence in the network meta-analysis about lifestyle interventions, diet + exercise had the greatest probability of being the most effective intervention (probability=0.812).

There was insufficient evidence over the short and mid-term to suggest that age and BMI were treatment effect modifiers.

Evidence statement 5:

South Asian populations

For populations comprising of south Asian individuals (Asian Indian, Chinese, Japanese and Japanese Americans), both a diet combined with exercise intervention and oral diabetes drug interventions have an effect on the progression from IGT to diabetes. The diet and exercise lifestyle intervention seems to have more effect on the progression from IGT to diabetes (overall pooled effect of 0.58, 95% CI 0.47 – 0.73), than pharmacological interventions (overall pooled effect of 0.72, 95% CI 0.52 – 0.99).

The hazard ratio for diet combined with exercise intervention was based on five studies, one study in each of the following countries, US (Liao et al. 2002 +), Japan (Kosaka et al. 2005 ++), India (Ramachandran et al. 2006 ++) and two Chinese studies (Li et al. 1997 ++; Li et al. 2008 -).

For oral diabetes drugs, the hazard ration was based on four studies, one study each in the following countries, Japan (Kawamori et al. 2009 ++), India (Ramachandran et al. 2009 ++) and two Chinese studies (Li et al. 1999 ++; Pan et al 2003 ++).

Evidence statement 6:

Reduction in BMI

In the short-term (two to five years), both lifestyle intervention and pharmacological interventions, showed a greater reduction in BMI than control groups. Lifestyle interventions (range -1.3 to +0.8) had a smaller range effect on BMI than pharmacological interventions (range -1.6 to +1.4).

The changes in BMI in the diet intervention are based on one Australian study (Wein et al. 1999 -), and the diet combined with lifestyle interventions are based on four studies, one from each of the following countries, US (Liao et al. 2002 +), Finland (Lindstrom et al. 2003 ++), Netherlands (Roumen et al. 2008 ++) and Sweden (Lindahl et al. 2009 ++). The changes in BMI in pharmacological studies are based on four studies, one from each of the following countries China (Li et al. 1999 ++), India (Ramachandran et al. 2009 ++), US (DeFronzo et al 2011. +) and Finland (Eriksson et al. 2006 ++).

Evidence statement 7:

Weight change

In the short-term (two to five years), both lifestyle intervention and pharmacological interventions, showed a greater weight change than control groups. Lifestyle interventions appear to have a greater weight change (range -5.6 kg to +0.16 kg) than pharmacological interventions (range -2.9 kg to +3.8 kg).

The changes in weight in lifestyle interventions was based seven studies, one each from the following countries, Sweden (Lindhal et al. 2009 ++), Netherlands (Roumen et al. 2008 ++), Japan (Kosaka et al. 2005 ++), and two from each of the following countries, US (Knowler et al. 2002 ++; Liao et al. 2002 +) and Finland (Lindstrom et al. 2003 ++; Lindstrom et al. 2006 ++ ++).

The changes in weight in pharmacological interventions were based on nine studies, two multi-country studies (NAVIGATOR Study Group[a] 2010 ++, NAVIGATOR Study Group[b] 2010 ++), one from Canada/Europe (Chiasson et al. 2002 ++), US/Europe (Heymsfield et al. 2000 ++) , two US (Knowler et al. 2002 ++, DeFronzo et al. 2011 +), and one each from the following countries, Sweden, (Torgerson et al. 2004 ++), India (Ramachandran et al. 2009 ++) and China (Pan et al. 2003 ++).

Maintenance of the weight loss was mentioned briefly by three studies, with one Finnish study (Linstrom et al. 2003 ++), saying weight maintenance was satisfactory and two studies one Japanese (Kosaka et al. 2005 ++) and one Netherlands (Roumen et al. 2008 ++) saying weight decreased after one year but increased slightly afterwards.

Evidence statement 8:

Change in blood pressure

In the short-term (two to five years), both lifestyle and pharmacological interventions showed a slightly greater reduction in systolic blood pressure (a range of -10.0 to 4.4 mmHg, compared to a range of -4.3 to 5.5 mmHg) and diastolic blood pressure than control groups (a range of -6.2 to 2.0 mmHg, compared to a range of -4.0 to 3.6 mmHg).

In the long-term, based on one study with a 20-year follow-up, the diet and exercise intervention had a slightly smaller increase in systolic blood pressure than the control group (11 mmHg and 13 mmHg respectively) as well as having a slightly greater reduction in diastolic blood pressure than the control group (-7 mmHg and -5 mmHg respectively). However, this follow up is vastly different to the other studies in this review, and with a 20 year follow-up many of these participants would be well into in their 60s and therefore a rise in blood pressure would naturally be expected.

The changes in blood pressure in lifestyle interventions was based three studies, one Swedish (Lindahl et al. 2009 ++), one Chinese (Li et al. 2008 -) and one Netherlands (Roumen et al. 2008 ++). The changes in blood pressure in pharmacological interventions were based on seven studies, one from each of the following countries, Finland (Eriksson et al. 2006 ++), Sweden (Torgerson et al. 2004 ++), India (Ramachandran et al. 2009 ++), US (DeFronzo et al. 2011 +), two from China (Li et al 1999 ++; Pan et al. 2003 ++) and two multi-country study (NAVIGATOR Study Group[b] 2010 ++, NAVIGATOR Study Group[a] 2010 ++).

Evidence statement 9:

Change in blood glucose

In the short-term (two to six years), both lifestyle and pharmacological interventions tended to show a slightly greater reduction in fasting blood glucose and two hour glucose than control groups. In the long-term, based on one study with a 20-year follow-up, the diet and exercise intervention had a slightly smaller increase in both fasting blood glucose and two hour glucose than the control group.

For diet only and exercise only interventions, these were based on one Chinese study Pan et al. 1997 ++). The diet combined with exercise intervention was based on five studies, one each from the following countries, Netherlands (Roumen et al. 2008 ++), Sweden (Lindahl et al. 2009 ++), Finland (Lindstrom et al. 2003 ++) and two Chinese studies (Li et al. 2008 -; Pan et al. 1997 ++). The pharmacological interventions was based on six studies, one each from the following countries, US (DeFronzo et al. 2011 +) Sweden (Torgerson et al. 2004 ++), Finland (Eriksson et al. 2006 ++), China (Li et al 1999 ++), India (Ramachandran et al. 2009 ++) and one multi country study (NAVIGATOR Study Group[b] 2010 ++).

Evidence statement 10:

Change in waist circumference

Both lifestyle and pharmacological interventions tended to show a slightly greater reduction waist circumference than control groups.

The diet combined with exercise intervention was based on four studies, one each from the following countries, Netherlands (Roumen et al. 2008 ++), Sweden (Lindahl et al. 2009 ++), Finland (Lindstrom et al. 2003 ++) and India (Ramachandran et al. 2006 ++) The pharmacological interventions was based on one study, from Sweden (Torgerson et al. 2004 ++).

Evidence statement 11:

Change in cholesterol

For both lifestyle and pharmacological interventions there was mixed evidence on the change in cholesterol in the intervention groups and the control groups.

The diet combined with exercise intervention was based on three studies, one each from the following countries, Netherlands (Roumen et al. 2008 ++), Sweden (Lindahl et al. 2009 ++) and Finland (Lindstrom et al. 2003 ++). The pharmacological interventions was based on four studies, one each from the following countries, Sweden (Torgerson et al. 2004 ++), China (Pan et al. 2003 ++), US (DeFronzo et al. 2011 +) and Finland (Eriksson et al. 2006 ++).

3. INTRODUCTION

Type 2 diabetes is associated with significant clinical and social consequences. The National Institute for Health and Clinical Excellence has been asked by the Department of Health to develop public health guidance on the prevention of type 2 diabetes among high-risk groups. The referral is divided into two separate pieces of guidance. The first addresses the prevention of pre-diabetes (raised and impaired glucose levels) in populations and communities of high risk adults using community based interventions. The second piece of guidance addresses how to prevent the progression from pre-diabetes to type 2 diabetes. To inform development of this second piece of guidance, four reviews of international evidence will be carried out that address the prevention of progression to type 2 diabetes as well as a health economic / modelling review. The aim of this review was to update a previous systematic review and meta-analysis of published randomised controlled trials (RCTs) by investigating the effects of lifestyle, pharmacological and surgical (weight reduction) interventions to prevent or delay type 2 diabetes mellitus (T2DM) in people with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). Since that initial review (Gillies et al. 2007), further additional randomised controlled studies and longer term follow up data from the earlier trials have been published. The current systematic review by ScHARR was designed to include these new studies along with the previously included data and will include any studies missed by the initial review (Gillies et al. 2007). The effect of adding new data to the meta-analyses has been examined, comparing our results with the results in the initial review (Gillies et al. 2007).

Type 2 diabetes has a long preclinical phase, with the condition remaining undiagnosed for many years in a significant number of cases (Woolthius et al. 2007). A group of conditions defined by blood glucose levels that fall between normal and those defining type 2 diabetes are typically known as Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) or collectively as ‘pre-diabetes’. It is recognised that the term ‘pre-diabetes’ is not ideal, as not everyone with raised or impaired blood glucose levels will go on to develop type 2 diabetes. However, the term ‘pre-diabetes’ has been chosen because of its widespread use and recognition by a broad range of stakeholder groups and because of the lack of consensus on a suitable alternative.

The increase in obesity and type 2 diabetes may be attributed to changes in lifestyle over the past few decades that will likely continue in the foreseeable future. The loss of traditional dietary habits and the increasing consumption of unhealthy diets and

increasing portion sizes, together with less physical activity at work, home, and during leisure time, are strongly associated with an increase in diabetes. Lifestyle factors, such as diet and physical activity, are modifiable, and disease manifestation from these factors can be preventable. The World Health Organization describes obesity as one of the most blatantly visible, yet most neglected, public health problems and it threatens to overwhelm both developed and developing countries. Excess body weight is now the sixth most important risk factor contributing to the overall burden of disease worldwide (Ezzati et al. 2002). Sedentary lifestyle and being overweight has serious public health and economic consequences. It has been estimated that about 30% of new cases of obesity could be prevented by adopting a relatively active lifestyle, including more than 30 minutes of brisk walking daily and less than 10 hours of television viewing per week (Hu et al. 2003).

Risk factors for the development of diabetes include obesity, a family history of diabetes, physical inactivity, insulin resistance, hypertension, dyslipidemia, vascular disease, and polycystic ovary syndrome. Body mass index (BMI), expressed as weight (kilograms) divided by height (meters) squared, is often used to classify overweight (BMI>25) and obesity (BMI>30).

3.1 Description of the health problem

An individual's risk factors for pre-diabetes include: obesity (a BMI of more than 30 kg/m^2); a high waist circumference measurement (more than 80 cm in women and 94 cm in men); a sedentary lifestyle; a close family history of type 2 diabetes; a history of gestational diabetes in women; and being older than 40 (or older than 25 for some black and minority ethnic groups). In addition, certain groups of people are at greater overall risk of developing pre-diabetes, for example people of south Asian, African–Caribbean and black African descent. This means that waist circumference criteria can not be uniformly applicable to all populations and ethnic groups. The International Diabetes Federation (The Metabolic Syndrome Institute 2011) proposed a new definition of the metabolic syndrome and recommended using ethnic specific waist circumference cut-offs. Those proposed use criteria for Asian population groups that are substantially lower than those recommended for European populations, but that it implies the same risk of diabetes. With rates of obesity on the increase and the population becoming more sedentary (The Health and Social Care Information Centre 2009) type 2 diabetes and pre-diabetes are becoming more prevalent.

For many people, both pre-diabetes and type 2 diabetes can be prevented by being supported in changing lifestyle behaviours such as improving diet and increasing

physical activity levels (Tuomilehto et al. 2001). In some cases where these are not possible or have not been successful, certain relevant drug therapies and surgical procedures are available.

3.2 Aims and objectives

The aims of this review were to undertake an update of the initial review (Gillies et al. 2007) and where possible, conduct sub-group analysis.

The objectives of this current review were:

1. To update the searches carried out in the initial review and identify any relevant studies not included in the initial review;
2. To identify any additional effectiveness evidence from these studies;
3. To update the meta-analysis including additional data now available;
4. To explore the effect of study duration on risk reduction;
5. To conduct sub-group analysis, where data are available, for population subgroups for example, baseline age, ethnicity, socio-economic status or risk factors.

Following on from the searches undertaken by the initial review (Gillies et al. 2007) a search strategy which was based upon the initial review (Gillies et al. 2007), with some modifications, was adopted to identify additional papers to those identified in the searches of the initial review (Gillies et al. 2007). These revised searches by ScHARR used a wider number of databases for relevant evidence.

4. SEARCH STRATEGY

4.1 Methods for identification of evidence

The ScHARR review largely adopted the methods, including the inclusion criteria and meta-analysis methods used in the initial review (Gillies et al. 2007). As in that review, study selection was restricted to randomised controlled trials (RCTs). Studies were selected where an intervention had been applied with the aim of delaying or preventing T2DM in a sample or sub-sample of individuals with IGT or IFG. Development of T2DM is a required outcome measure. Trials selected for inclusion in the current review were included in the meta-analysis if they supplied sufficient data.

4.1.1 Search Strategy

The standard NICE Methods, as outlined in the Methods for the Development of NICE Public Health Guidance (2009) were used to guide the development of the search strategy. The aim of the search strategy was to retrieve the best available evidence to inform the effectiveness review and meta-analysis. The details of the search strategy are displayed in appendix 1.

The search strategy developed by Gillies et al. (2007) was used as a starting point in the development of the search strategy. The Gillies search strategy was modified to meet the need for a more sensitive search strategy (henceforth referred to as the ScHARR search strategy). These modifications are outlined below and in appendix 1.

The Gillies et al. (2007) search strategy combined terms for Type 2 diabetes with terms for prevention. This set of terms was then combined with a set of terms which were excluded from the review. Then this set was combined with terms for pre-diabetes. Finally, an RCT filter was applied to the results of the search to limit the search to randomised controlled trials.

The ScHARR search strategy combined terms for Type 2 diabetes (and diabetes) with terms for prevention. Then a search for pre-diabetes was developed. The diabetes prevention terms and the pre-diabetes terms were then combined with a set of terms to be excluded from the review. Finally, an RCT filter was applied to the results of the search to limit the search to randomised controlled trials.

The terms used in the ScHARR search strategy for diabetes and Type 2 diabetes were the terms that were tested and used successfully in the searches for Review One (identification of adults with pre-diabetes).

A smaller set of exclusion terms were included in the ScHARR review to be consistent with Review One and ensure that relevant papers were not excluded from the search

Both the ScHARR and the Gillies et al. (2007) search strategies included an RCT filter. As with any review, further scrutiny at the sifting stage ensured that any included papers fulfilled the criteria of being RCTs. Any other (non RCT) papers retrieved by a search were not included in the review.

Gillies et al. (2007) ran their search in three databases (Medline, Embase and the Cochrane Library). The ScHARR search strategy searched additional databases to those searched by Gillies et al. The databases selected were consistent with Review One and were as follows: Medline In Process and Other Non Indexed Citations and Medline 1950-Current via OVID SP, Embase via OVID SP, Cochrane Library (DARE, CENTRAL, HTA) via Wiley, CINAHL via EBSCO, BNI via OVID, Science and Social Science Citation Indices via Web of Knowledge, PsycINFO via OVID SP and EPPI Centre.

In addition to the database searches outlined above, we scrutinised reference lists, undertook cited reference searches of included papers and liaised with topic experts including from NICE and the PDG. The following sources were searched:

- **Grey Literature**: British Library Integrated Catalogue, Conference Papers Index, Medical Research Council and Economic and Social Research Council;
- **Websites**: Association of Public Health Observatories, NHS Evidence: National Library for Public Health, Joseph Rowntree Foundation, Diabetes UK; The Diabetes Research Network, Diabetes and Obesity Research Network (DORN), Scottish Diabetes Research Network, US Diabetes Prevention Program Outcomes Study (DPPOS) website , Diabetes Prevention Forum, International Diabetes Forum, Current Controlled Trials Register, EPPI Centre.

All database and additional searches were limited by date to 1990-2011.

The full details of the search terms used in the search strategy are included in this report for information, clarity, and consistency with Review One (appendix 1).

4.2 Study selection

All of the retrieved literature was screened by one of two reviewers (RJ and CF) and double-checked by one other reviewer at title and abstract level for relevance, and those relevant were taken through to full paper appraisal (see section 4.4 for full process details) Study inclusion and exclusion were based on the following:

4.2.1 Inclusion/exclusion criteria

The inclusion criteria were randomised controlled trials that considered populations, interventions, and outcomes as set out below:

- Population – people with pre-diabetes
- Intervention – lifestyle, drug, and surgical interventions.
- Outcomes – progression to diabetes

The exclusion criteria were:

- People younger than 18 years of age.
- People with a diagnosis of type 2 diabetes or other forms of diabetes.
- Pregnant women.

The criteria for pre-diabetes and diabetes are displayed in appendix 2.

4.3 Data Extraction

Data were extracted with no blinding to authors or journal. Data were extracted by one of two reviewers (RJ and CF) using a standardised form. As highlighted in the Cochrane Collaboration guidelines for systematic reviews of health promotion and public health interventions, extraction forms should be developed for each review in order to make them relevant to the information that is required. The forms for extracting data on diagnostic tools were based on the sample forms presented within the NICE public health guidance (2009a).

The forms were piloted on two randomly selected articles that assess identification and risk assessment strategies in order to confirm appropriateness for use. Information relating to the review question, study design, outcomes and conclusions were collated. The data extracted for effectiveness evidence included information relating to the intervention and comparator, sub-group analysis, mode of delivery, setting and population. Data extracted by each reviewer was checked by a second reviewer to ensure reliability. Any discrepancies were resolved by discussion.

4.4 Quality assessment

The initial review (Gillies et al. 2007) used the Jadad quality score (Jadad et al. 1996), also known as Jadad scoring or the Oxford quality scoring system, which is a

procedure to independently assess the methodological quality of a clinical trial. The score lies in the range 0-5. Studies are scored according to the presence of three key methodological features of randomization, blinding and accountability of all patients, including withdrawals. The basic Jadad Score was assessed based on the answer to the following questions.

Each *yes* would recieved a single point, each *no* received zero points; there were to be no fractional points. The maximum achievable score was 5.

The questions were as follows:

1 .Was the study described as randomised?

2. Was the study described as double blind?

3. Was there a description of withdrawals and dropouts?

To receive the corresponding point, an article should have describe the number of withdrawals and dropouts, in each of the study groups, and the underlying reasons. Additional points were given if:

The method of randomisation was described in the paper, and that method was appropriate.

The method of blinding was described, and it was appropriate.

However points would were deducted if:

The method of randomisation was described, but was inappropriate.

The method of blinding was described, but was inappropriate.

The range of score quality is, 0–2 Low and 3–5 High.

All studies, both those used in the initial review (Gillies et al. 2007) and those identified for this review were graded with ++, + or – as recommended by NICE (see Table 1). For consistency, the quality of randomised controlled trials were also assessed using the same Jadad quality score (Jadad et al. 1996). Greater consideration was given to the performance of the study on criteria fundamental to the robustness of the findings. Study quality did not determine inclusion into or exclusion from the review. Quality assessment was confirmed by a second reviewer in order to minimise any potential bias.

The NICE checklist for quantitative studies contained the following items:

1. Is the source population or source area well described?

2. Is the eligible population or area representative of the source population or area?

3. Do the selected participants or areas represent the eligible population or area?

4. How was selection bias minimised?

5. Were interventions (and comparisons) well described and appropriate?

6. Was the allocation concealed?

7. Were participants and/or investigators blind to exposure and comparison?

8. Was the exposure to intervention and comparison adequate?

9. Was contamination acceptably low?

10. Where the other interventions similar in both groups?

11. Were all participants accounted for at study conclusion?

12. Did the setting reflect usual UK practice?

13 Did the intervention or control comparison reflect usual practice?

14. Were outcomes measures reliable?

15. Were all outcome measurements complete?

16. Were all the important outcomes assessed?

17. Were all outcomes relevant?

18. Were there similar follow up times in exposure and comparison groups?

19. Was follow-up time meaningful?

20. Were exposure and comparison groups similar at baseline?

21. Was intention to treat (ITT) analysis conducted?

22. Was the study sufficiently powered to detect an intervention effect (if one exists)?

23. Were the estimates of effect size given or calculable?

24. Were the analytical methods appropriate?

25. Was the precision of intervention effects given or calculable? Were they meaningful?

26. Are the study results internally valid (i.e. unbiased)?

27. Are the findings generalisable to the source population (i.e. externally valid)?

These criteria are then used to generate the grade shown in table 1.

Table 1: Study quality (using NICE methodology)

Grade	Criteria
++	All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions are thought very unlikely to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or adequately described are thought unlikely to alter the conclusions.
–	Few or no criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter.

4.5 Data analysis and synthesis

The meta-analyses by Gillies et al. (2007) were conducted using a log hazard ratio scale. A random effects meta-analyses model was used to allow for heterogeneity between studies. In the random effects model, the studies were assumed to estimate different underlying effect sizes due to differences between studies. The pooled hazard ratios for progression to diabetes from the meta-analyses were used, together with the pooled hazards of developing type 2 diabetes from the control arms of the trials, under the assumption of a constant hazard. For trials that did not report the necessary data, the reported data was transformed and estimated.

The initial review (Gillies et al. 2007) examined lifestyle, comprising diet and exercise interventions, or pharmacological and herbal interventions. In this review, lifestyle (comprising diet and exercise interventions), pharmacological, and herbal, and surgical interventions were examined. While the intent of this current review was to review studies examining the effect of surgical interventions on the progress to type 2 diabetes, the ScHARR search strategy identified no such studies for inclusion in the current review.

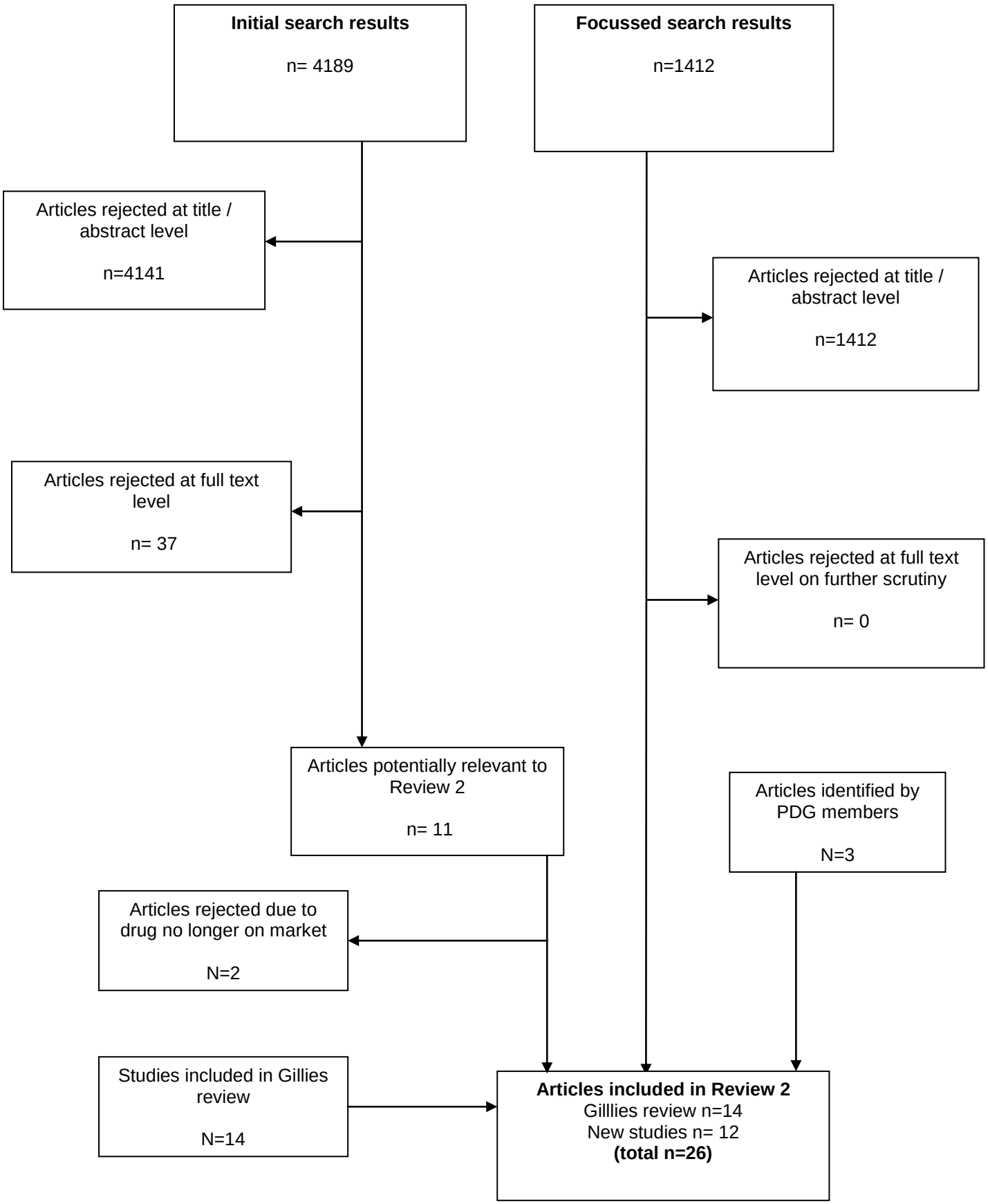
All the interventions were examined for sub-group data and, where there the data were available, the potential for analysis by sub-group. This allowed the current systematic review to examine (where possible) the effectiveness of the interventions in specific sub groups, such as ethnic minorities, socially deprived groups etc; while the baseline analysis replicated the methods used in the Gillies study.

In addition, this review examined the impact of study duration and the assumption that the relative hazards are constant. If possible, additional meta-analyses that account for these issues by incorporating relevant additional variables in the model will be undertaken. The current review used Review Manager statistical software for the meta-analyses.

Clare Gillies kindly provided the original data used for the meta-analysis in the initial review (Gillies et al. 2007) and was used, as appropriate, in the current review.

5. RESULTS

Figure 1: Flow chart of paper selection



5.1 Included studies from Gillies et al. review

From the initial review (Gillies et al. 2007) there were 21 studies (see appendix 3), of which 17 were included in the meta-analysis, these are shown in bold in appendix 3. Three of these 17 studies (Tao et al. 2004, Fang et al. 2004, Fan et al. 2004) were foreign languages studies. As it was not possible to obtain translation of these papers for data extraction and quality assessment these papers were excluded from this review, leaving 14 studies from the initial review to include the current review.

5.2 Included studies additional to Gillies et al. review

From an initial total of 5,601 references, 48 were examined at full paper stage with 37 being excluded (see appendix 4 for details), leaving a total of eleven papers of varying quality that met the inclusion criteria for the current review (appendix 5). Although studies on surgical interventions were searched for, none was found that could be included in this review. As phenformin was withdrawn from most markets in the late 1970s due to a high risk of lactic acidosis, the data from the Jarrett study (Jarrett et al. 1979 +) on phenformin have not been included in any of the updated pharmacological intervention meta-analyses, although the information on the diet arms have been included. Of the remaining papers, there were six additional papers published after the initial review and three papers detailing additional follow-up data, and updated data from these studies (Li et al. 2008 -; Lindstrom et al. 2006 ++ and Diabetes Prevention Program Research Group 2009 ++) have been used to replace the original data. A further three papers were identified by PDG members, along with the included papers from the initial review, in total there were 26 papers identified for the current review. Fourteen of these papers were from the initial review (Gillies et al. 2007). For each of these studies, a calculated hazard ratio was used in the production of further meta-analyses (see appendix 6). As some of the results originally reported in the initial review (Gillies et al. 2007) are replaced with longer term data there is a risk of under reporting the effect of the initial intervention.

The DREAM study examining rosiglitazone was not included in the main analysis, as this drug was withdrawn from clinical use in the UK following concerns over excess cardiovascular risks. However for completeness appendix 7 displays the results from this study and a discussion.

5.2.1 Quality assessment

The quality of papers was on the whole very good, with 21 papers were rated as very good (++), three as good (+) and two as poor (-) using the NICE quality assessment criteria checklist. Of the papers in the initial review (Gillies et al.), 11 were rated as very good (++), two as good (+) and one as poor (-) using the NICE checklist.

When using the Jadad quality score (Jadad et al. 1996), which allocates randomised controlled trials a score of between zero (very poor) and five (rigorous) points, two studies scored 4 points, eight studies scored 3 points, 12 studies scored 2 points and four studies scored 1 point. Of the papers in the initial review (Gillies et al. 2007), one study scored 4 points, five studies scored 3 points, seven studies scored 2 points and one study scored 1 point, see table 2.

There may appear to be some discrepancies between the Jadad score allocated by Gillies and those by the current review team, and between the Jadad score and the NICE checklist score, for example, the studies scoring 1 on the Jadad score scored ++ when using the NICE quality assessment checklist. It must be acknowledged that the Jadad score is not a perfect instrument. For example, the Jadad score places greater emphasis on the quality of reporting as opposed to the actual methodological quality of a trial. In addition, it does not assess allocation concealment. The Jadad score does has relative merit as it uses a simple and easy to understand approach that incorporates the most important individual components of methodological quality. There is ample justification for using the Jadad score to evaluate the quality of a RCT, but this may need to be supplemented by the use of another quality assessment tool.

Table 2: Quality assessment of included studies

Study	Jadad score (Gillies)	Jadad score	NICE score
Jarrett 1979	3	-	+
Da Qing 1997	2	-	++
Li 1999	3	-	++
Wein 1999	2	-	-
Heymsfield 2000	2	-	++
DPP 2002	2	-	++
Liao 2002	2	-	+
STOP-NIDDM 2002	3	-	++
DPS 2003	1	-	++
Pan 2003	3	-	++
Torgerson 2004	3	-	++
Kosaka 2005	2	-	++
Erkisson 2006	4	-	++
IDPP 2006	2	-	++
DPP 2009	-	2	++
DPS (Lindstrom) 2006	-	1	++
Da Qing (Li) 2008	-	2	-
DREAM (ramipril) 2006	-	3	++
Roumen 2008	-	2	++
Kawamori 2009	-	4	++
Penn 2009	-	2	++
Ramachandran 2009	-	1	++
Lindahl 2009	-	1	++
NAVIGATOR (Valsartan) 2010	-	3	++
NAVIGATOR (Nateglinide) 2010	-	3	++
DeFronzo 2011	-	2	+

5.2.2 Lifestyle interventions

Lifestyle trials – diet and physical activity

There were 14 interventions (eight from the initial review, three updated studies from the initial review, and three new studies) examining diet and physical activity lifestyle changes. Table 3 gives a brief description of the study populations and interventions and additional details for each study is presented in the text of this section. Data on the study were extracted for the primary outcome of interest (progression from IGT to diabetes), and where reported, for secondary outcomes (changes in BMI/weight, etc); a full evidence table is given in appendix 8.

Table 3: Characteristics of studies on lifestyle interventions

Author	Country	Populations	Interventions
Jarrett 1979	UK	N=204, all males with impaired glucose tolerance.	The men were randomly allocated to one of four groups. Group 1 was recommended 120g/day carbohydrate diet + placebo capsule. Group 2 recommended to 'limit sucrose (i. e. table sugar) intake' + placebo capsule. Group 3 recommended 120g/day carbohydrate diet + 50mg. phenformin S. A. once daily. Group 4 recommended to 'limit sucrose intake' and 50 mg phenformin S. A. once daily.
Da Qing 1997	China	N=577 Chinese individuals with IGT were recruited and 530 completed the study.	Diet group - In clinics assigned to the diet-only intervention, participants with BMI <25 were prescribed a diet containing 25-30 kcal/kg body wt (105-126 kJ/kg), 55-65% carbohydrate, 10-15% protein, and 25-30% fat. These participants were encouraged to consume more vegetables, control their intake of alcohol, and reduce their intake of simple sugars. Exercise group. - Participants in clinics assigned to the exercise group were taught and encouraged to increase the amount of their leisure physical exercise by at least one unit per day (such as slow walking for 30 minutes, fast walking for 20 minutes etc) and by two units per day if possible Diet-plus-exercise group - Participants from clinics assigned to this group received instructions and counselling for both diet and exercise interventions that were similar to those for the diet-only and the exercise-only intervention groups Subjects from clinics assigned to the control group were exposed to general information about diabetes and IGT. Clinic physicians also dispensed informational brochures with general instructions for diet and/or increased leisure physical activities to control group subjects, but no individual instruction or formal group counselling sessions were conducted.
Wein 1999	Australia	N=200, all women with impaired glucose tolerance.	All participants were reminded of the need for regular exercise (e.g. brisk walking for 30 minutes three times per week). The control group were given dietary questionnaires and the standard diet advice sheet ('TARGET ON HEALTHY EATING' recommended by the Health Department Foundation and the Food and Nutrition Project). The intervention group was given the same dietary advice and telephone contact with the dietician was arranged three-monthly.

Author	Country	Populations	Interventions
Diabetes Prevention Program (DPP) 2002	US	N=3,234, people with elevated fasting and post-load plasma glucose concentrations were eligible for inclusion.	Metformin at a dose of 850 mg taken orally once a day for first month then increased to 850 mg twice a day, placebo, or a lifestyle intervention, where participants were encouraged to follow a food guide to reduce their weight and increase their physical activity. Self-reported levels of leisure physical activity were assessed annually using a Modifiable Activity Questionnaire.
Liao 2002	US	N=64, All participants were of full Japanese ancestry.	Endurance exercise training and a dietary prescription for the intervention group. Stretching exercises three times a week for one hour for the control group.
Diabetes Prevention Study (DPS) 2003	Finland	N= 522 (172 men and 350 women) with IGT. All were middle-aged (40–64 years) and overweight (BMI>25 kg/m2) at baseline.	For the participants in the control group the lifestyle advice was given as 'standard care counselling' at baseline. The participants in the intensive intervention group were given individualised, detailed dietary counselling, with seven sessions during the first year and every 3 months thereafter.
Kosaka 2005	Japan	N= 458, all males (356 control, 102 intervention), with a mean BMI of 23.8 in the control group and 24.0 in the intervention group.	The subjects in the control group and in the intervention group were advised to maintain a BMI of <24.0 kg/m2 and of <22.0 kg/m2, respectively, by diet and exercise. In the intervention group, detailed instructions on lifestyle were repeated every three to four months during hospital visits.
Ramachandran (IDPP) 2006	India	N= 531 (420 males).	Group 1 was the control, Group 2 was given advice on lifestyle modification (LSM), Group 3 was treated with metformin (MET) and Group 4 was given LSM plus MET.
Lindstrom (DPS update) 2006	Finland	N=522 (172 males) with a mean age of 55 years. The mean BMI was 31.4 in the intervention group and 31.1 in the control group.	The participants in the intervention group were given detailed and individualised counselling to achieve the lifestyle goals. They had seven personal counselling sessions with the study nutritionist during the first year and every 3 months thereafter. The participants in the control group were given general verbal and written health behaviour information at baseline without specific individualised advice
Roumen (SLIM study) 2008	Netherlands	N= 147 (58 males) with a mean age of 54.2 years in the intervention group and 58.4 years in the control group. The mean BMI was 29.6 in the intervention group and 29.2 in the control group.	The intervention programme consisted of a dietary and physical activity part. Dietary recommendations were based on the Dutch guidelines for a healthy diet (Dutch Nutrition Council). Control subjects were only briefly informed about the beneficial effects of a healthy diet and physical activity, whereas no individual advice was provided.
Penn 2009	UK	N= 102 (41 males), with a mean age of 56.8 years in the intervention group and 57.4 years in the control group. The mean BMI was 34.1 in the intervention group and 33.5 in the control group.	Study participants were randomised to an intervention of intensive behavioural interventions to promote dietary modification and increased physical activity or to a minimal intervention control group.

Author	Country	Populations	Interventions
Li 2008	China	N= 577 Chinese with impaired glucose tolerance, were randomised into either a control group or one of three lifestyle interventions: diet, exercise, or diet plus exercise.	The aim of the diet intervention was to increase participants' vegetable intake and lower their alcohol and sugar intake. Those who were overweight or obese were also encouraged to lose weight by reducing their total calorie intake. The aim of the exercise intervention was to increase leisure time physical activity.
Diabetes Prevention Program Research Group 2009	US	N= 3234 (68% women, 45% from ethnic and racial minority groups, and 20% aged 60 years or older) with impaired glucose tolerance.	Participants were randomised to one of three interventions: intensive lifestyle (aimed to help participants to achieve and maintain 7% weight loss and 150 minutes or more per week of moderate-intensity physical activity); metformin or placebo.
Lindahl 2009	Sweden	N= 301 (58 males). The mean age was 52.2 years in the intervention group and 53.5 years in the control group, the mean BMI was 31.2in the intervention group and 30.2 in the control group	The intensive intervention group was divided into two halves, and 50 individuals were simultaneously admitted on each occasion. This residential programme was implemented during a 1-month stay with full boarding at Sorsele (n=20) and Vindeln (n=30) wellness centres, owned by the Vasterbotten County Council. The intervention programme included approximately 140 hours of scheduled activities. Aerobic physical activity of moderate intensity was performed daily for 2.5 hours, e.g. brisk walks, gymnastics, bicycling, and swimming. For the control group, a health survey was performed, including a physical examination, a 2-h OGTT, and blood sampling. The survey was followed by a 30–60-min counselling session, where the participants were given both oral and written advice.

Jarrett Study 1979

In the Jarrett study (Jarrett et al. 1979 +), 204 males with IGT were randomly allocated to one of four groups. Group 1 was recommended 120g/day carbohydrate diet + placebo capsule. Group 2 was recommended to 'limit sucrose (i. e. table sugar) intake' + placebo capsule. Group 3 was recommended 120g/day carbohydrate diet + 50mg. phenformin S. A. once daily. Group 4 was recommended to 'limit sucrose intake' and 50 mg phenformin S. A. once daily. The authors stated that the interventions ran for five years and the primary outcome of the study was severe or sustained worsening of glucose tolerance. The study reported that 13.3% (6/45) of group 2, 18.4% (9/49) of group 4, 18.2% (8/44) in group 1 and 9.3% (4/43) in group 2 develop diabetes.

Da Qing Study 1979

In the Da Qing study (Pan et al. 1997 ++), 577 subjects with IGT as defined by the WHO criteria were randomised into diet-only, exercise only, diet plus exercise groups, and a control group over a 6-year period. The primary outcome was the incidence of diabetes. Among individual subjects in the control group, the incidence of diabetes was 15.7 per 100 person-years (95% CI, 12.7-18.7%). In each of the three intervention groups, the incidence of diabetes was significantly lower than in the control group (10.0 [95% CI, 7.5-12.5], 8.3 [6.4-10.3], and 9.6 [7.2-12.0] per 100 person-years in the diet, exercise, and diet-plus-exercise groups, respectively) ($p< 0.05$ for all). Incidence rates did not differ significantly among the three intervention groups ($p> 0.05$). (The actual number of cases of diabetes by group was 57 out of 130 participants in the diet group, 58 out of 141 participants in the exercise group, 58 out of 126 participants in the diet & exercise group, and 90 out of 133 participants in the control group.)

Wein Study 1999

The Australian study by Wein recruited women with IGT who were then encouraged to follow a healthy diet and increase their exercise level (Wein et al.1999). During the period November 1989 to July 199I, all women who were diagnosed as having IGT and who could communicate directly or through translation were randomised to one of two forms of intervention. The study was continued until 100 women were enrolled in each arm of the study, the authors reported that the trial ran over a period of about four years. The control group were given dietary questionnaires and a standard diet advice sheet. The group randomised to the intervention group was given the same dietary advice but, in addition, telephone contact with the dietician was arranged three-monthly. The primary outcome was progression to diabetes. The authors reported that there were 796.4 women-years of follow-up, with diabetes being diagnosed in 53 women, giving an overall incidence of diabetes of 6.7 cases per 100 women-years. At the final follow-up test, after a median length of follow-up of 51 months, there was no significant difference between the intervention and control groups in the prevalence of diabetes (26/97 [26.8%] intervention group, 27/96 [28.1%] control group). However the intervention group had a significantly longer median length of follow-up than the control group, 58.6 months (range 11.7 to 81 .1) versus 47.9 (range 7.1 to 78.0), $p = 0.021$. Because of this longer follow-up, the intervention group had more opportunity to develop diabetes, and so a comparison of

the annual rates of conversion to diabetes was made. The annual incidence rates of diabetes mellitus for the 2 groups were 6.1 % (intervention) and 7.3% (control), an incident rate ratio of 0.83, with a 95% confidence interval of 0.47- 1.48, p ~0.50.

Diabetes Prevention Program (DPP) Study 2002

The Diabetes Prevention Program (DPP) study was a double-blind randomized controlled trial involving a larger number of subjects, 3234 with IGT or IFG with BMI >24 kg/m^2 (>22 in Asian population) and ran for three years, 1996 to 1999 (Knowler et al. 2002 ++). They were randomised to standard lifestyle recommendations with placebo or with metformin or to an intensive program of lifestyle modifications. The primary outcome was diabetes, diagnosed on the basis of an annual oral glucose tolerance test or a semi-annual fasting plasma glucose test. The incidence of diabetes was 11.0 cases per 100 person years in placebo group, 7.8 cases per 100 person years in metformin group, and 4.8 cases per 100 person years in the lifestyle group. Lifestyle interventions reduced the incidence of diabetes by 58% (95% CI 48%-66%) and metformin by 31% (95% CI 17%-43%) compared to placebo, with the lifestyle intervention being more effective than metformin. The estimated cumulative incidence of diabetes at three years was 28.9% in the placebo group, 21.7% in the metformin group and 14.4% in the lifestyle intervention group.

Liao Study 2002

The Liao study (Liao et al. 2002 +) recruited 64 participants (29 males, 35 females) with IGT, all of whom were of full Japanese ancestry. Each participant was assigned to the treatment or control group using adaptive randomisation. The treatment group received endurance exercise training and a dietary prescription, while the control group performed stretching exercises three times a week for one hour (each session under staff supervision) and were prescribed an isocaloric diet. An isocaloric diet is one in which you consume similar caloric amounts of proteins, carbohydrates and fats. After six months, all participants were simply instructed to continue their prescribed diet and exercise for an additional 18 months, the study follow-up ran for 24 months in total and the primary outcome was glucose tolerance. At 12 months, one person from the intervention group had diabetes (1/32, 3.1%), and two from the control group had diabetes (2/32, 6.3%), no further results were available as the study was not designed to demonstrate prevention of diabetes.

Diabetes Prevention Study (DPS) 2003

The Finnish Diabetes Prevention Study (DPS) randomised 522 overweight (average BMI 31) middle-aged individuals to either intensive lifestyle modification or a control group (Lindstrom et al. 2003 ++). The intervention group had both specific dietary recommendations and exercise guidelines, including a weight-loss goal of 5% of total body weight and at least 30 minutes per day of combined aerobic activity and resistance training. Primary outcome was the incidence of diabetes. The first subject was assigned to a group in November 1993 and the last in June 1998. At that time, 90 percent of the study subjects had been enrolled in the trial for at least 2 years, the trial was prematurely terminated in March 2000 by an independent end point committee, as the incidence of diabetes in the intervention group was highly significantly lower than in the control group. During the first three years of the study, 22 subjects (9%) in the intervention group and 51 (20%) in the control group developed diabetes (p= 0.0001, χ^2 test).

Kosaka Study 2005

The study by Kosaka (Kosaka et al. 2005 ++) recruited 458 male subjects with IGT from health-screening examinees and these were randomly assigned in a 4:1 ratio to a standard intervention group (control group) and intensive intervention group (intervention group). The final numbers of subjects were 356 and 102, respectively. The subjects in the control group and in the intervention group were advised to maintain body mass index (BMI) of <24.0 kg/m2 and of <22.0 kg/m2, respectively, by diet and exercise. In the intervention group, detailed instructions on lifestyle were repeated every 3–4 months during hospital visits for a period of four years. The primary outcome in this study was the incidence of type 2 diabetes. The cumulative incidence of diabetes in the intervention group during the 4 years was 3.0% (3/102), and in the control group it was 9.3% (33/356)

Ramachandran Study 2006

The Indian Diabetes Prevention Programme (IDPP) study (Ramachandran et al. 2006 ++) recruited 531 subjects with IGT from the middle-class population working in service organisations and also from their families. They were identified by work-place announcements and circulars. These were non-diabetic subjects with no major

illness aged 35–55 years and of both sexes, and were screened from March 2001 to July 2002. The participants were randomised to one of four groups: Group 1 participants were given standard health care advice (control), Group 2 participants followed lifestyle modification (LSM), Group 3 participants were treated with metformin (MET), and Group 4 participants were given LSM plus MET. All participants underwent annual reviews for three years, and the primary outcome measure was type 2 diabetes. At the end of three years, 44.4% of 502 participants had developed diabetes, group 1 (control) 55% (n=133), group 2 (LSM) 39.3% (n=120), group3 (MET) 40.5% (n=128) and group 4 (LSM + MET) 39.5% (n=121).

Lindstrom Study 2006

In the follow-up of the Finnish Diabetes Prevention Study, the extent to which the originally-achieved lifestyle changes and risk reduction remain after discontinuation of active counselling was assessed (Lindstrom et al. 2006 ++). In this follow-up, overweight, middle-aged adults with impaired glucose tolerance were randomly assigned to intensive lifestyle intervention or control group. After a median of 4 years of active intervention period, participants who were still free of diabetes were further followed up for a median of 3 years, with median total follow-up of 7 years. Diabetes incidence, bodyweight, physical activity, and dietary intakes of fat, saturated fat, and fibre were measured. The total number of cases of diabetes diagnosed during the overall follow-up of seven years was 75 in the intervention group and 110 in the control group. The incidence rates were 4.3 (95% CI 3.4–5.4) and 7.4 (6.1–8.9) per 100 person-years in the intervention and control group, respectively (p=0.0001 log-rank test). The corresponding hazard ratio was 0.57 (0.43–0.76). The cumulative incidence of diabetes at year 6 was 23% in the intervention group and 38% in the control group, with an absolute risk reduction of 15% (7.2–23.2). The number of people needed to be treated to prevent one case of type 2 diabetes by lifestyle intervention was 22 for one year.

Roumen Study 2008

The Study on Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM) study (Roumen et al. 2008 ++) was a randomized controlled lifestyle intervention over 3 years. The aim of the study was to investigate the impact of the lifestyle intervention on glucose homeostasis after an oral glucose tolerance test (OGTT) in IGT subjects. A total of 147 subjects with IGT (75 male, 72 female) were randomized

to the intervention (INT) group or control (CON) group; 106 subjects (52 INT, 54 CON) completed 3 years of intervention. Annually, glucose, insulin and free fatty acid (FFA) concentrations were determined both fasting and after an oral glucose tolerance test. Measurements of body weight, serum lipids, blood pressure, and maximal aerobic capacity were also performed. In the analysis of the subjects who completed the full 3 years of the study, the cumulative incidence of diabetes was 18% (8/44) in the intervention group and 38% (18/47) in the control group. The p-value of the log-rank test was 0.025, and the relative risk was 0.42 [95% confidence interval (CI) 0.18–0.96]. In the intention-to-treat analysis, the cumulative incidence of diabetes in the intervention group was 18% (11/61) compared with 32% (19/60) in the control group. The p-value from the log-rank test was 0.07 and the relative risk 0.52 (95% CI 0.25–1.10).

Penn Study 2009

The European Diabetes Prevention Study (EDIPS) extends the Finnish Diabetes Prevention Study (DPS) to different European populations, using the same study design (Penn et al. 2009 ++). In the Newcastle arm of this study (EDIPS-Newcastle), 102 participants (42 men and 60 women, mean age 57 years, mean BMI 34 kg/m^2) with IGT were recruited and randomised to 'intervention' and 'usual care control' groups. The intervention included individual motivational interviewing aimed at: weight reduction, increase in physical activity, fibre and carbohydrate intake and reduction of fat intake (secondary outcomes) and was planned to last for up to five years. The primary outcome was diagnosis of T2D. T2D was diagnosed in a total of 16 participants (I = 5, C = 11). The absolute incidence of T2D was 32.7 (95% CI: 10.7 to 74.6) per 1000 person years of follow-up in the intervention group, and 67.1 (95% CI: 34.2 to 117.5) per 1000 person years of follow-up in the control group. The relative risk of T2D in the intervention group, compared with the control group was 0.45 (95% CI: 0.2 to 1.2). After year two of follow-up, there were no further incidences of T2D in the Intervention group, and overall the cumulative incidence of diabetes was 55% less in the intervention group compared with the control group.

Li Study 2008

The China Da Qing Diabetes Prevention Study (CDQDPS) was the first large-scale trial to examine the effect of different lifestyle interventions in a group setting among Chinese people with impaired glucose tolerance (Li et al. 2008). In 1986, 577 adults

with impaired glucose tolerance from 33 clinics in China were randomly assigned to either the control group, or to one of three lifestyle intervention groups (diet, exercise, or diet plus exercise). Active intervention took place over 6 years until 1992. In 2006, study participants were followed-up to assess the long-term effect of the interventions. The primary outcomes were diabetes incidence, CVD incidence and mortality, and all-cause mortality. Of the 577 participants in 1986, 435 had developed diabetes by the end of a 6-year follow-up. 265 cases were identified by oral glucose tolerance tests during the active intervention phase, 145 were identified by report from the patient or relative, with additional evidence of either use of hypoglycaemic medication or raised glucose level recorded in the medical record at time of diagnosis during the post-intervention period. Finally, 25 cases were identified by oral glucose tolerance tests at the end of the study. The diabetes status of 14 participants was unknown. During the active intervention, the cumulative diabetes incidence was 43% in the intervention group and 66% in the control group, and the number needed to treat to prevent a case of diabetes was five people. During the 20 year follow-up, the cumulative diabetes incidence was 80% in the intervention group and 93% in the control group, and the authors stated that the number needed to treat to prevent a case of diabetes was six people. Participants in the intervention group had an average of 3.6 fewer years with diabetes. In people with diabetes, comparing the active intervention group to the controls at the end of follow-up, fewer were on insulin (26% [82 of 314] vs. 34% [41 of 121]) and they had lower average haemoglobin A1c levels (7.34% vs. 7.76%), but these differences were not significant (p=0.11 and p=0.07, respectively).

Diabetes Prevention Program Research Group Study 2009

The Diabetes Prevention Program Outcomes Study (DPPOS) was a long-term follow-up of the DPP to investigate whether the delay in development of diabetes seen during the DPP can be sustained, and to assess long-term effects of the interventions on health (Diabetes Prevention Program Research Group 2009 ++). In this follow-up, the intervention effects on diabetes incidence, weight change, and cardiovascular disease risk factors and their treatment during 10 years of follow-up since DPP randomisation are reported. In this follow-up, overweight, middle-aged adults with impaired glucose tolerance were randomly assigned to intensive lifestyle intervention or control group. After a median of four years of active intervention period, participants who were still free of diabetes were further followed up for a median of three years, with median total follow-up of seven years. Diabetes

incidence, bodyweight, physical activity, and dietary intakes of fat, saturated fat, and fibre were measured. During the Diabetes Prevention Program Outcomes Study (DPPOS), diabetes incidence rates did not significantly differ between groups. Incidence rates were stable in the lifestyle group, but fell in the placebo and metformin groups during the DPPOS. During the combined DPP, bridge, and DPPOS periods, the incidence rate of the lifestyle group was reduced by 34% (95% CI 24–42) and metformin by 18% (7–28) compared with placebo. The lifestyle effect was greatest in participants aged 60–85 years at randomisation (49% rate reduction), in whom metformin had no significant effect. The median delay to onset of diabetes was approximately four years by lifestyle and two years by metformin, compared with placebo. At the most recent yearly examination, 23% in the lifestyle, 19% in the metformin, and 19% of participants in the placebo groups had become normoglycaemic by criteria defined and reported previously (fasting glucose <6.1 mmol/L, 2-h glucose <7.8 mmol/L, and no previous diagnosis of diabetes.

Lindahl Study 2009

Since 1985, there has been an ongoing community intervention programme on CVD and diabetes in the province of Vasterbotten in northern Sweden – the Vasterbotten Intervention Programme (VIP). Subjects who fulfilled the inclusion criteria of the VIP were invited by mail to participate in a randomized clinical trial. This study was the randomized lifestyle intervention trial conducted in northern Sweden for five years between 1995 and 2000 (Lindahl et al. 2009 ++), in 168 individuals with IGT and body mass index above 27 at start. The intensive intervention group (n=83) was subjected to a 1-month residential lifestyle programme. The usual care group (n=85) participated in a health examination ending with a single counselling session. Follow-up was conducted at 1, 3, and 5 years. In addition to the on-treatment analysis, a complementary intention-to-treat (ITT) analysis was created by imputation of missing values in subjects still on treatment as well as in dropouts. At the first year follow-up, five subjects in the intensive intervention group and 20 in the usual care group developed diabetes (7% vs. 25%, p=0.003). The relative risk reduction between groups was 70%. At 3-year follow-up, 12 (17%) vs. 20 (25%) new cases were discovered. The relative risk reduction was 40%. At 5-year follow-up, there were 17 (24%) vs. 23 (29%) new cases. The relative risk reduction was 25%. The risk reductions at 3 and 5 years were not significant.

Meta-analysis

The log hazard ratios (HR) and their standard error (SE) were calculated from the data in the initial review (Gillies et al. 2007), and were used to produce a meta-analysis of lifestyle interventions (in figure 2). The data from the review were analysed in Review Manager and a random effects model was used (as in the initial review). In the initial review Gillies et al. 2007 presented data from four foreign language papers (Fan et al. 2004; Fang et al. 2004; Tao et al. 2004 and Sakane et al.). As it was not possible to obtain a translated version of these papers, they were exclude from this review because without a full translation of the papers it was not possible to do a full data extraction or a quality assessment. Figure 3 displays the meta-analysis of lifestyle interventions using data from the initial review (Gillies et al. 2007). The removal of the foreign language papers did not affect the overall pooled effect for the prevention of type 2 diabetes, with both meta-analysis having an overall HR of 0.51 (95% CI 0.44 – 0.60).

Figure 2: Replication of Gillies meta-analysis of lifestyle interventions

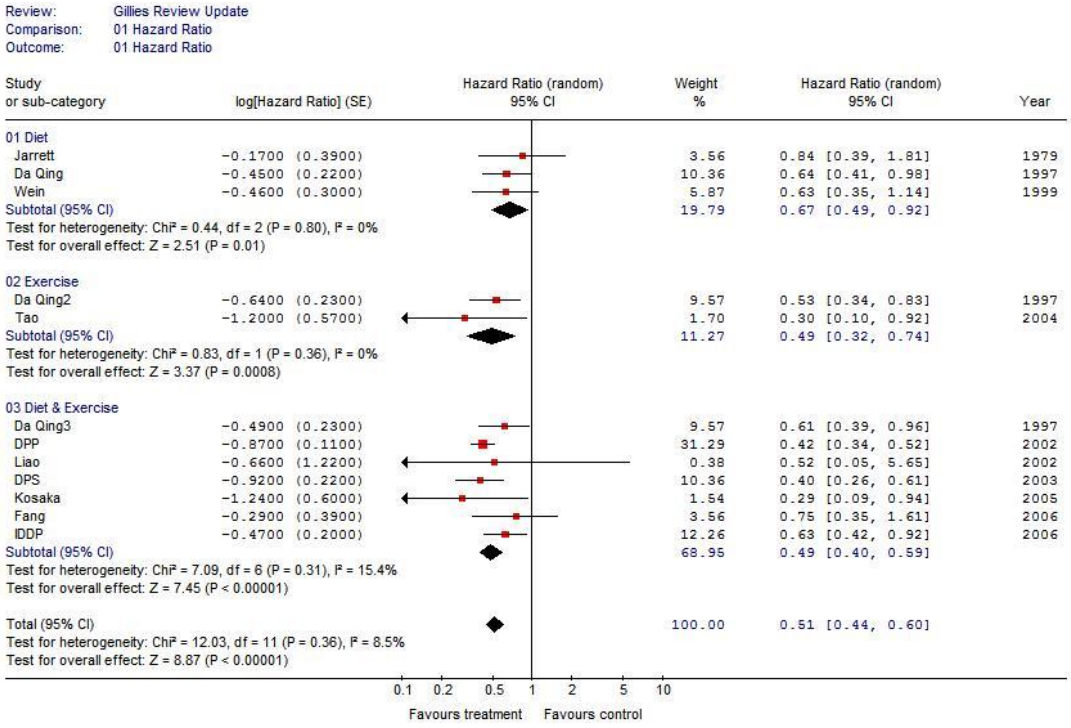
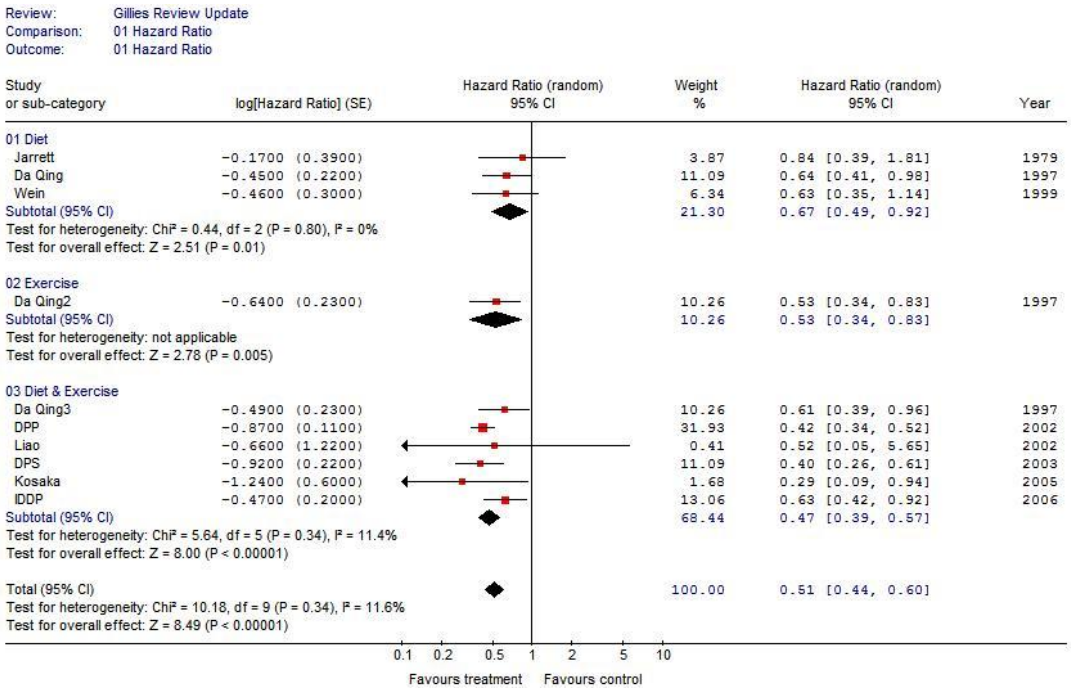


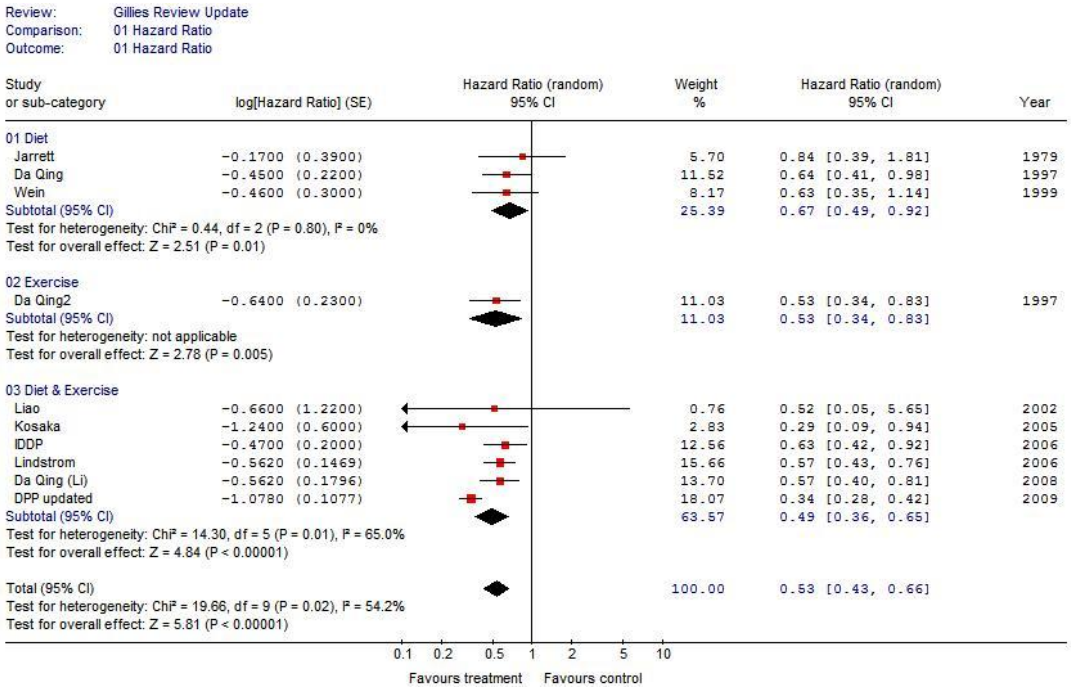
Figure 3: Gillies meta-analysis of lifestyle interventions without foreign language studies



For lifestyle interventions, there were three studies (DPS – Lindstrom et al. 2003; Da Qing - Pan et al. 1997 ++; DPP - Knowler et al. 2002 ++) with longer-term follow-up reported. The Da Qing study published data on a 20 year follow-up (Li et al. 2008) and the DPP published data on a ten year follow-up (Diabetes Prevention Program Research Group 2009 ++) and the DPS published data on a median follow-up of seven year follow-up (Lindstrom et al. 2006 ++).

The results on the meta-analysis of replacing data with the updated data are displayed in figure 4. Replacing data with latest updated data only slightly altered the overall pooled effect for the prevention of type 2 diabetes, from 0.51 (95%CI 0.44 – 0.60) in figure 3 to 0.53 (95%CI 0.43 – 0.66) in figure 4. The pooled effect for diet and exercise studies also only slightly altered, from 0.47 (95%CI 0.39 – 0.57) in figure 3 to 0.49 (95%CI 0.36 – 0.65) in figure 4.

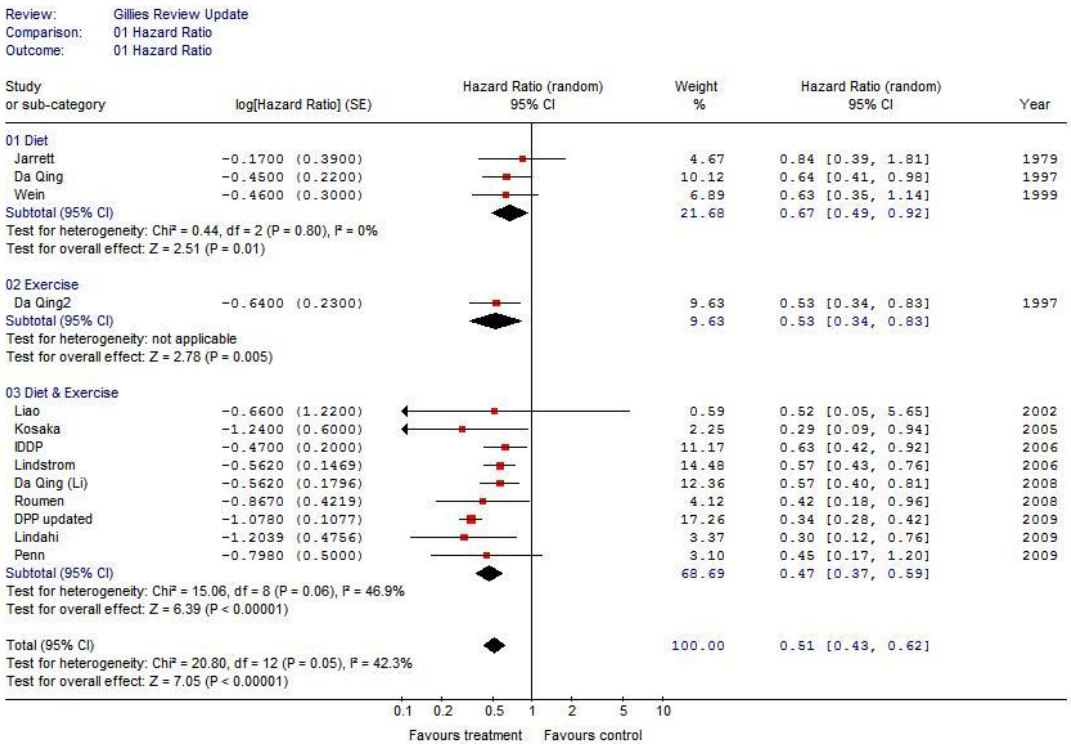
Figure 4: Meta-analysis of lifestyle interventions with updated studies



After replacing the studies that had more recent data, the studies on lifestyle interventions published after the initial review (Gillies et al. 2007), were added to the meta-analysis. There were three lifestyle intervention studies (Roumen et al. 2008 ++; Lindahl et al 2009 and Penn et al. 2009 ++), all three studies reported on diet combined with exercise. Figure 5 displays the meta-analysis, the addition of the new studies slightly altered the overall pooled hazard ratio for the prevention of type 2 diabetes, from 0.53 (95%CI 0.43 – 0.66) in figure 4 to 0.51 (95% CI 0.43 – 0.62) in figure 5. The pooled effect for diet and exercise studies also only slightly altered, from 0.49 (95%CI 0.36 – 0.65) in figure 4 down to 0.47 (95%CI 0.37 – 0.59) in figure 5.

For diet alone, there was no change with both meta-analyses having an overall effect estimate of 0.67 (95%CI 0.49 – 0.92), see figures 4 and 5. For exercise alone, again there was no change with both meta-analyses having an overall effect estimate of 0.53 (95%CI 0.34 – 0.83), see figures 4 and 5.

Figure 5: Gillies meta-analysis of lifestyle interventions with updated studies & new studies



Three studies reported on a diet only lifestyle intervention (Wein et al. 1999 -; the Da Qing study - Pan et al. 1997 ++; Jarrett et al. 1979 +), all three were in the initial review (Gillies et al. 2007). The pooled effect for diet only interventions was a HR of 0.67 (95% CI 0.49 – 0.92).

Only one study reported on an exercise only lifestyle intervention (the Da Qing study - Pan et al 1997 ++), from the initial review (Gillies et al. 2007), the hazard ratio for this study was 0.53 (95% CI 0.34 – 0.83).

Ten studies reported on a diet and exercise intervention, four (Liao et al. 2002 +; DPS - Lindstrom et al. 2003 ++; Kosaka et al. 2005 ++; IDDP 2006) from the initial review (Gillies et al. 2007) and six identified from this review (Lindstrom et al. 2006 ++; Li et al. 2008 -; Diabetes Prevention Program Research Group 2009 ++; Lindahl et al. 2009 ++; Roumen et al. 2009; Penn et al 2009). The pooled hazard ratio for diet and exercise intervention was 0.41 (95% CI 0.35 – 0.49).

Summary

From the evidence in this review, it appears that lifestyle interventions have an effect in delaying or preventing progress to diabetes in people with IGT. Three studies examined a diet only intervention, one study examined an exercise only intervention and ten studies examined a combination of diet and exercise. From the meta-analysis in figure 5, the combination of diet and exercise appears to have more effect in the delaying or preventing the progression from IGT to a diagnosis of diabetes. In all studies, the intervention group had lower rates of progress to diabetes than the control group, although not every result was statistically significant.

Evidence statement 1:

Lifestyle interventions

The meta-analysis of hazard ratios shows that lifestyle interventions (pooled HR 0.51 95% CI 0.43-0.62) can reduce the progress to diabetes for people with IGT. Each type of lifestyle intervention, whether diet (HR 0.67 95% CI 0.49-0.92), exercise (0.53 95% CI 0.34-0.83), or a combination of diet and exercise (HR 0.47 95% CI 0.37-0.59) had a beneficial effect, although a combination of diet and exercise appeared to have more effect that either diet or exercise alone.

The hazard ratio for diet only intervention was based on three studies, one UK (Jarrett et al. 1979 +), one Chinese (Da Qing, Pan et al. 1997 ++) and one Australian (Wein et al. 1999 -). The hazard ratio for exercise only intervention was based on one Chinese study (Da Qing, Pan et al. 1997 ++). The hazard ratio for the diet combined with exercise intervention was based on nine studies, one study in each of the following countries, UK (Penn et al. 2009 ++), Japan (Kosaka et al. 2005 ++), China (Li et al. 2008 -), India (Ramachandran et al. 2008 ++), Netherlands (Roumen et al. 2008 ++), Finland (Lindstrom et al. 2006 ++), Sweden (Lindahl et al. 2009 ++) and two US studies (Diabetes Prevention Program Research group 2009 ++; Liao et al. 2002 +).

5.2.3 Pharmacological interventions

There were 14 interventions (eight from the initial review, one updated study from the initial review and five new studies) looking at pharmacological interventions. A brief description of each study is given below, see also table 4. Two of these studies also reported on diet and physical activity lifestyle changes (DPP 2002; IDDP 2006) the brief descriptions these studies are in section 5.2.2. Data from the studies were extracted for the primary outcome of interest (progression from IGT to diabetes) and where reported for secondary outcomes, for example changes in BMI/weight, a full evidence table is given in appendix 8. As phenformin was withdrawn from most markets in the late 1970s due to a high risk of lactic acidosis, the data from the Jarrett study (Jarrett et al. 1979 +) on phenformin has not been included in any of the updated meta-analyses, although it is included in the replication of Gillies meta-analysis of pharmacological interventions.

Table 4: Characteristics of studies on pharmacological interventions

Author	Country	Populations	Interventions
Metformin			
Li 1999	China	N=90 (50 males, 40 women) with impaired glucose tolerance.	Metformin or a placebo at a dosage of 250 mg three times daily for 12 months.
Ramachandran (IDPP) 2006	India	N= 531 (420 males).	Group 1 was the control, Group 2 was given advice on lifestyle modification (LSM), Group 3 was treated with metformin (MET) and Group 4 was given LSM plus MET.
Diabetes Prevention Program Research Group 2009	US	N= 3234 (68% women, 45% from ethnic and racial minority groups, and 20% aged 60 years or older) with impaired glucose tolerance.	Participants were randomised to one of three interventions: intensive lifestyle (aimed to help participants to achieve and maintain 7% weight loss and 150 minutes or more per week of moderate-intensity physical activity); metformin or placebo.
Acarbose			
Chiasson (STOP_NIDDM) 2002	Canada and Europe	N= 1,368, males accounted for 48% (329/682) in the intervention group and 50% (344/686) in the control group. The mean BMI was 31.0 in the intervention group and 30.9 in the control group.	100 mg acarbose, or placebo, three times daily, taken with the first bite of a meal.
Pan 2003	China	N= 252, (125 Intervention group, 127 Control group) with a mean age of 53.4 years in the intervention group and 55.6 years in the control group. The mean BM was 25.6in the intervention group and 25.8 in the control group.	Acarbose or placebo, 50 mg t.i.d. for a period of 16 weeks.
Glipizide			
Eriksson 2006	Finland	N= 34, 25 males, nine females. The mean age was 59 years in the intervention group and 54 years in the control group. The mean BMI was 27.9 in the intervention group and 28.8 in the control group	Participants were randomised glipizide 2.5 mg or matching placebo, once daily for six months.

Author	Country	Populations	Interventions
Pioglitazone			
Ramachandran (IDPP-2) 2009	India	N= 407, non-diabetic participants persistent IGT (353 males)	Lifestyle modification with pioglitazone or lifestyle modification with placebo.
DeFronzo 2011	US	N=602, adults with a mean age of 53.0 years in the intervention and 51.5 years in the control group. The mean BM was 33.0 in the intervention group and 34.5 in the control group	Participants underwent randomization according to center and sex and received 30 minutes of dietary instruction which was reinforced on follow-up visits. Participants were randomly assigned to receive pioglitazone or placebo. Participants initially received 30 mg of pioglitazone per day or placebo. One month after randomization, the dose of pioglitazone was increased to 45 mg per day.
Voglibose			
Kawamori 2009	Japan	N= 1780 (1071 males), with a mean age of 55.7 years in the intervention and 55.7 years in the control group. The mean BM was 25.76 in the intervention group and 25.89 in the control group.	Participants were randomly allocated to voglibose 0.2mg or an identical looking placebo three times per day before meals
Ramipril			
Dream Trial Investigators 2006	Multi Country	N= 5,269, adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease with a mean age of 54.7 and a mean BMI 0f 30.9.	Participants were randomly assigned to receive either ramipril (5 mg daily for the first 2 months, with an increase to 10 mg at the 2-month visit and 15 mg after 1 year) or matching placebo (and rosiglitazone or matching placebo) (4 mg once daily for the first 2 months and then 8 mg thereafter).
Valsartan			
NAVIGATOR Study Group 2010	Multi Country	N=9,306, adults with a mean age of 63.7 years in the intervention and 63.8 years in the control group. The mean BM was 30.4 in the intervention group and 30.6 in the control group	Participants were randomly assigned to receive either valsartan or matching placebo. Valsartan was started at a dose of 80 mg once daily, with an increase after 2 weeks to 160 mg once daily; dose reduction or interruption because of adverse events or for other clinical reasons was permitted.
Nasteglinide			
NAVIGATOR Study Group 2010	Multi Country	N=9,306, adults with a mean age of 63.7 years in the intervention and 63.8 years in the control group. The mean BM was 30.5 in the intervention group and 30.5 in the control group	Participants were randomly assigned to receive either nateglinide (6 0mg taken before meals three times dialy) or matching placebo. Nateglinide was started at a dose of 30 mgy, with an increase after 2 weeks to 60 mg); dose reduction or interruption because of adverse events or for other clinical reasons was permitted.
Orlistat			
Heymsfield 2000	US and Europe	N=675, with 118 males (69 in intervention group, 49 in control group). The mean age was : 43.9 years ± 0.6 (intervention group), 44.3 years ± 0.7 (control group) and the mean BMI: 35.6 ± 0.1 (intervention group), 36.0 ± 0.9 (control group)	Orlistat, or a placebo, 120 mg 3 times a day, for 104 weeks
Torgerson (XENDOS) 2004	Sweden	N= 3,277 (1,640 Intervention group, 1,637 Control group), with a mean age of 43.0 years in the intervention group and 43.7 years in the control group. The mean BMI was 37.3 in the intervention group and 37.4 in the control group.	Participants were randomised to lifestyle changes plus either orlistat 120 mg or placebo, three times daily.

Metformin

Li Study 1999

The Li study (Li et al. 1999 ++) undertook a population screening of all the employees over the age of 30, working in the 32 units of the Shougang Corporation, a heavy industry enterprise based in Beijing. Those whose results met the 1985 WHO criteria for IGT in both 1992 and 1994 were eligible for the study. People meeting the entry criteria were randomised under double-blind conditions to receive either placebo or metformin at a dosage of 250 mg three times daily for 12 months. The primary outcomes were improvements in fasting glucose, glucose tolerance, and insulin sensitivity. After one year of treatment, there was one case of diabetes (3%) in the metformin group and six cases (16.2%) in the control group, this was statistically significant (p=0.011).

Ramachandran Study 2006

The Indian Diabetes Prevention Programme (IDPP) study (Ramachandran et al. 2006 ++) recruited 531 subjects with IGT from the middle-class population working in service organisations and also from their families. These were non-diabetic subjects with no major illness aged 35–55 years and of both sexes, and were screened from March 2001 to July 2002. The participants were randomised to one of four groups: Group 1 participants were given standard health care advice (control), Group 2 participants followed lifestyle modification (LSM), Group 3 participants were treated with metformin (MET), and Group 4 participants were given LSM plus MET. All participants underwent annual reviews for three years, and the primary outcome measure was type 2 diabetes. The IDPP study (Ramachandran et al. 2006 ++) reported that the cumulative incidence of diabetes at three years was 40.5% (95% CI 32.0 – 49.7) in the metformin intervention group and 55.0% (95% CI 46.0 – 63.5) in the control group. The relative risk reduction was 25.4% (95% CI 19.1 – 35.1) and this was statistically significant (p= 0.029).

Diabetes Prevention Program Research Group Study 2009

The Diabetes Prevention Program Outcomes Study (DPPOS) was a long-term follow-up of the DPP to investigate whether the delay in development of diabetes seen during the DPP can be sustained, and to assess long-term effects of the interventions on health (Diabetes Prevention Program Research Group 2009 ++). In

this follow-up, overweight, middle-aged adults with impaired glucose tolerance were randomly assigned to metformin or placebo (850 mg twice daily) After a median of four years of active intervention period, participants who were still free of diabetes were further followed up for a median of three years, with median total follow-up of seven years. Diabetes incidence, bodyweight, physical activity, and dietary intakes of fat, saturated fat, and fibre were measured. During the Diabetes Prevention Program Outcomes Study (DPPOS), diabetes incidence rates did not significantly differ between groups. Incidence rates were stable in the lifestyle group, but fell in the placebo and metformin groups during the DPPOS. During the combined DPP, bridge, and DPPOS periods, the incidence rate of the lifestyle group was reduced by 34% (95% CI 24–42) and metformin by 18% (7–28) compared with placebo. The updated data from the 10-year follow-up DPP trial (Diabetes Prevention Program Research Group 2009 ++) stated that diabetes incidence rate of 4.9 per 100 person-years (95% CI 4.2 – 5.7) for the metformin intervention group and 5.6 per 100-person years (95% CI 4.8 – 6.5) for the control group. Diabetes incidence rates during the DPP trial were 7.8 per 100 person-years (95% CI 6.8 – 8.8) in the metformin intervention group and 5.6 per 100-person years (95% CI 4.8 – 6.5) in the control group. Diabetes incidence in the ten years since DPP trial was reduced by 18% (95% CI 7 - 28) in the diet and exercise intervention group compared with the control group.

Adverse effects

The Li study (Li et al. 1999 ++), reported that three patients reported mild diarrhoea and nausea when starting metformin, but the symptoms resolved with long-term treatment.

Acarbose

Chiasson Study 2002

The STOP-NIDDM (Study To Prevent Non-insulin-dependent diabetes Mellitus) study (Chiasson et al. 2002 ++) was a double-blind, placebo-controlled randomised trial conducted in Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel, and Spain. Patients were recruited mainly through screening of high-risk populations, and in particular from first-degree relatives of patients with type 2 diabetes. The first patient with impaired glucose tolerance was enrolled in December, 1995, and the last in July, 1998, the study was completed in August, 2001. All

patients remained in the study until the last randomised patient had been treated for 3 years, the mean follow-up time was 3•3 years Eligible patients were randomly allocated to placebo or 100 mg acarbose three times daily, taken with the first bite of a meal. The primary outcome was the development of diabetes on the basis of a yearly oral glucose tolerance test. Based on one abnormal plasma glucose concentration two hours after 75 g glucose load, the cumulative incidence of diabetes was 32.4 % (221/682) in the intervention group and 41.5% (285/686) in the control group, the hazard ratio was 0.75 (p=0.0015). The incidence rate of diabetes was 101 cases per 1000 person-years in the intervention group and 121 cases per 1000 person-years in the control group, with a risk difference of 9·1% over 3.3 years.

Pan Study 2003

The Pan study (Pan et al. 2003 ++) was a multicentre, double-blind, placebo-controlled study investigated the efficacy of acarbose in Chinese individuals with impaired glucose tolerance (determined using a 75 g oral glucose tolerance test). Subjects were recruited by five centres in the mainland of China and were randomised to either placebo or acarbose 50 mg t.i.d. for a period of 16 weeks. The primary outcome was development of diabetes. Nineteen individuals (7.54%) converted to type 2 diabetes during the study period: 12 subjects in the placebo (9.45%) and seven in the acarbose arm (5.6%). The comparison between treatments showed no significant difference (p=0.245).

Adverse effects

In the STOP-NIDDM trial (Chiasson et al 2002), almost a quarter of patients discontinued early, of whom almost a half (48%) discontinued during the first year. The commonest single cause of early discontinuation was gastrointestinal side-effects (93 patients in the intervention group and 18 in the control group). The Pan study (Pan et al. 2003 ++) reported that adverse events with a ‘possible’ or ‘probable’ relation to the study drug were reported by 35.7% of acarbose subjects compared to 18.2% patients on placebo. The difference between the treatment arms primarily resulted from the higher frequency of gastrointestinal events in the acarbose group. The most frequently reported events were flatulence (15.9% acarbose versus 6.1% placebo), abdomen enlarged (13.5 vs. 3.8%) and diarrhoea (9.5 vs. 2.3%); all were mild to moderate in intensity. Five subjects (two acarbose and three placebo) were prematurely withdrawn from the study because of adverse events and all study

medication was permanently discontinued. No fatalities occurred. Four subjects experienced serious adverse events: one in the placebo group (tenosynovitis) and three in the acarbose group (cerebral infarction, hepatitis and glaucoma). Relation to the study medication was considered to be remote or none.

Glipizide

Eriksson Study 2006

The Eriksson study (Eriksson et al. 2006 ++) randomised (in a double-blind fashion) 37 first-degree relatives of patients with type 2 diabetes fulfilling WHO criteria for IGT treatment with either glipizide 2.5 mg once daily or matching placebo for 6 months. The primary outcome was glucose tolerance. It was reported that, at the 18 month follow-up, 5.9% (1/16) of those in the intervention group had developed diabetes, compared to 29.4% (5/16) in the control group. The absolute risk reduction observed in the intervention group was 23.5% and the relative risk reduction was 80%.

Adverse effects

The Eriksson study (Eriksson et al. 2006 ++), stated that a similar number of subjects in both groups reported hypoglycaemic symptoms (e.g. hunger, fatigue, palpitations, tremor) during the study; however, numbers were not given only percentages (41% in the glipizide group and 32% in the placebo group). One subject in the glipizide group discontinued the study early due to hypoglycaemic symptoms. All other side effects were mild.

Pioglitazone

Ramachandran Study 2009

The IDPP-2 study (Ramachandran et al. 2009 ++) was started while the IDPP-1 was in progress as a second-phase study of another cohort of participants with IGT who were selected using criteria similar to those used for IDPP-1 (Ramachandran et al. 2006 ++). The objective of IDPP-2 was to find out if, by adding pioglitazone, the efficacy of lifestyle modification could be enhanced. In this community-based, placebo-controlled 3 year study, 407 participants with impaired glucose tolerance (mean age 45.3 ± 6.2 years, mean BMI 25.9 ± 3.3 kg/m^2) that received either: lifestyle modification plus pioglitazone, 30 mg (n=204) or lifestyle modification plus

placebo (n=203). The participants and investigators were blinded to the assignment. The primary outcome was development of diabetes. The cumulative incidence of diabetes at 36 months, corrected for the confounding variables such as age, sex, BMI and family history using the Kaplan–Meier survival test, was similar in both groups (pioglitazone=29.8% and placebo= 31.6%; unadjusted HR for placebo vs pioglitazone 1.084 [CI 0.753–1.560], p=0.665); adjusted HR 0.984 [CI 0.672–1.443], p=0.93.

DeFronzo Study 2011

The DeFronzo study (DeFronzo et al. 2011 +) was a three-year double-blind placebo-controlled study, that randomised 602 patients to receive pioglitazone or placebo. Participants initially received 30 mg of pioglitazone per day or placebo. One month after randomization, the dose of pioglitazone was increased to 45 mg per day. Participants returned at 2, 4, 6, 8, 10, and 12 months during the first year of the study and once every 3 months thereafter, the median follow-up period was 2.4 years. The primary outcome was development of diabetes. The annual average incidence of diabetes, calculated on the basis of person-years, was 7.6% in the placebo group and 2.1% in the pioglitazone group (P<0.001). The hazard ratio for development of diabetes in the pioglitazone group was 0.28 (95% confidence interval, 0.16 to 0.49; p<0.001). confidence interval, 0.16 to 0.49; P<0.001). Adjustment for baseline characteristics did not alter the hazard ratio. The number of people who would need to be treated to prevent one case of diabetes was 8 for 2.2 years of the trial and 18 for 1 year.

Adverse effects

The IDPP-2 study (Ramachandran et al. 2009 ++), reported that in the pioglitazone group, cardiac problems accounted for two deaths and two non-fatal hospital admissions. There were two cases of cardiac disease in the placebo group. More participants in the placebo group than in the pioglitazone group were hospitalised for other reasons such as bone fractures, infectious diseases and treatment for renal stones. Of the four participants with elevated transaminases, three were in the placebo group. None of these individuals had values greater than 120 U/l.

The DeFronzo study (DeFronzo et al. 2011 +) reported that adverse events occurred in 121 patients in the placebo group and 151 patients in the pioglitazone group (p=

0.03). Oedema increased at some point during the trial in 19 patients receiving placebo (6.4%) and 39 patients receiving pioglitazone (12.9%) (p= 0.007). Events related to the cardiovascular system numbered 23 in the placebo group (7.7%) and 26 in the pioglitazone group (8.6%), with 1 case of congestive heart failure in each group (0.3%). One unexplained sudden death occurred in the placebo group, and three deaths occurred in the pioglitazone group (one unexplained sudden death, one death from biliary carcinoma, and one death from a carcinoid tumor). Nine fractures occurred in 8 of the patients receiving pioglitazone (3%) and eight fractures occurred in 7 of the patients receiving placebo (2.6%).

Voglibose

Kawamori Study 2009

The Kawamori study (Kawamori et al. 2009 ++) was a multicentre, randomised, double-blind, parallel group comparison of voglibose and placebo in Japanese individuals with impaired glucose tolerance. 1780 eligible patients on a standard diet and taking regular exercise with impaired glucose tolerance were randomly assigned to oral voglibose 0.2 mg three times a day (n=897) or placebo (n=883). Treatment was continued until participants developed type 2 diabetes (primary endpoint) or normoglycaemia (secondary endpoint), or for a minimum of 3 years, subject to the findings of an interim analysis. The cumulative number of cases that progressed to diabetes at the end of the study was 50 of 897 in the voglibose group versus 106 of 881 in the placebo group. The HR was 0.595 (95% CI 0.433–0.818), showing that voglibose-treated individuals had a 40.5% lower risk of developing type 2 diabetes than did placebo-treated individuals (p=0.0014). The cumulative progression rate to type 2 diabetes after 48 weeks was 9.4% (7.1–11.8) for placebo and 3.6% (2.0–5.2) for voglibose. After 96 weeks, the corresponding rates were 23.5% (18.5–28.5) and 12.1% (6.9–17.3), respectively, and after 144 weeks they were 36.2% (27.7–44.8) and 30.2% (19.5–41.0), respectively.

Adverse effects

The study authors (Kawamori et al. 2009 ++), reported that gastrointestinal symptoms were the most common and more frequent in the voglibose group than in the placebo group. However, they were generally thought to be mild to moderate in

severity. The rate of serious adverse effects was low. No deaths occurred in the placebo group versus six in the voglibose group (two accidents, and one each of suicide, possible self-intoxication with insecticide resulting in heart failure, lung cancer, and myocardial infarction); none of the deaths were thought to be related to the drug treatment.

Ramipril

Dream Trail Investigators Study 2006

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial (Dream Trial Investigators 2006 ++) is a double-blind, randomised clinical trial with a 2-by-2 factorial design, 5,269 participants without cardiovascular disease but with impaired fasting glucose levels (after an 8-hour fast) or impaired glucose tolerance were randomly assigned to receive ramipril (up to 15 mg per day) or placebo and were then followed for a median of 3 years. The effects of ramipril on the development of diabetes or death, whichever came first (the primary outcome), and on secondary outcomes, including regression to normoglycemia were examined. Diabetes or death occurred in 475 participants (18.1%) in the ramipril group, as compared with 517 (19.5%) in the placebo group (hazard ratio, 0.91; 95% confidence interval [CI], 0.81 to 1.03; P = 0.15). There were 31 deaths in the ramipril group and 32 in the placebo group, whereas diabetes developed in 449 participants in the ramipril group (17.1%) and in 489 in the placebo group (18.5%; hazard ratio, 0.91; 95% CI, 0.80 to 1.03). The effect of ramipril on the development of diabetes was consistent, even after controlling for the use of diuretics, beta-blockers, or angiotensin-receptor blockers. The results for the primary outcome were similar among participants with impaired fasting glucose levels and in those with impaired glucose tolerance.

Adverse effects

The authors of the DREAM trial (Dream Trial Investigators 2006 ++) reported that the numbers of cardiovascular events were similar in the two groups (67 events in the ramipril group and 63 in the placebo group, p= 0.68). The numbers of hospitalizations for all events were also similar (497 in the ramipril group and 489 in the placebo group, p= 0.67). Angioedema occurred in three participants receiving ramipril (0.1%) and in four participants receiving placebo (0.2%).

Valsartan

NAVIGATOR Study Group 2010

The NAVIGATOR Study (NAVIGATOR Study Group[a] 2010 ++) is a double-blind, randomized clinical trial which evaluated the postprandial glucose lowering effects of Valsartan, in addition to lifestyle modification. The study randomly assigned 9,306 participants with impaired glucose tolerance and either cardiovascular disease or cardiovascular risk factors to receive valsartan (up to 160 mg daily) or placebo, in a 2-by-2 factorial design with nateglinide or placebo, in addition to participation in a lifestyle modification program. Participants were treated with valsartan for five years and followed for a median of 5.0 years for development diabetes (and a median of 6.5 years for vital status). The primary outcome was the development of diabetes. The cumulative incidence of diabetes was 33.1% in the valsartan group, as compared with 36.8% in the placebo group (hazard ratio in the valsartan group, 0.86; 95% CI, 0.80 to 0.92; p<0.001).

Adverse effects

Nasopharyngitis, back pain, and arthralgia were the most commonly reported individual adverse events. There was no excess of renal dysfunction or hyperkalemia in the valsartan group, but hypotension-related adverse events were more common in the valsartan group (occurring in 42.4% of patients) than in the placebo group (35.9%) and this was statistically signiifcant (p<0.0 01). During the course of the study, 556 patients (12.0%) in the valsartan group and 531 (11.4%) in the placebo group discontinued the study drug because of an adverse event (p=0.33).

Nateglinide

NAVIGATOR Study Group 2010

The NAVIGATOR Study (NAVIGATOR Study Group[b] 2010 ++) The NAVIGATOR Study (NAVIGATOR Study Group[a] 2010 ++) is a double-blind, randomized clinical trial which evaluated the postprandial glucose lowering effects of Nateglinide, in addition to lifestyle modification. The study randomly assigned 9,306 participants with impaired glucose tolerance and either cardiovascular disease or cardiovascular risk factors to receive nateglinide (up to 60 mg three times daily) or placebo, in a 2-by-2

factorial design with valsartan or placebo, in addition to participation in a lifestyle modification program. Participants were followed for a median of 5.0 years for incident diabetes (and a median of 6.5 years for vital status). The primary outcome was the development of diabetes. Nateglinide, as compared with placebo, did not significantly reduce the cumulative incidence of diabetes (36% and 34%, respectively; hazard ratio, 1.07; 95% confidence interval [CI], 1.00 to 1.15; P=0.05). Nateglinide did, however, increase the risk of hypoglycemia. Among persons with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors, assignment to nateglinide for 5 years did not reduce the incidence of diabetes.

Adverse effects

A total of 520 participants in the nateglinide group (11.2%) and 485 in the placebo group (10.4%) discontinued the study drug owing to an adverse event (p= 0.23). Rates of adverse events did not differ significantly between the groups, except that more participants in the nateglinide group reported hypoglycemia (mostly mild events) (911 participants [19.6%], vs. 527 [11.3%] in the placebo group; p<0.001).

Orlistat

Heymsfield study 2000

The Heymsfield study (Heymsfield et al. 2000 ++) was a pooled analysis of three two-year randomised placebo-controlled clinical trials in which 675 obese individuals (BMI, 30-43) received either orlistat, 120 mg three times daily, or placebo three times daily with a mildly low-energy diet for 1 year; subjects who were treated for 2 years had a weight maintenance diet in the second year. Weight loss was the primary outcome. Of the subjects with IGT at baseline, 3.0% who were treated with orlistat progressed to diabetes vs. 7.6% in the control group, after a mean follow-up of 582 days.

Torgerson Study 2004

The XENDOS study (Xenical in the prevention of Diabetes in Obese Subjects) was a four-year, double-blind, prospective study, that randomised 3,305 patients to lifestyle changes plus either orlistat 120 mg or placebo, three times daily for four years

(Torgerson et al. 2004 ++). Participants had a BMI ≥30 kg/m^2 and normal (79%) or impaired (21%) glucose tolerance (IGT). Primary endpoints were time to onset of type 2 diabetes and change in body weight. Analyses were by intention to treat. During four years of treatment, orlistat plus lifestyle changes significantly decreased the progression to type 2 diabetes compared with placebo plus lifestyle changes (log-rank p=0.0032). Cumulative incidence rates after four years were 6.2% vs. 9.0%. The hazard ratio (0.627 [95% CI 0.455–0.863]) corresponds to a 37.3% decrease in the risk of developing diabetes with orlistat compared with placebo.

Adverse effects

The Heymsfield study (Heymsfield et al. 2000 ++), did not report any adverse effects. In the XENDOS study (Torgerson et al. 2004 ++), it was reported that orlistat was well tolerated during the study, and that the overall incidence of adverse events was similar in the two treatment groups, with the exception of a higher incidence of gastrointestinal events. Most gastrointestinal events were mild to moderate in intensity and occurred during the early phase of treatment. During the first year of treatment, the proportion of patients experiencing at least one gastrointestinal event with orlistat or placebo was 91 vs. 65%, respectively. This compares with 36 vs. 23% for orlistat or placebo, respectively, during the 4th year. Over the four year period, a similar proportion of placebo-treated patients had at least one serious adverse event as compared with orlistat-treated patients (13% vs. 15%). Similar proportions of serious gastrointestinal events occurred in the placebo (n= 32; 2%) and orlistat (n= 32; 2%) groups. No deaths were attributed to study medication. Overall, 4% of placebo patients and 8% of orlistat patients withdrew from the study because of adverse events or laboratory abnormalities; the difference was primarily due to gastrointestinal events.

Meta-analysis

For pharmacological interventions (excluding foreign language papers), calculated data were analysed with review manager for the meta-analyses. The meta-analysis of pharmacological interventions used in the initial review (Gillies et al. 2007) was replicated and is displayed in figure 6. Figure 7 shows the meta-analysis with the DPP study updated data, and with the Jarrett study (Jarrett et al. 1979 +) using phenformin excluded. The overall pooled effect went to 0.45 (95% CI 0.28 – 0.71) from 0.69 (95% CI 0.61 – 0.78). When the data from studies published after the initial

review were added (Dream Trial Investigators 2006 ++; Kawamori et al. 2009 ++; Ramachandran et al. 2009 ++, DeFronzo et all. 2011 +, NAVIGATOR Study Group[a] 2010 ++, NAVIGATOR Study Group[b] 2010 ++), the overall pooled effect was 0.64 (95% CI 0.53 – 0.76), see figure 8.

Figure 6: Replication of Gillies Meta-analysis of Pharmacological interventions

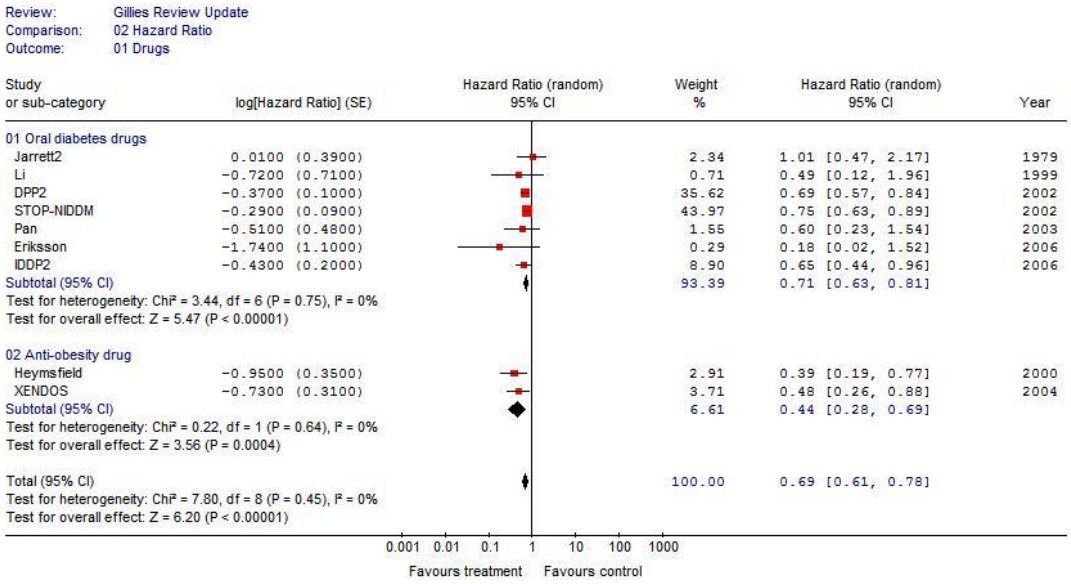


Figure 7: Gillies Meta-analysis of Pharmacological interventions updated with longer term follow-up

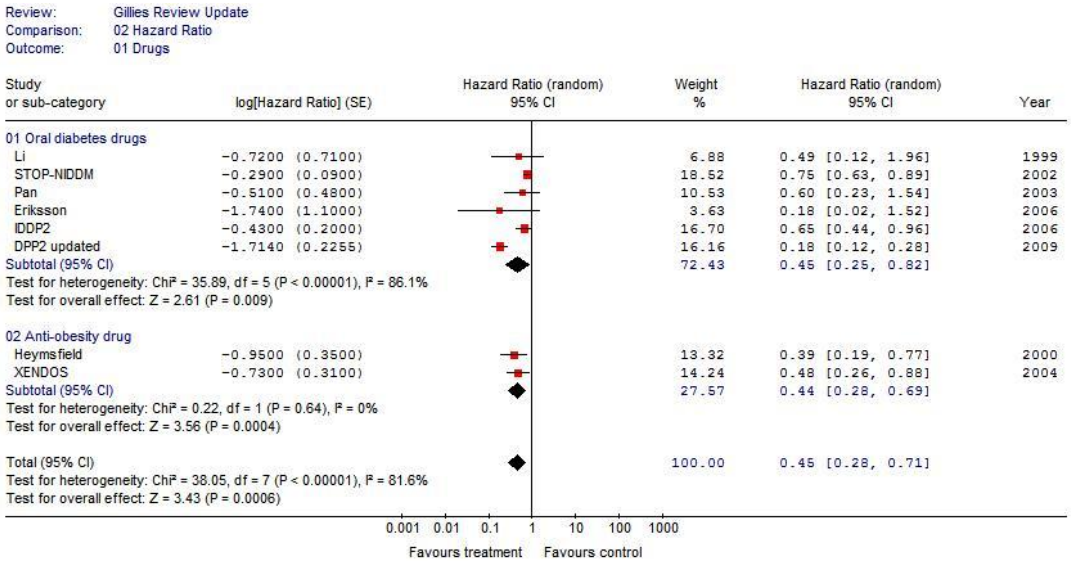
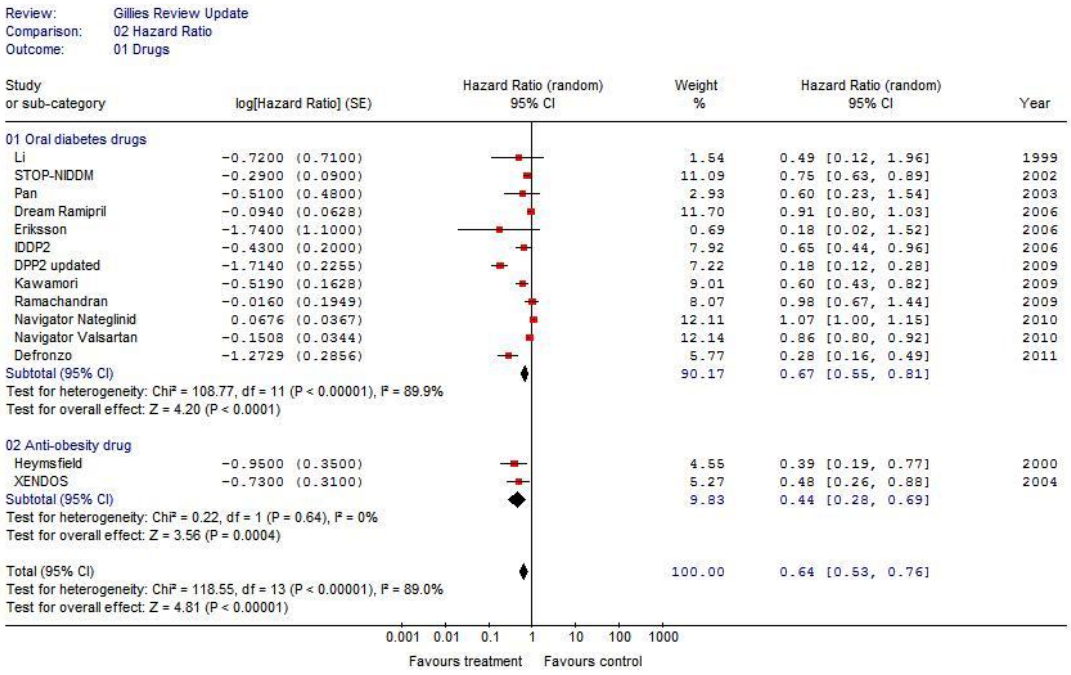


Figure 8: Gillies Meta-analysis of Pharmacological interventions updated with longer term follow-up and addition of new studies



There were 14 studies in total that examined the effect of pharmacological interventions, seven from the initial review, one updated study from the initial review and six studies published after the initial review. Three studies examined the effect of metformin (Li et al. 1999 ++; Diabetes Prevention Program Research Group 2009 ++; IDPP - Ramachandran et al. 2006 ++), two studies examined acarbose (Chiasson et al 2002; Pan et al. 2003 ++, one study examined glipizide (Eriksson et al. 2006 ++), two studies examined pioglitazone (Ramachandran et al 2009 ++, DeFronzo et al. 2011 +), one study examined voglibose (Kawamori et al. 2009 ++), one study examined ramipril (Dream Trial Investigators 2006 ++), one study examined valsartan (NAVIGATOR Study Group[a] 2010 ++), one study examined Nateglinide (NAVIGATOR Study Group[b] 2010 ++), and two studies examined the anti-obesity drug orlistat (Heymsfield et al. 2000 ++; (Torgerson et al. 2004 ++).

Summary

From the evidence presented in this review, it appears that pharmacological interventions have an effect in delaying or preventing progress to diabetes in people

with IGT. Twelve studies examined the effectiveness of oral diabetes drugs two studies examined the effectiveness of an anti-obesity drug. From the meta-analysis in figure 8, the anti-obesity drug orlistat appears to have more effect in the delaying or preventing the progression from IGT to a diagnosis of diabetes than the combined results of the oral diabetes drugs. In all but one studies, the intervention group had lower rates of progress to diabetes than the control group.

Evidence statement 2:

Pharmacological interventions

The meta-analysis of hazard ratios shows that pharmacological interventions (pooled HR 0.64 95% CI 0.53-0.76) can reduce the progress to diabetes for people with IGT. Both types of intervention, oral diabetes drugs (HR 0.60 95% CI 0.44-0.82), and anti-obesity drugs (HR 0.67 95% CI 0.55-0.81) had a beneficial effect.

The hazard ratio for oral diabetes drugs was based on twelve studies, Three multi-country study (Dream Trial Investigators 2006 ++, NAVIGATOR Study Group[a] 2010 ++, NAVIGATOR Study Group[b] 2010 ++),one study in each of the following countries Canada/Europe (Chiasson et al. 2002 ++), Finland (Erkisson et al. 2006 ++), Japan (Kawamori et al. 2009 ++), two US (Diabetes Prevention Program Research Group 2009 ++, DeFronzo et al. 2011 +) , two Indian (Ramachandran et al. 2006 ++; Ramachandran et al. 2009 ++)` and two Chinese (Li et al. 1999 ++; Pan et al. 2003 ++).

For anti-obesity drugs, the hazard ratio was based two studies, one US/Europe (Heymsfiled et al. 2000 ++) and one Swedish (Torgerson et al. 2004 ++).

5.2.4 Network analysis

Evidence synthesis

The objective of the analysis was to synthesise the evidence for the effects of various interventions for the prevention of type 2 diabetes available from various RCTs.

The intervention effects were extracted as hazard ratios from each RCT. It was believed *a priori* that hazards associated with each intervention were not proportional within each RCT so that the hazard ratio was not constant over time. In an attempt to ensure that the hazard ratios were reasonably comparable across RCTs, the RCTs were classified as being one of short-term (0-3 years follow-up), medium-term (3-6 years follow-up) or long-term (>6 years follow-up) duration depending on the length of follow-up. Separate analyses were performed for RCTs of short-term and medium-term duration. A formal synthesis of the long-term evidence was not performed because there were only two long-term RCTs available.

The hazard ratios were synthesised using a random effects network meta-analysis model (Woods *et al*., 2010). The analysis was conducted using the Markov chain Monte Carlo simulation software WinBugs (Lunn *et al*., 2000). The RCTs formed a network of direct and indirect evidence linked according to whether there were common interventions in the individual trials. Two analyses were conducted for each of the short-term and medium-term RCTs: 1) an unadjusted analysis, 2) a meta-regression adjusted for the mean age (years) and mean body mass index (BMI) in each RCT. Formal descriptions of the statistical models used are presented in Appendix 9.

Results are presented in terms of the posterior mean hazard ratios with associated 95% credible intervals and the posterior mean between study standard deviations with associated 95% credible intervals. In addition, in the case of the meta-regression, adjusted hazard ratios together with coefficients (95% credible intervals) associated with the effect of mean age and BMI are also presented.

Unadjusted short-term effects

The evidence network for interventions evaluated over short-term RCTS is presented in Figure A in Appendix 9. The numbers within the figure represent the number of time that specific interventions were compared across RCTs.

There were 12 (NI) interventions and 15 (NC) unique comparisons between interventions so that there were
4 = NC – (NI – 1) = 15 – (12 -1) = 15 – 11
possible inconsistencies between the direct and indirect evidence. Inconsistency between direct and indirect evidence may be a consequence of various factors including differences in patient population and study conduct. Any inconsistency in the effect of interventions will manifest itself as heterogeneity between studies and contributed to the estimate of the between-study standard deviation.

The unadjusted results of the short-term effect of interventions are presented in Table 5.

2.5mg Glipizide (Daily) produced the largest intervention effect (HR 0.18, 95% CrI: 0.02, 1.58), although there was considerable uncertainty as to whether this was a true effect.

Diet + Exercise (HR 0.43, 95% CrI: 0.31, 0.59), Metformin (at doses from one of 750mg, 500-1000mg & 1700mg (Daily)) (HR 0.65, 95% CrI: 0.43, 0.90), 360mg Orlistat (Daily) (HR 0.39, 95% CrI: 0.17, 0.89), Diet + Exercise + Metfirmin (HR 0.56, 95% CR: 0.30, 0.99), Diet + Exercise + 360mg Orlistat (Daily) (HR, 0.21, 95% CrI: 0.09, 0.47), Diet + Exercise + 20mg Pioglitazone (Daily) (HR 0.35, 95% CrI: 0.22, 0.59) and Diet + Exercise + 0.6mg Voglibose (HR 0.25, 95% CrI: 0.13, 0.49) all resulted in statistically significant intervention effects relative to placebo.

Tables 6 and 7 present the probabilities of intervention rankings for all interventions and lifestyle interventions respectively.

Diet + Exercise + 0.6mg Voglibose (Daily) had the greatest probability overall of being the best intervention (probability=0.589) followed by Diet + Exercise + 20 mg Pioglitazone (Daily) (probability=0.324), although there was considerable uncertainty as to which is likely to be the best.

Of the lifestyle interventions, Diet + Exercise had the greatest probability of being the best intervention (probability=0.900).

Goodness-of-fit was assessed by calculating the observation-specific and total residual deviance. The total residual deviance was 17.95, which is somewhat less than would have been expected compared with the 21 data points being analysed. The observation-specific deviance terms suggested that the model was not a good representation of the sample results from the following RCTs: (Roumen et al 2008 ++, Kosaka et al 2005 ++, Li et al 1999 ++, Liao et al 2002 ++ and Pan et al 2003 ++). Two of these RCTs included interventions that were defined after combining interventions across different doses of Acarbose and Metformin, and three compared Diet + Exercise with Placebo.

The between study standard deviation was estimated to be 0.15 (95% CrI: 0.01, 0.56), which is indicative of mild heterogeneity between studies but with reasonably high uncertainty as to the true value.

Adjusted short-term effects

The adjusted results of the short-term effect of interventions are presented in Table 8.

The adjustment for the mean age and mean BMI increased the uncertainty associated with the hazard ratios to the extent that only Diet + Exercise and Diet + Exercise + 20 mg Pioglitazone (Daily) resulted in statistically significant intervention effects relative to placebo.

There was insufficient evidence for an effect of mean age or mean BMI (Table 9).

Unadjusted medium-term effects

The evidence network for interventions evaluated over medium-term RCTS is presented in Figure B in Appendix 9. The numbers within the figure represent the number of time that specific interventions were compared across RCTs.

There were 8 (NI) interventions and 13 (NC) unique comparisons between interventions so that there were
6 = NC – (NI – 1) = 13 – (8 -1) = 13 – 7
possible inconsistencies between the direct and indirect evidence. Inconsistency between direct and indirect evidence may be a consequence of various factors including differences in patient population and study conduct. Any inconsistency in the effect of interventions will manifest itself as heterogeneity between studies and contributed to the estimate of the between-study standard deviation.

The unadjusted results of the short-term effect of interventions are presented in Table 10.

Diet + 50mg Phenformin (Daily) produced the largest intervention effect (HR 0.48, 95% CrI: 0.11, 2.10), although there was considerable uncertainty as to whether this was a true effect.

Diet + Exercise (HR 0.56, 95% CrI: 0.30, 0.93) was the only intervention that resulted in a statistically significant intervention effect relative to placebo.

Tables AA.2 and AA.3 present the probabilities of intervention rankings for all interventions and lifestyle interventions respectively.

Diet + 50mg Phenformin had the greatest probability overall of being the best intervention (probability=0.345), followed by Diet + Exercise + up to 60mg Nateglinide (3 times daily) (probability=0.338) and 50mg Phenformin (probability=0.153), although there was considerable uncertainty as to which is likely to be the best.

Of the lifestyle interventions, Diet + Exercise had the greatest probability of being the best intervention (probability=0.812).

Goodness-of-fit was assessed by calculating the observation-specific and total residual deviance. The total residual deviance was 12.86, which compares favourably with the 13 data points being analysed.

The between study standard deviation was estimated to be 0.26 (95% CrI: 0.01, 1.27), which is indicative of mild to moderate heterogeneity between studies and with considerable uncertainty as to the true value.

Adjusted medium-term effects

The adjusted results of the medium-term effect of interventions are presented in Table 13.

The adjustment for the mean age and mean BMI increased the uncertainty associated with the hazard ratios to the extent that none of the comparisons resulted in statistically significant intervention effects relative to placebo.

There was insufficient evidence for an effect of mean age or mean BMI (Table 14).

Discussion

The only interventions that were evaluated over both the short-term and medium-term were Diet and Diet + Exercise. In both cases the hazard ratios for the intervention effects relative to Placebo were bigger in short-term trials compared to medium-term trials, 0.63 and 0.73 for Diet, and 0.43 and 0.56 for Diet + Exercise, respectively. Although there was reasonable uncertainty as to the true effects, these results are consistent with the opinion *a priori* that the hazard ratio varies over time and is shrinking back to unity. There may be various reasons for this including the possibility that the patients randomised to Placebo switch to alternative strategies to delay their onset of type 2 diabetes rather than continuing with their previous lifestyle, and the possibility that patients randomised to an active intervention may not be as compliant with their intervention over the medium term as they were at the start of their intervention.

Some analysts have suggested one way to assess the effect of study duration on intervention effects is to perform a meta-regression with study duration as a covariate. A limitation with this approach is that it is effectively estimating an average interaction effect conditional on the duration of study; there is no avoiding the fact that a time dependent treatment effect cannot be estimated directly from a hazard ratio that explicitly assumes that the treatment effect is constant over time. A proper analysis would need access to individual patient-level data and model a time varying treatment effect.

The heterogeneity estimated in these analyses is generally consistent with what is observed in random effects meta-analysis. Although the heterogeneity between intervention effects may be because of differences in patient characteristics between RCTs, some may also be as a consequence of combining different strategies for treatment with Metformin and Acarbose into single interventions respectively.

The only interventions that were evaluated in at least three RCTs were Diet + Exercise (5 short-term RCTs, 3 medium-term RCTs) and Metformin (3 short-term RCTs). Thus, there was very little information with which to conduct a meta-regression adjusting for mean age and mean BMI in each trial. The meta-regression models are over-specified in terms of the number of parameters to be estimated given the number of observations available. A more informative meta-regression would require more replication of interventions in different RCTs and in patients whose mean ages and BMIs were sufficiently different to enable the identification of these as potential intervention effect modifiers.

Evidence statement 3:

Network meta-analysis

Network meta-analysis

The network meta-analysis comparison of the effect of diet only and diet + exercise for short-term and medium-term interventions showed a greater effect in short-term studies (diet v placebo: population HR 0.63 95% CrI 0.29-1.34; diet + exercise v placebo : population HR 0.43 95% CrI 0.31-0.59) compared to medium-term studies (diet v placebo : population HR 0.73 95% CrI 0.37-1.79; diet + exercise v placebo : population HR 0.56 95% CrI 0.30-0.93)

The network meta-analysis comparison of diet versus placebo incorporates indirect evidence about the treatment effect from related studies as well as direct evidence from one short-term study (Wein et al. 1999 -) and two mid-term studies (Pan et al. 1997 ++, Jarrett et al. 1979 +). The network meta-analysis comparison of diet plus exercise versus placebo incorporates indirect evidence about the treatment effect from related studies as well as direct evidence from five short-term studies (Roumen et al. 2008 ++, Ramachandran et al. 2006 ++, Kosaka et al. 2005 ++, Knowler et al. 2002 ++, Liao et al. 2002 +) and three medium-term studies (Lindahl et al. 2009 ++, Penn et al. 2009 ++, Lindstrom et al. 2006 ++).

Evidence statement 4:

Probability of treatment ranking

Probability of treatment ranking
The network meta-analysis of the short-term trials showed that, of all 12 interventions being compared, diet + exercise + 0.6 mg voglibose (daily) had the greatest probability of being the most effective intervention (probability=0.589) followed by diet + exercise + 20 mg pioglitazone (daily) (probability=0.324). When considering the evidence in the network meta-analysis about lifestyle interventions, diet + exercise had the greatest probability of being the most effective intervention (probability=0.900).

For the mid-term trials, the network meta-analysis showed that, of all interventions being compared, diet + 50mg phenformin had the greatest probability of being the most effective intervention (probability=0.345), followed by diet + exercise + up to 60mg nateglinide (3 times daily) (probability=0.338) and 50mg phenformin (probability=0.153). When considering the evidence in the network meta-analysis about lifestyle interventions, diet + exercise had the greatest probability of being the most effective intervention (probability=0.812).
There was insufficient evidence over the short and mid-term to suggest that age and BMI were treatment effect modifiers..

Table 5: Unadjusted hazard ratios and 95% credible intervals – Short-term trials

	Hazard Ratio	95% CrI
Diet		
Wein et al (1999)	0.63	0.35, 1.14
Population	0.63	0.29, 1.34
Diet + Exercise		
Knowler et al (2002)	0.43	0.36, 0.49
Liao et al (2002)	0.43	0.25, 0.75
Kosaka et al (2005)	0.42	0.24, 0.64
Ramachandran et al (2006)	0.51	0.39, 0.73
Roumen et al (2008)	0.43	0.27, 0.65
Population	0.43	0.31, 0.59
75-150mg, 150mg & 300mg Acarbose (Daily)		
STOP-NIDDM (2002)	0.74	0.63, 0.89
Pan et al (2003)	0.72	0.41, 1.13
Population	0.73	0.45, 1.11
2.5mg Glipizide (Daily)		
Eriksson et al (2006)	0.18	0.02, 1.49
Population	0.18	0.02, 1.58
750mg, 500-1000mg & 1700mg Metformin (Daily)		
Li et al (1999)	0.64	0.35, 1.02
Knowler et al (2002)	0.68	0.60, 0.77
Ramachandran et al (2006)	0.71	0.52, 0.92
Population	0.65	0.43, 0.90
360mg Orlistat (Daily)		
Heymsfield et al (2000)	0.39	0.20, 0.77
Population	0.39	0.17, 0.89
15 mg Ramipril (Daily during year one)		
DREAM Trial Investigators (2006)	0.91	0.81, 1.03
Population	0.91	0.54, 1.50
Diet + Exercise + 750mg, 500-1000mg & 1700mg Metformin (Daily)		
Ramachandran et al (2006)	0.63	0.44, 0.90
Population	0.56	0.30, 0.99
Diet + Exercise + 360mg Orlistat (Daily)		
Population	0.21	0.09,0.47
Diet + Exercise + 20 mg Pioglitazone (Daily)		
DeFronzo et al (2011)	0.34	0.21, 0.52
Population	0.35	0.22, 0.59
Diet + Exercise + 0.6mg Voglibose (Daily)		
Population	0.25	0.13, 0.49

Table 6: Probability of treatments rankings for short-term trials – All treatments

	Ranking											
Treatment	1	2	3	4	5	6	7	8	9	10	11	12
1	0.000	0.002	0.000	0.000	**0.510**	0.000	0.032	0.000	0.001	**0.326**	0.010	**0.118**
2	0.000	0.009	0.002	0.001	**0.113**	0.000	0.091	0.001	0.005	**0.389**	0.053	**0.335**
3	0.000	0.020	0.024	0.003	0.082	0.001	**0.149**	0.001	0.019	**0.166**	**0.184**	**0.351**
4	0.000	0.043	**0.142**	0.006	0.054	0.005	**0.192**	0.003	0.045	0.063	**0.326**	**0.122**
5	0.000	0.062	**0.334**	0.011	0.038	0.013	**0.150**	0.005	0.079	0.027	**0.241**	0.040
6	0.000	0.096	**0.348**	0.028	0.036	0.052	**0.141**	0.007	**0.155**	0.013	**0.109**	0.015
7	0.000	**0.169**	0.115	0.074	0.033	**0.168**	0.098	0.015	**0.265**	0.007	0.049	0.008
8	0.003	**0.158**	0.028	**0.151**	0.022	**0.326**	0.060	0.033	**0.194**	0.004	0.017	0.004
9	0.012	**0.147**	0.005	**0.276**	0.023	**0.290**	0.040	0.076	**0.118**	0.003	0.007	0.003
10	0.073	**0.143**	0.001	**0.332**	0.021	**0.118**	0.026	**0.205**	0.076	0.001	0.003	0.002
11	**0.324**	0.072	0.000	0.085	0.014	0.023	0.013	**0.438**	0.028	0.001	0.001	0.001
12	**0.589**	0.079	0.000	0.033	0.054	0.004	0.009	**0.216**	0.014	0.001	0.000	0.001

Treatments: 1. Placebo; 2. Diet; 3. Diet + Exercise; 4. 75-150mg, 150mg & 300mg Acarbose (Daily); 5. 2.5mg Glipizide (Daily); 6. 750mg, 500-1000mg & 1700mg Metformin (Daily); 7. 360mg Orlistat (Daily); 8. 15 mg Ramipril (Daily during year one); 9. Diet + Exercise + 750mg, 500-1000mg & 1700mg Metformin (Daily); 10. Diet + Exercise + 360mg Orlistat (Daily); 11. Diet + Exercise + 20 mg Pioglitazone (Daily); 12. Diet + Exercise + 0.6mg Voglibose (Daily) Probabilities highlighted in yellow are those greater than or equal to 0.100

Table 7: Probability of treatments rankings for short-term trials – Lifestyle treatments

	Ranking		
Treatment	1	2	3
1	0.000	**0.159**	**0.841**
2	**0.101**	**0.741**	**0.159**
3	**0.900**	0.100	0.000

Treatments: 1. Placebo; 2. Diet; 3. Diet + Exercise. Probabilities highlighted in yellow are those greater than or equal to 0.100

Table 8: Adjusted hazard ratios and 95% credible intervals – Short-term trials

Intervention	**Hazard Ratio**	**95% CrI**
Diet	0.45	0.01, 13.23
Diet + Exercise	0.45	0.26, 0.76
75-150mg, 150mg & 300mg Acarbose (Daily)	0.85	0.16, 3.98
2.5mg Glipizide (Daily)	0.22	0.01, 3.91
750mg, 500-1000mg & 1700mg Metformin (Daily)	0.63	0.33, 1.08
360mg Orlistat (Daily)	0.31	0.03, 3.88
15 mg Ramipril (Daily during year one)	1.06	0.18, 5.35
Diet + Exercise + 750mg, 500-1000mg & 1700mg Metformin (Daily)	0.52	0.11, 2.59
Diet + Exercise + 360mg Orlistat (Daily)	0.21	0.01,3.05
Diet + Exercise + 20 mg Pioglitazone (Daily)	0.37	0.17, 0.79
Diet + Exercise + 0.6mg Voglibose (Daily)	0.28	0.03, 2.67

Table 9: Covariate effects and 95% credible intervals – Short-term trials

	Coefficient	95% CrI
Diet		
Age	-0.03	-0.33, 0.26
BMI	0.00	-0.24, 0.25
Diet + Exercise		
Age	-0.03	-0.16, 0.11
BMI	-0.00	-0.12, 0.12
75-150mg, 150mg & 300mg Acarbose (Daily)		
Age	-0.03	-0.34, 0.27
BM	0.01	-0.15, 0.19
2.5mg Glipizide (Daily)		
Age	-0.03	-0.35, 0.27
BMI	0.00	-0.24, 0.24
750mg, 500-1000mg & 1700mg Metformin (Daily)		
Age	-0.02	-0.25, 0.20
BMI	0.02	-0.12, 0.17
360mg Orlistat (Daily)		
Age	-0.03	-0.34, 0.28
BMI	0.00	-0.24, 0.24
15 mg Ramipril (Daily during year one)		
Age	-0.03	-0.33, 0.28
BMI	0.01	-0.24, 0.25
Diet + Exercise + 750mg, 500-1000mg & 1700mg Metformin (Daily)		
Age	-0.03	-0.35, 0.28
BMI	0.00	-0.24, 0.24
Diet + Exercise + 360mg Orlistat (Daily)		
Age	-0.03	-0.34, 0.28
BMI	0.01	-0.24, 0.24
Diet + Exercise + 20 mg Pioglitazone (Daily)		
Age	-0.05	-0.28, 0.16
BMI	-0.01	-0.20, 0.17
Diet + Exercise + 0.6mg Voglibose (Daily)		
Age	-0.03	-0.34, 0.27
BMI	0.00	-0.23, 0.25
Overall		
Age	-0.03	-0.23, 0.17
BMI	0.00	-0.15, 0.15

Table 10: Unadjusted hazard ratios and 95% credible intervals - Mid-term trials

	Hazard Ratio	95% CrI
Diet		
Jarrett et al (1979)	1.11	0.60, 2.23
Pan et al (1997)	0.69	0.55, 0.87
Population	0.73	0.37, 1.79
Exercise		
Pan et al (1997)	0.53	0.42, 0.67
Population	0.53	0.21, 1.36
Diet + Exercise		
Lindstrom et al (2006)	0.59	0.40, 0.87
Lindahl et al (2009)	0.49	0.20, 0.79
Penn et al (2009)	0.54	0.26, 0.90
Population	0.56	0.30, 0.93
50mg Phenformin (Daily)		
Jarrett et al (1979)	1.45	0.70, 2.98
Population	1.04	0.30, 3.81
Diet + 50mg Phenformin (Daily)		
Jarrett et al (1979)	0.67	0.24, 1.86
Population	0.48	0.11, 2.10
Diet + Exercise + up to 60mg Nateglinide (3 times daily)		
NAVIGATOR (2011b)	1.07	1.00, 1.15
Population	1.07	0.40, 3.00
Diet + Exercise + up to 160mg Valsartan (Daily)		
NAVIGATOR (2011a)	0.86	0.80, 0.92
Population	0.86	0.32, 2.45

Table 11: Probability of treatments rankings for mid-term trials – All treatments

	Ranking							
Treatment	1	2	3	4	5	6	7	8
1	0.000	0.019	**0.273**	**0.155**	0.035	**0.461**	0.019	0.039
2	0.003	0.070	**0.330**	**0.326**	0.069	**0.124**	0.027	0.051
3	0.016	**0.194**	**0.193**	**0.303**	0.067	**0.108**	0.038	0.080
4	0.054	**0.317**	0.096	**0.142**	0.092	0.090	0.057	**0.153**
5	**0.153**	**0.203**	0.048	0.051	**0.128**	0.064	0.089	**0.264**
6	**0.345**	**0.102**	0.028	0.016	**0.111**	0.046	**0.144**	**0.208**
7	**0.338**	0.065	0.019	0.006	**0.131**	0.058	**0.273**	**0.109**
8	0.090	0.031	0.012	0.002	**0.367**	0.050	**0.351**	0.096

Treatments: 1. Placebo; 2. Diet; 3. Exercise; 4. Diet + Exercise; 5. 50mg Phenformin; 6. Diet + 50mg Phenformin; 7. Diet + Exercise + up to 60mg Nateglinide (3 times daily); 8. Diet + Exercise + up to 160mg Valsartan (Daily). Probabilities highlighted in yellow are those greater than or equal to 0.100

Table 12: Probability of treatments rankings for mid-term trials – Lifestyle treatments

	Ranking			
Treatment	1	2	3	4
1	0.004	0.064	**0.559**	**0.373**
2	0.033	**0.180**	**0.300**	**0.487**
3	**0.151**	**0.615**	**0.103**	**0.132**
4	**0.812**	**0.142**	0.038	0.008

Treatments: 1. Placebo; 2. Diet; 3. Exercise; 4. Diet + Exercise. Probabilities highlighted in yellow are those greater than or equal to 0.100

Table 13: Adjusted hazard ratios and 95% credible intervals – Mid-term trials

Intervention	Hazard Ratio	95% CrI
Diet	0.85	0.16, 4.36
Exercise	0.71	0.03, 13.89
Diet + Exercise	0.86	0.12, 5.27
50mg Phenformin (Daily)	0.83	0.08, 9.33
Diet + 50mg Phenformin (Daily)	0.38	0.03, 4.76
Diet + Exercise + up to 60mg Nateglinide (3 times daily)	0.72	0.02, 32.17
Diet + Exercise + up to 160mg Valsartan (Daily)	0.58	0.02, 41.08

Table 14: Covariate effects and 95% credible intervals – Mid-term trials

	Coefficient	95% CrI
Diet		
Age	0.08	-0.15, 0.29
BMI	-0.18	-0.86, 0.52
Exercise		
Age	0.08	-0.31, 0.46
BMI	-0.18	-0.86, 0.52
Diet + Exercise		
Age	0.09	-0.29, 0.44
BMI	-0.18	-0.77, 0.45
50mg Phenformin (Daily)		
Age	0.08	-0.32, 0.46
BM	-0.18	-0.86, 0.52
Diet + 50mg Phenformin (Daily)		
Age	0.08	-0.32, 0.47
BMI	-0.18	-0.86, 0.52
Diet + Exercise + up to 60mg Nateglinide (3 times daily)		
Age	0.08	-0.33, 0.46
BMI	-0.18	-0.86, 0.53
Diet + Exercise + up to 160mg Valsartan (Daily)		
Age	0.08	-0.34, 0.46
BMI	-0.18	-0.87, 0.52
Overall		
Age	0.08	-0.24, 0.38
BMI	-0.18	-0.82, 0.49

5.2.5 Sub-group analysis

None of the trials reported to date have separate data on sub-groups such as those in socio-economic or ethnic groups. However, number of trials included in this review, recruited the whole trial population only from a south Asian population, enabling a meta-analysis of trials with a south Asian population.

South Asian populations

There are five studies on diet and exercise intervention, with populations of; Chinese (Li et al 2009; Pan et al. 1997 ++), Asian Indian (Ramachandran et al. 2006 ++), Japanese (Kosaka et al. 2005 ++) and Japanese American (Liao et al 2002). Four studies on pharmacological interventions had a south Asian population; Chinese (Li et al. 1999 ++ [metformin], Pan et al. 2003 ++ [acarbose]), Asian Indian (Ramachandran et al. 2009 ++ [pioglitazone]), and Japanese (Kawamori et al. 2009 ++ [voglibose]).

Figure 9 displays the meta-analysis of a diet and exercise lifestyle interventions on south Asian populations, the overall pooled effect on the incidence of diabetes is 0.58 (95% CI 0.47 – 0.73).

Figure 10 displays the meta-analysis of pharmacological interventions (all oral diabetes drugs) on south Asian populations, the overall pooled effect on the incidence of diabetes is 0.72 (95% CI 0.52 – 0.99).

Figure 9: Meta-analysis of Lifestyle interventions on South Asian populations

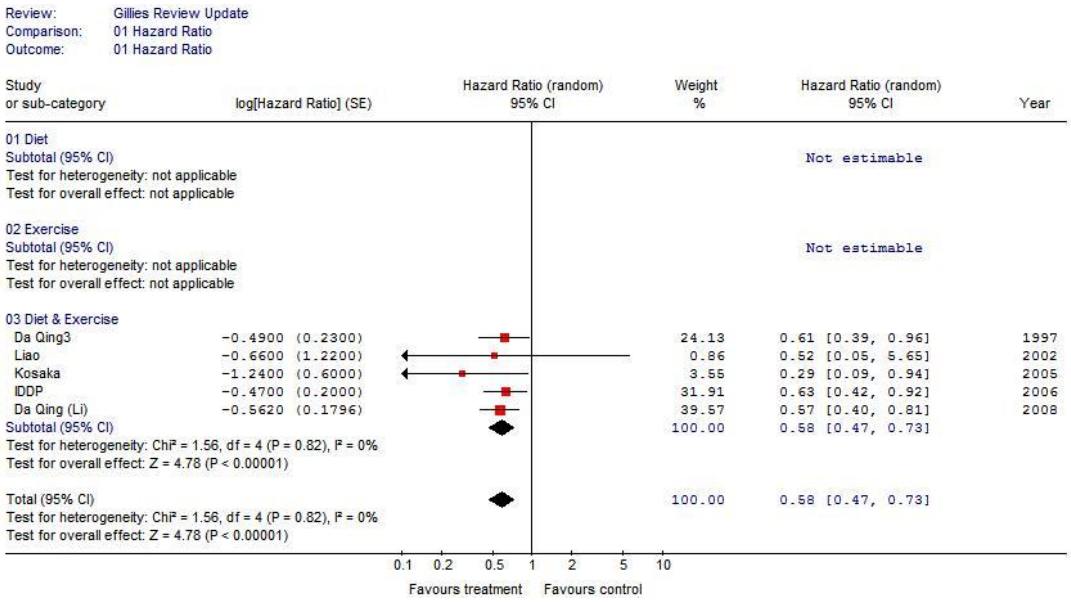
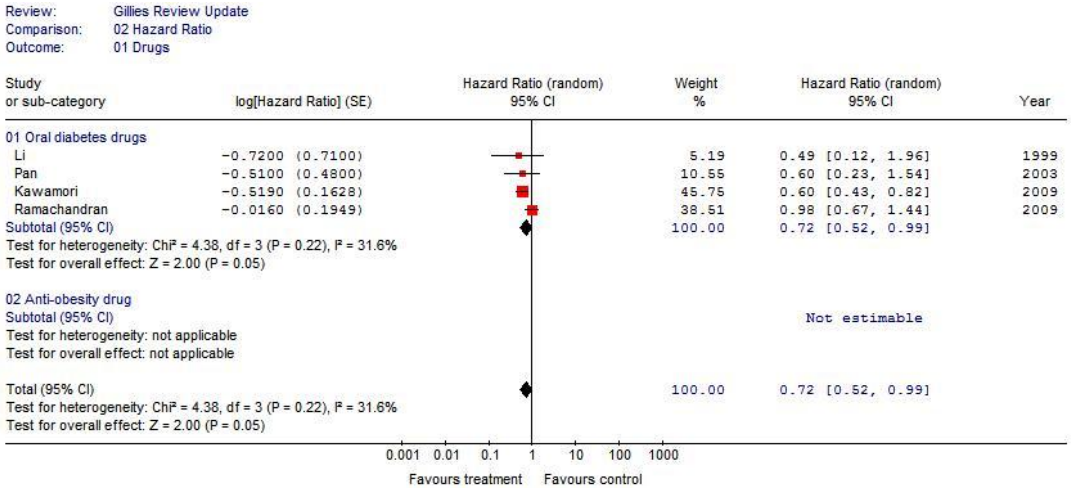


Figure 10: Meta-analysis of Pharmacological interventions on South Asian populations



Summary

For south Asian populations, in the short-term, it would appear both a lifestyle intervention of diet combined with exercise and pharmacological interventions have an effect in delaying or preventing the progression from IGT to a diagnosis of diabetes. The diet and exercise lifestyle intervention seems to have more effect on the progression from IGT to diabetes (overall pooled effect of 0.58, 95% CI 0.47 – 0.73), than pharmacological interventions (overall pooled effect of 0.72, 95% CI 0.52 – 0.99).

Evidence statement 5:

South Asian populations

For populations comprising of south Asian individuals (Asian Indian, Chinese, Japanese and Japanese Americans), both a diet combined with exercise intervention and oral diabetes drug interventions have an effect on the progression from IGT to diabetes. The diet and exercise lifestyle intervention seems to have more effect on the progression from IGT to diabetes (overall pooled effect of 0.58, 95% CI 0.47 – 0.73), than pharmacological interventions (overall pooled effect of 0.72, 95% CI 0.52 – 0.99).

The hazard ratio for diet combined with exercise intervention was based on five studies , one study in each of the following countries, US (Liao et al. 2002 +), Japan (Kosaka et al. 2005 ++), India (Ramachandran et al. 2006 ++) and two Chinese studies (Li et al. 1997 ++; Li et al. 2008 -).

For oral diabetes drugs, the hazard ration was based on four studies, one study each in the following countries, Japan (Kawamori et al. 2009 ++), India (Ramachandran et al. 2009 ++) and two Chinese studies (Li et al. 1999 ++; Pan et al 2003 ++).

5.2.6 Secondary outcomes analysis

Data Requirements for Additional Analysis of Secondary Outcomes

Meta-regressions are, in essence, similar to simple regressions, in which an outcome variable is predicted according to the values of one or more explanatory variables. In meta-regression, the outcome variable is the effect estimate (a mean difference, a risk difference, a log odds ratio or a log risk ratio), whilst the covariates (e.g., weight) are characteristics of studies that might influence the size of the intervention effect (Thompson & Sharp 1999). The resulting regression coefficient obtained from a meta-regression analysis will describe how the outcome variable (the intervention effect) changes with a unit increase in the covariate or “effect modifier”. The statistical significance of the regression coefficient is a test of whether there is a linear relationship between intervention effect and the explanatory variable. If the intervention effect is a ratio measure, the log-transformed value of the intervention effect should always be used in the regression model, and the exponential of the

regression coefficient will give an estimate of the relative change in intervention effect with a unit increase in the explanatory variable (Thompson & Sharp 1999).

In order to perform additional analyses on the secondary outcomes of interest in the present study, a statistical model would need to be created which incorporates the change in each of the covariates from baseline to the end of follow-up. For the majority of studies included in the current review, the necessary covariate data for each of the studies included in the meta-analysis are not provided or easily obtained in order to perform a meta-regression . There are six secondary outcomes of interest in the prevention to progression to type 2 diabetes project (BMI, weight, fasting glucose, HbA1c, systolic blood pressure, diastolic blood pressure). The RCTs included in the current review are all of varying lengths and it is likely that the response to treatment such as the change from baseline body weight varies over time according to some non-linear model. However, the change from baseline to the end of the intervention (or follow-up) for secondary outcomes of interest is not available for the majority of the included RCTs (see appendix 10 for details).

Network Meta-Analysis of Secondary Outcomes

The data required for a network meta-analysis of continuous outcomes are the sample mean responses and sample sizes in each treatment arm together with the sample standard deviations. As with the data requirements for performing a meta-regression of the secondary outcomes, the required sample standard deviations to perform a network meta-analysis are not available for most, if not all RCTs and outcome measures, and there is generally no information with which to retrospectively derive them (see appendix 10 for details).

A network meta-analysis involves estimating treatment effects in each trial relative to their trial-specific baseline treatments and combining estimates across trials based on functions of treatment effects relative to a standard baseline treatment. For many of the outcome measures (and ignoring the issue of time dependent responses) there are many trials that do not provide any sample data with which to estimate trial-specific treatment effects. Any attempt to performing a network meta-analysis (ignoring time dependent responses and lack of sample standard deviations) would generate extremely uncertain results.

In the absence of any other relevant sample data it might be possible to construct more complex statistical models taking into account the longitudinal nature of the data and use elicitation techniques to formulate genuine prior information about the

parameters in the model, including the changes over time and time-specific sampling variation. In addition, it might be possible to use multivariate meta-analysis methodology to "borrow strength" across outcome measures by modelling the correlation between outcome measures. This would also involve elicitation of expert opinion because the sample data does not provide any information on the correlation between outcome measures within patients.

In conclusion, a conventional network meta-analysis based on weak or non-informative prior information is not feasible given the sparseness of the data across RCTs. More complex model structures could be developed but inferences would only be possible with the inclusion of external information elicited from experts which is beyond the time and scope of this project. As seen in the table in appendix 10, only 5 of 26 RCTs provide both baseline and follow-up measures, and sample sizes for at least one of the six secondary outcomes. Given this result, a meta-regression should not be considered, since the general belief is that a minimum of ten studies should be included when completing a meta-regression analysis.

Where possible, data on secondary outcomes have been extracted and are presented in this section for information.

BMI change

Some studies reported and commented on the changes in BMI in the intervention and control groups at the end of the follow-up periods, but others did not. Where changes were reported these have been included, where changes were not reported or commented on, but BMI measurements for baseline and end of follow-up were in tables of characteristics, the change has been calculated, see table 15.

While the study by Wein reported BMI at baseline and at follow-up, other than saying paired testing showed that there were significant rises in BMI, the study authors do not explore this further (Wein et al.1999). The DPS study (Lindstrom et al. 2003 ++) and the Eriksson study (Eriksson et al. 2006 ++) reported BMI change at the end of the follow-up in a table but did not refer to it in the text. The Eriksson study (Eriksson et al. 2006 ++) included a table that reported on BMI measurement at baseline and after 18 months, stating that the mean difference between the two groups was -0.22 (95% CI -1.07 to 0.62). The DPS study (Lindstrom et al. 2003 ++) changes are shown in table 15.

The study by Liao (Liao et al. 2002 +) reported that at 24 months, the diet and exercise intervention group showed significantly greater reduction in BMI (-0.7 ± 0.2 vs. 0.2 ± 0.2, p= 0.0023) than the control group.

The study by Lindahl did not report on the changes in BMI, from information obtained from the published paper, the change in BMI was calculated by the authors of this review (Lindahl et al. 2009 ++). The BMI in the diet and exercise intervention group decreased by 0.4, remained the same in the control group at the end of the 5-year follow-up period.

The study by Roumen reported on the changes in BMI in a table but did not comment in the text of the report (Roumen et al. 2008 ++). From information obtained from the published paper, the change in BMI was calculated by the authors of this review. The BMI in the diet and exercise intervention group decreased by 0.36, but the BMI of the control group increased by 0.8 at the end of the 3-year follow-up period (p=0.014)

The study by Li also did not report on the changes in BMI (Li et al. 1999 ++), from information obtained from the published paper, the change in BMI was calculated by the authors of this review. The BMI in the metformin intervention group decreased by 1.6, while the BMI of the control group increased by 0.4 after one year of treatment.

The study by Ramachandran did not report on the changes in BMI (Ramachandran et al. 2009 ++). From information obtained from the published paper, again the change in BMI was calculated by the authors of this review. The BMI in the pioglitazone intervention group increased by 0.3, but decreased by 0.1 in the control after at the end of the 3-year follow-up period.

The study by DeFronzo did not report on the changes in BMI (DeFronzo et al. 2011 +). From information obtained from the published paper, again the change in BMI was calculated by the authors of this review. The BMI in the control group increase by 0.2 and the pioglitazone intervention group increased by 1.4 at the end of the follow-up period.

Table 15: BMI change

Intervention	Study	Baseline Mean (95% CI)	At follow-up Mean (95% CI)	Length of follow-up	Change
Lifestyle					
Diet	Wien 1999 intervention	25.2 (24.1-6.4)	26.0 (24.8-27.2)	2 years	+ 0.8†
	Wien 1999 Control	25.6 (24.5-26.8	26.2 (25.0-27.5)	2 years	+ 0.6†
Diet & exercise	Liao 2002 intervention	25.6 (24.8-26.4)	NR	2 years	-0.7 (-05.to -0.9)
	Liao 2002 control	26.6 (25.8-27.4)	NR	2 years	+ 0.2 (0-0.4)
	DPS 2003 intervention	31.4 (26.9-35.9)	NR	3 years	-1.3 (--2.2 to 0.6)
	DPS 2003 control	31.1 (26.6-35.6)	NR		-0.3 (-2.3 to 1.7)
	Roumen 2008 intervention	29.6 (25.8-30.4)	NR	3 years	-0.36 (-1.83 to 1.11)
	Roumen 2008 control	29.2 (25.9-32.5)	NR		+ 0.08 (-1.72 to 1.88)
	Lindahl 2009 intervention	31.2	30.8	5 years	-0.4†
	Lindahl 2009 control	30.2	30.2		0†
Pharmacological					
Metformin	Li 1999 intervention	26.4 (24.0-28.8)	25.0 (22.8-27.2	1 year	-1.6†
	Li 1999 control	26.0 (23.7-28.3)	26.4 (22.0-28.8)		+ 0.4†
Pioglitazone	Ramachandran 2009 intervention	25.9 (22.5-29.3)	26.2 (22.7-29.7)	3 years	+ 0.3†
	Ramachandran 2009 control	26.0 (22.9-29.1)	25.9 (22.7-29.1)		-0.1†
	DeFronzo 2011 intervention	34.1	35.5	Mean 2.2 years	+1.4†
	DeFronzo 2011 control	34.5	34.7		+0.2†
Glipzide	Erkisson 2006 intervention	27.9 (26.4-29.4)	28.2 (26.8-29.6)	18 months	+ 0.3†
	Erkisson 2006 control	28.8 (27.6-30.0)	29.3 (28.1-30.5)		+ 0.5†

NR= Not reported †Calculated

Summary

For lifestyle interventions, the mean changes in BMI in the intervention groups ranged from -1.3 to +0.8, while mean changes in the control groups ranged from -0.3 to +0.6. The follow-up periods ranged from two years to five years, with the most BMI reductions happening within three years, although at a 5-year follow-up (Lindahl et al. 2009 ++) the intervention group had maintained a reduction in BMI while the control group had not. In the pharmacological interventions, the mean changes in BMI in the intervention groups ranged from -1.6 to +1.4, while mean changes in the control groups ranged from -0.1 to +0.5. The follow-up periods in the pharmacological

interventions were shorter than the lifestyle interventions, ranging from one year to three years. For both lifestyle and pharmacological interventions, the intervention groups had a greater reduction in BMI than control groups, -1.3 in lifestyle intervention compared to -0.3 in lifestyle control and -1.6 in pharmacological interventions compared to -0.1 in pharmacological control. Although, in both pioglitazone studies (Ramachandran et al. 2009 ++, DeFronzo et al. 2011 +), the intervention group has a greater mean increase in BMI than the control group.

Evidence statement 6:

Reduction in BMI

In the short-term (two to five years), both lifestyle intervention and pharmacological interventions, showed a greater reduction in BMI than control groups. Lifestyle interventions (range -1.3 to +0.8) had a smaller range effect on BMI than pharmacological interventions (range -1.6 to +1.4).

The changes in BMI in the diet intervention are based on one Australian study (Wein et al. 1999 -), and the diet combined with lifestyle interventions are based on four studies, one from each of the following countries, US (Liao et al. 2002 +), Finland (Lindstrom et al. 2003 ++), Netherlands (Roumen et al. 2008 ++) and Sweden (Lindahl et al. 2009 ++). The changes in BMI in pharmacological studies are based on four studies, one from each of the following countries China (Li et al. 1999 ++), India (Ramachandran et al. 2009 ++), US (DeFronzo et al 2011. +) and Finland (Eriksson et al. 2006 ++).

Weight Change

Not every study reported and commented on the changes in weight in the intervention and control groups at the end of the follow-up periods. Where changes were reported these have been included, where changes were not reported or commented on, but weight measurements for baseline and end of follow-up were in tables of characteristics, the change has been calculated, see table 16.

In the DPP study (Knowler et al. 2002 ++), 50% of the participants in the lifestyle intervention group had achieved the goal of a 7% or more weight loss by the end of 24 weeks, and 38% had a weight loss of at least 7% at the time of the most recent follow-up visit. Participants in the lifestyle intervention group had a greater weight loss and a greater increase in leisure activity than the participants in the metformin

and placebo groups. The average weight loss was 0.12 kg in the placebo group, 2.1 kg in the metformin group and 5.6 kg in the lifestyle intervention group (p≥0.001).The DPP study (Knowler et al. 2002 ++) reported that mean bodyweight decreased from 87.6 kg (SD 15.2) to 87.1 kg (15.3) during the study in patients given acarbose and increased from 87.0 kg (14.1) to 87.3 kg (15.2) in those on placebo (difference 0.77 kg [95% CI 0.01–1.54], p=0.0184).

The Liao study (Liao et al. 2002 +) reported weight change in a table of characteristic of subjects at follow-up but did not comment on it in the text as weight reduction was not a goal for either group. From the information in the paper, the intervention group had a mean weight reduction of 1.8 kg and the control group had a mean weight increase of 0.7 kg. Similarly, the DPS study (Lindstrom et al. 2003 ++) reported weight change at the end of the follow-up in a table but did not refer to it in the text. In the study by the DPS, years, weight reductions were 3.5 kg in the diet and exercise intervention group and 0.9 kg in the control group.

The DPS follow-up study (Lindstrom et al. 2006 ++) did report mean weight at baseline and at the end of the extended follow-up period. The authors did not examine weight loss on its own, but as part of whether participants achieved all or some of five set goals (weight reduction of 5% or more; less than 30% of the daily energy intake from fat; less than 10% of the daily energy intake from saturated fat; fibre intake 15 g per 1000 kcal or more; and moderately intense physical activity 30 minutes per day or more). The mean weight reduction for the intervention group was 2.4 kg and the control group had a mean weight increase of 0.1 kg.

The study by Kosaka identified that body weight decreased by 0.39 kg in the control group and by 2.18 kg in the diet and exercise intervention group at the end of the 4-year follow-up period (Kosaka et al. 2005 ++). The study further reported that in the diet and exercise intervention group, mean body weight had decreased by 2.5 kg after the first year and tended to increase slightly thereafter, but remained significantly lower (by 2.18 kg) than the baseline value at the end of the 4 year follow-up period. Although body weight significantly decreased in the control group as well (decreased by 0.39 kg at the end of the 4 year follow-up period, the decrease in weight in the diet and exercise intervention group was significantly greater than the control group (p<0.001).

The study by Roumen did not report on the changes in weight in the text of the paper (Roumen et al. 2008 ++). From information obtained from tables the published paper,

weight in the diet and exercise intervention group decreased by an average of 1.08 kg, but increased by 0.16 kg in the control group at the end of the 3-year follow-up period (p=0.011).

The study by Lindahl did not report on weight change in the text of the paper, using information obtained from the published paper it was possible to calculate the change in weight from baseline to end of follow-up (Lindahl et al. 2009 ++). The diet and exercise intervention group had a mean weight reduction of 1.0 kg, while the mean weight of the control group was the same at the end of the 5-year follow-up period as it was at baseline.

The study by Ramachandran did not report on weight changes in detail (Ramachandran et al. 2009 ++), from information obtained from the published paper, the weight of subjects in the pioglitazone intervention group increased by 0.8, but decreased by 0.4 in the control after at the end of the 3-year follow-up period.

The DeFronzo study reported that weight gain was greater with pioglitazone than with placebo, and that although pioglitazone was associated with significant weight gain, it reduced the risk of diabetes (DeFronzo et al. 2011 +).

The Pan study in 2003 reported a statistically significant reduction in body weight (Pan et al. 2003 ++), with the acarbose intervention group losing a mean of 2.9 kg and the control group a mean of 1.6 kg during the 16 week treatment period. The estimated difference at endpoint between the two groups was -1.34 kg (95% CI -.95 to 0.74, p=0.0001).

The NAVIGATOR study (NAVIGATOR Study Group[b] 2010 ++) on nateglinide reported that there was a reduction in mean body weight during the study, with 10.1% of participants losing 5% of their baseline weight by 6 months, but the mean body weight was higher among participants in the nateglinide group than among those in the placebo group throughout the course of the study (mean difference, 0.35 kg; 95% CI, 0.22 to 0.48; p<0.001).

The NAVIGATOR study (NAVIGATOR Study Group[a] 2010 ++) on valsartan reported that there was a small decline in weight during follow-up that was slightly less in the valsartan group (0.31 ± 3.9 kg) than in the placebo group (0.60 ± 4.0 kg), a difference of 0.28 kg (95% CI, -0.05 to +0.45, p=0.12), although the reported standard deviations seem very large, this may be a reporting error.

In the one study (Heymsfield et al. 2000 ++) it was reported that 52.9% of subjects in the orlistat group lost 5% or more of initial body weight and 30.1% lost 10% or more

of initial weight, while 37.7% of subjects in the placebo group lost 5% or more of initial body weight and 16.5% lost 10% or more of initial weight (p<001 for orlistat vs. placebo for both ≥5% and ≥10% weight loss).

The XENDOS study (Torgerson et al. 2004 ++) reported that mean weight loss was statistically significantly greater with orlistat than placebo at one year (10.6 vs. 6.2 kg; p<0.001) and remained significantly greater at the end of the four year study (5.8 vs. 3.0 kg; p<0.001). For those patients who completed four years of treatment (52% of the orlistat patients and 34% of the placebo patients initially randomised), weight loss was statistically significantly greater with orlistat than placebo at the end of the first year (11.4 vs. 7.5 kg; p<0.001) and at the end of the 4 year follow-up (6.9 vs. 4.1 kg; p<0.001). Statistically significantly more orlistat patients (72.8%) than placebo patients (45.1%) achieved weight loss ≥5% after one year of treatment (p<0.001). A similar statistically significant difference was apparent for patients achieving a weight loss ≥10% (41.0% with orlistat vs. 20.8% with placebo; p<0.001). For those patients who completed four full years of treatment, 52.8 and 37.3%, respectively, lost ≥5% of baseline body weight (p<0.001) and 26.2 and 15.6%, respectively, lost ≥10% of baseline body weight (p<0.001).

Table 16: Weight change (kg)

Intervention	Study	Baseline Mean (95% CI)	At follow-up Mean (95% CI)	Length of follow-up	Mean change
Lifestyle					
Diet & exercise					
	DPP 2002 intervention	94.1 (73.3-114.9)	NR	Mean of 2.8 years	-5.6
	DPP 2002 control	94.3 (74.1-114.5)	NR		-0.1
	Liao 2002 intervention	66.1 (63.2-69.0)	NR		-1.8 (-2.3 to -1.3)
	Liao 2002 control	69.7 (67.1-72.3)	NR		0.7 (0.1-1.3)
	DPS 2003 intervention	86.7 (72.7-100.7)	NR	3 years	-3.5 (-8.6 to 1.6
	DPS 2003 control	85.5 (71.1-99.9)	NR		-0.9 (-6.3 to 4.5
	Kosaka 2005 intervention	NR	NR	4 years	-2.18 (-3.81 to –0.55
	Kosaka 2005 control	NR	NR		-0.39 (-1.81 to 1.03
	Roumen 2008 intervention	87.5 (73.8-101.80	NR	3 years	-1.08 (-5.38 to 3.22)
	Roumen 2008 control	83.0 (71.3- 94.7)	NR		0.16 (-4.75 to 5.07)
	Lindahl 2009 intervention	86.0	85.0	5 years	-1.0†
	Lindahl 2009 control	83.9	83.9		0†
	DPS 2006 intervention	86.7	84.3	7 years	-2.4†
	DPS 2006 control	85.5	85.6		0.1†

Intervention	Study	Baseline Mean (95% CI)	At follow-up Mean (95% CI)	Length of follow-up	Mean change
Pharmacological					
Metformin	DPP 2002 intervention	94.3 (74.4-114.2)	NR	Mean of 2.8 years	-2.1
	DPP 2002 control	94.3 (74.1-114.5)	NR		-0.1
Acarbose	STOP-NIDDM 2002 intervention	87.6	87.1	Mean of 3.3 years	-0.5†
	STOP-NIDDM 2002 control	87.0	87.3		0.3†
	Pan 2003 intervention	67.5 (57.1-77.9)	64.6 (54.4-74.6	16 weeks	-2.9†
	Pan 2003 control	68.0 (56.4-79.6)	66.4 (55.2-77.6)		-1.6†
Pioglitazone	Ramachandran 2009 intervention	68.9 (58.7-79.1)	69.7 (59.6-79.8)	3 years	0.8†
	Ramachandran 2009 control	68.7 (59.6-77.8)	68.3 (59.3-77.3)		-0.4†
	DeFronzo 2011 intervention	94.9 (93.7-96.1)	98.7 (97.4-100.0)	Mean 2.2 years	+3.8†
	DeFronzo 2011 control	96.7 (95.5-97.9)	97.3 (96.0-98.6)		+0.1†
Nateglinide	NAVIGATOR 2010 intervention	83.6 (66.4-100.8)	NR	Median of 5 years	See text
	NAVIGATOR 2010 intervention	83.6 (66.4-100.8)	NR		See text
Valsartan	NAVIGATOR 2010 intervention	83.5 (66.1-100.9)	NR	Median of 5 years	See text
	NAVIGATOR 2010 intervention	83.8 (66.7-100.9)	NR		See text
Orlistat	Heymsfield 2006 intervention	99.0 (93.0-105.0)	NR	2 years	See text
	Heymsfield 2006 control	99.8 (90.8-108.8)	NR		See text
	XENDOS 2004 intervention	110.4 (94.1-126.7)	NR	4 years	See text
	XENDOS 2004 control	110.6 (94.1-127.1)	NR		See text

NR=not reported †Calculated

Summary

For lifestyle interventions, the mean weight change in the intervention groups ranged from -5.6 kg to +0.16 kg, while mean changes in the control groups ranged from -3.5 kg to +0.7 kg. The follow-up periods ranged from two years to seven years, with the best reductions in weight happening within three years, although at a 7-year follow-up the intervention group had maintained a weight loss (- 2.4 kg) while the control group had not (+0.1 kg). In the pharmacological interventions, the mean weight change in the intervention groups ranged from -2.9 kg to +0.8 kg, while mean changes in the control groups ranged from -1.6 kg to +0.3 kg. The follow-up periods in the pharmacological interventions were shorter than the lifestyle interventions, ranging from 16 weeks to four years. For both lifestyle and pharmacological interventions, the intervention groups had a higher weight change than control

groups. The DeFronzo study stated that one of the reasons for not completing the study included weight gain (in 9 patients in the pioglitazone group and 3 in the placebo group).

The maintenance of weight loss, was mentioned briefly by some studies, The DPS study (Lindstrom et al. 2003 ++) only stated that the maintenance of weight reduction after the diet combined with exercise intervention was satisfactory. The study by Roumen reported that the diet and exercise lifestyle intervention resulted in modest weight reduction after 1 year, with a gradual regain in the following years (Roumen et al. 2008 ++). A similar result was found by the Kosaka study, which stated that in the intervention group, mean body weight had decreased after 1 year but tended to increase slightly thereafter (Kosaka et al. 2005 ++).

Evidence statement 7:

Weight change

In the short-term (two to five years), both lifestyle intervention and pharmacological interventions, showed a greater weight change than control groups. Lifestyle interventions appear to have a greater weight change (range -5.6 kg to +0.16 kg) than pharmacological interventions (range -2.9 kg to +3.8 kg).

The changes in weight in lifestyle interventions was based seven studies, one each from the following countries, Sweden (Lindhal et al. 2009 ++), Netherlands (Roumen et al. 2008 ++), Japan (Kosaka et al. 2005 ++), and two from each of the following countries, US (Knowler et al. 2002 ++; Liao et al. 2002 +) and Finland (Lindstrom et al. 2003 ++; Lindstrom et al. 2006 ++ ++).

The changes in weight in pharmacological interventions were based on nine studies, two multi-country studies (NAVIGATOR Study Group[a] 2010 ++, NAVIGATOR Study Group[b] 2010 ++), one from Canada/Europe (Chiasson et al. 2002 ++), US/Europe (Heymsfield et al. 2000 ++) , two US (Knowler et al. 2002 ++, DeFronzo et al. 2011 +), and one each from the following countries, Sweden, (Torgerson et al. 2004 ++), India (Ramachandran et al. 2009 ++) and China (Pan et al. 2003 ++).

Maintenance of the weight loss was mentioned briefly by three studies, with one Finnish study (Linstrom et al. 2003 ++), saying weight maintenance was satisfactory and two studies one Japanese (Kosaka et al. 2005 ++) and one Netherlands (Roumen et al. 2008 ++) saying weight decreased after one year but increased slightly afterwards.

Change in blood pressure

Some studies reported and commented on the changes in blood pressure in the intervention and control groups at the end of the follow-up periods, but others did not. Where changes were reported these have been included, where changes were not reported or commented on, but where systolic and/or diastolic blood pressure measurements for baseline and end of follow-up were in tables of characteristics, the change has been calculated, see table 17.

Two studies on lifestyle intervention (Kosaka et al. 2005 ++; DPPOS 2009) and three studies on pharmacological interventions (Dream Trial Investigators 2006 ++; Ramachandran et al. 2006 ++; Chiasson et al. 2002 ++), reported baseline mean

systolic blood pressure and mean diastolic blood pressure for intervention and control groups, but did not reported any follow-up data on these variables.

One study on a diet only intervention (Jarrett et al. 1979 +) did not report the baseline or follow-up data for mean systolic blood pressure and mean diastolic blood pressure. The authors did reported that all diagnosed with diagnosed with diabetes (intervention and control groups combined) had an increase in systolic blood pressure of 21.4 mmHg compared to an increase of 26.9 mmHg in those not diagnosed with diabetes.

The Pan study in 2003 reported a reduction in both systolic and diastolic blood pressure (Pan et al. 2003 ++), between intervention and control groups at the end of a 16 week follow-up. There was a difference of -1.29 mmHg in systolic blood pressure and -1.34 mmHg in diastolic blood pressure between the intervention group and the control group at the end of the 16 week treatment period.

The study by Roumen did not report on the changes in systolic blood pressure or diastolic blood pressure in the text of the paper, but reported the mean change in a table (Roumen et al. 2008 ++). At the end of a 3-year follow-up, systolic blood pressure in the diet and exercise intervention group decreased by an average of 3.6, and by 3.5 in the control group. Diastolic blood pressure in the diet and exercise intervention group decreased by an average of 5.6, and by 3.1 in the control group

The study by Li did not report on change in blood pressure in the text of the paper, using information obtained from the published paper it was possible to calculate the change in blood pressure from baseline to end of a 1-year follow-up (Li et al. 2008 -). The mean systolic blood pressure change in the diet and exercise intervention group was an increase of 11 mmHG, and an increase of 13 mmHg in the control group at the end of the 20-year follow-up period. The intervention group had a mean decrease of -7 mmHg in diastolic blood pressure and the control group had a mean decrease of -5 mmHg. However, this follow up is vastly different to the other studies in this review, and with a 20 year follow-up many of these participants would be well into in their 60s and therefore a rise in blood pressure would naturally be expected.

The study by Lindahl did not report on change in blood pressure in the text of the paper, using information obtained from the published paper it was possible to calculate the change in blood pressure from baseline to end of follow-up (Lindahl et al. 2009 ++). The study by Li also did not report on the changes in blood pressure (systolic or diastolic), from information obtained from the published paper (Li et al. 1999 ++), the changes were calculated by the authors of this review. After one year of treatment systolic blood pressure in the metformin intervention group decreased by 10 mmHg, and by 3 mmHG in the control group. The diastolic blood pressure decreased by 5 mmHg in the intervention group and by 4 mmHG in the control group.

The study by Ramachandran did not report on changes in blood pressure in detail (Ramachandran et al. 2009 ++), other than to report that systolic and diastolic blood pressure showed modest increases in both groups. At the end of the 3-year follow-up, systolic blood pressure had a mean change of 4.4 mmHg in the intervention group and 5.5 mmHg in the control group. Diastolic blood pressure had increase by 2.0 in the intervention group and by 3.6 in the control group.

The study by DeFronzo did not report on changes in blood pressure in detail (DeFronzo et al. 2011 +), other than to report that systolic blood pressure declined slightly in both groups, but the difference in decline between the groups was not significant, but diastolic blood pressure was consistently lower in the pioglitazone group (p= 0.01).

The NAVIGATOR study on nateglinide (NAVIGATOR Study Group[b] 2010 ++), reported that no significant between group differences were seen in systolic or diastolic blood pressure.

The NAVIGATOR study on valsartan (NAVIGATOR Study Group[a] 2010 ++), reported that blood-pressure levels decreased more in the valsartan group than in the placebo group, with a mean overall reduction in systolic pressure of 6.3 mm Hg in the valsartan group, as compared with a reduction of 3.8 mm Hg in the placebo group (between-group difference, 2.8 mm Hg; 95% CI, 2.4 to 3.2; p<0.001) with adjustment for region, cardiovascular history, and nateglinide treatment. The mean reduction in diastolic pressure was 4.4 mm Hg in the valsartan group, as compared with a

reduction of 3.0 mm Hg in the placebo group (difference, 1.4 mm Hg; 95% CI, 1.2 to 1.7; p<0.001).

The Eriksson study (Eriksson et al. 2006 ++) reported the change in systolic and diastolic blood pressure between groups at the end of the follow-up in a table but did not refer to it in the text. There was no mean change in systolic blood pressure in the intervention group, at the end of the 18 month follow-up, but a decrease of 3 mmHg in the control group. The mean change in diastolic blood pressure was -1 mmHg in the intervention group and – 4 in the control group.

The XENDOS study (Torgerson et al. 2004 ++) reported that mean reduction in systolic blood pressure was statistically significantly greater with orlistat than placebo at the end of the four year study(-4.9 vs. -3.4; p<0.01) and similarly for diastolic blood pressure (-2.6 vs. -1.9; p<0.01), see table 17.

Table 17: Change in blood pressure (mm Hg)

Intervention	Study	Systolic		Diastolic		Length of follow-up	Mean change
		Baseline Mean	At follow-up Mean	Baseline Mean	At follow-up Mean		
Lifestyle							
Diet & exercise	Roumen 2008 intervention	142	NR	90	NR	3 years	Systolic -3.6 Diastolic -6.2
	Roumen 2008 control	145	NR	88	NR		Systolic -3.5 Diastolic -3.1
	Li 2008 intervention	134	145	89	82	20 years	Systolic 11† Diastolic -7†
	Li 2008 control	132	145	88	83		Systolic 13† Diastolic -5†
	Lindahl 2009 intervention	141	142	84	83	5 years	Systolic 1† Diastolic -1†
	Lindahl 2009 control	141	145	86	85		Systolic 4† Diastolic -1†
Pharmacological							
Metformin	Li 1999 intervention	134	124	89	84	1 year	Systolic -10† Diastolic -5†
	Li 1999 control	132	129	88	84		Systolic -3† Diastolic -4†
	Pan 2003 intervention	125.4	120.5	78.0	75.1	16 weeks	Systolic -4.9† Diastolic -2.9†
	Pan 2003 control	126.8	122.5	78.1	76.4		Systolic -4.3† Diastolic -1.7†
Pioglitazone	Ramachandran 2009 intervention	117.8	122.2	75.3	77.3	3 years	Systolic 4.4† Diastolic 2.0†
	Ramachandran 2009 control	118.1	123.6	75.5	79.1		Systolic 5.5† Diastolic 3.6†
	DeFronzo 2011 intervention	127	NR	74	NR	Mean 2.2 years	See text
	DeFronzo 2011 control	128	NR	74	NR		See text
Valsartan	NAVIGATOR 2010 intervention	139.8	NR	82.6	NR	Median of 5 years	See text
	NAVIGATOR 2010 intervention	139.5	NR	82.5	NR		See text
Glipzide	Erkisson 2006 intervention	143	143	88	87	18 months	Systolic 0† Diastolic -1†
	Erkisson 2006 control	134	131	83	79		Systolic -3† Diastolic -4†
Orlistat	XENDOS 2004 intervention	130.8	NR	82.0	NR	4 years	Systolic -4.9 Diastolic -2.6
	XENDOS 2004 control	130.4	NR	82.3	NR		Systolic -3.4 Diastolic -1.9

NR=not reported †Calculated

Summary

For lifestyle interventions, the mean change in systolic blood pressure in the intervention groups ranged from -10.0 to 11.0 mmHg, while mean changes in the control groups ranged from -4.3 to 13.0 mmHg. The mean change in diastolic blood pressure in the intervention groups ranged from -7.0 to 2.0 mmHg, while mean changes in the control groups ranged from -5.0 to 3.6 mmHg. Most of the studies had a short-term follow-up period (range 1-year to 4-years). Looking only at studies with a short-term follow-up, the mean change in systolic blood pressure in the intervention groups ranged from -10.0 to 4.4 mmHg, while mean changes in the control groups ranged from -4.3 to 5.5 mmHg, and the mean change in diastolic blood pressure in the intervention groups ranged from -6.2 to 2.0 mmHg, while mean changes in the control groups ranged from -4.0 to 3.6 mmHg. Only one study (Li et al. 2008 -) had a long-term follow-up period of 20 years. This study reported that systolic blood pressure increase from baseline for both the intervention and control groups (11 mmHg and 13 mmHg respectively) while diastolic blood pressure decreased in the intervention and control groups (-7 mmHg and -5 mmHg respectively).

Evidence statement 8:

Change in blood pressure

In the short-term (two to five years), both lifestyle and pharmacological interventions showed a slightly greater reduction in systolic blood pressure (a range of -10.0 to 4.4 mmHg, compared to a range of -4.3 to 5.5 mmHg) and diastolic blood pressure than control groups (a range of -6.2 to 2.0 mmHg, compared to a range of -4.0 to 3.6 mmHg).

In the long-term, based on one study with a 20-year follow-up, the diet and exercise intervention had a slightly smaller increase in systolic blood pressure than the control group (11 mmHg and 13 mmHg respectively) as well as having a slightly greater reduction in diastolic blood pressure than the control group (-7 mmHg and -5 mmHg respectively). However, this follow up is vastly different to the other studies in this review, and with a 20 year follow-up many of these participants would be well into in their 60s and therefore a rise in blood pressure would naturally be expected.

The changes in blood pressure in lifestyle interventions was based three studies, one Swedish (Lindahl et al. 2009 ++), one Chinese (Li et al. 2008 -) and one Netherlands (Roumen et al. 2008 ++). The changes in blood pressure in pharmacological interventions were based on seven studies, one from each of the following countries, Finland (Eriksson et al. 2006 ++), Sweden (Torgerson et al. 2004 ++), India (Ramachandran et al. 2009 ++), US (DeFronzo et al. 2011 +), two from China (Li et al 1999 ++; Pan et al. 2003 ++) and two multi-country study (NAVIGATOR Study Group[b] 2010 ++, NAVIGATOR Study Group[a] 2010 ++).

Change in blood glucose

Not every study reported and commented on the changes in blood glucose in the intervention and control groups at the end of the follow-up periods. Where changes were reported these have been included, where changes were not reported or commented on, but blood glucose measurements for baseline and end of follow-up were in tables of characteristics, the change has been calculated, see table 18.

Three studies (Pan et al. 1997 ++; Li et al. 1999 ++; Lindahl et al. 2009 ++), did not report on change in blood glucose in the text of the paper, by using information obtained from the published paper it was possible to calculate the change in blood glucose from baseline to end of follow-up (see table 18).

The study by Roumen reported that two hour plasma glucose levels decreased in the intervention group from 8.59 ± 0.24 mmol/l at baseline to 7.96 ± 0.29 mmol/l after 1 year and returned to 8.55 ± 0.34 mmol/l after 3 years. In the control group, an increase was seen from 8.46 ± 0.23 mmol/l at baseline to 8.83 ± 0.29 mmol/l after1 year and to 9.35 ± 0.33 mmol/l after 3 years (p=0.023 time × group interaction). In the intention-to-treat analysis, the two hour plasma glucose levels were not significantly different in the two groups (p=0.086). The difference between groups was 0.87 mmol/l after 1 year and remained relatively constant throughout the study (p interaction=0.014). No differences were observed in fasting plasma glucose in the completers analysis, whereas the change in fasting glucose did become significantly different between groups in the intention-to-treat analysis (p=0.04).

In the DPS study (Lindstrom et al. 2003 ++), statistically significantly greater improvements were seen at year 1 in fasting plasma glucose (−0.2 vs. 0.0 mmol/l) and two hour plasma glucose (−0.9 vs. −0.3 mmol/l) in the intervention group compared with the control group. No other information regarding plasma glucose was reported, but by using information obtained from the published paper it was possible to calculate the change in blood glucose from baseline to end of follow-up (see table 18).

The study by Li also did not report on the changes in blood glucose in detail other than to say that statistically significant falls (p<0.01) in fasting glucose were reported at six and 12 months, respectively, and by the end of the study, the mean fasting glucose was 5 mmol/l for the metformin group and 6.2 mmol/l for the placebo group (Li et al. 1999 ++).

The study by Ramachandran did not report on changes in blood glucose in detail (Ramachandran et al. 2009 ++), other than to report that a Cox's proportional hazard model showed that only baseline two hour plasma glucose (per mmol) had a significant contribution to the conversion to diabetes with a HR of 1.014 (95% CI 1.002–1.026; β=0.014), p=0.024. The result was similar when either BMI or waist circumference was entered as an independent variable. Between- and within-group

variations at the 3-year follow-up showed that mean plasma glucose was significantly increased from baseline.

The study by DeFronzo did not report on changes in blood glucose in detail (DeFronzo et al. 2011 +), other than to report that greater reductions in fasting and two hour glucose levels were achieved in the pioglitazone group than in the placebo group ($p<0.001$ for both comparisons), with a between-group difference of 3.5±1.1 mg per deciliter (0.2±0.06 mmol per liter) and 14±3 mg per deciliter (0.8±0.17 mmol per liter), respectively, at the end of the study.

The DPP follow-up study (Diabetes Prevention Program Research Group 2009 ++) reported the baseline fasting glucose (mmol/L) and two hour glucose (mmol/L), actual figures at the end of the follow-up period was not reported (although a graph showing mean changes since randomisation was). The authors did report that metformin was at least as effective as lifestyle intervention in prevention of rises in fasting glucose. This finding became evident during the DPPOS, and could be a result of a greater effect of metformin when combined with lifestyle sessions, or a more sustained effect achieved with metformin than with that of the lifestyle intervention alone.

The Eriksson study (Eriksson et al. 2006 ++) reported the change in blood glucose at baseline and at the end of the follow-up in a table, the authors reported that compared with baseline values, changes in both fasting glucose ($p=0.04$) and two hour glucose concentrations ($p=0.03$) were significantly larger in the glipizide group than those observed in the placebo group. In addition, the change in the area under the glucose curve was larger in the glipizide group ($p=0.07$).

The NAVIGATOR study on nateglinide did not report on changes in blood glucose in detail (NAVIGATOR Study Group[b] 2010 ++), other than to report that during the course of the study, participants in the nateglinide group had lower mean fasting plasma glucose levels than did those in the placebo group; the mean difference was 0.47 mg per decilitre (95% CI, 0.05 to 0.90) (0.03 mmol per liter [95% CI, 0.003 to 0.05]) ($p= 0.03$). However, glucose levels two hours after a glucose challenge were higher in the nateglinide group than in the placebo group; the mean difference was

4.37 mg per deciliter (95% CI, 2.80 to 5.93) (0.24 mmol per liter [95% CI, 0.16 to 0.33]) (p<0.001).

The NAVIGATOR study on valsartan did not report on changes in blood glucose in detail (NAVIGATOR Study Group[a] 2010 ++), other than to report that during the study, the fasting plasma glucose level was reduced by a mean of 0.59 mg per deciliter (95% CI, 0.16 to 1.02) (0.03 mmol per liter [95% CI, 0.01 to 0.06]) in the valsartan group, as compared with the placebo group (p<0.01). The plasma glucose level two hours after a glucose load was reduced by a mean of 3.15 mg per deciliter (95% CI, 1.58 to 4.72) (0.17 mmol per liter [95% CI, 0.09 to 0.26]) in the valsartan group (p<0.001).

The XENDOS study (Torgerson et al. 2004 ++) reported that mean changes in fasting glucose and two hour glucose was statistically significantly with orlistat than placebo at the end of the four year study(p<0.01) see table 18.

Summary

For lifestyle interventions, the mean change in fasting blood glucose in the diet only and exercise only intervention groups was 0.38 and 1.27 mmol/L respectively, and 2.07 mmol/L in the control groups. The mean change in fasting blood glucose in the diet combined with exercise intervention groups ranged from 0.0 to 2.3 mmol/L, while mean changes in the control groups ranged from 0.1 to 3.18 mmol/L. For pharmacological interventions, the mean change in two hour glucose ranged from -1.9 to 0.24 mmol/L, while mean changes in the control groups ranged from -1.1 to 0.5 mmol/L.

A change in two hour glucose in the diet only and exercise only intervention groups was 1.51 and in the control groups it was 2.07 mmol/L. The mean change in two hour glucose in the diet combined with exercise intervention groups ranged from -0.5 to 2.53 mmol/L, while mean changes in the control groups ranged from -0.1 to 4.78 mmol/L. For pharmacological interventions, the mean change in two hour glucose ranged from -3.1 to 0.59 mmol/L, while mean changes in the control groups ranged from -1.6 to 0.68 mmol/L.

Only one study (Li et al. 2008 -) had a long-term follow-up period of 20 years. This study reported that fasting blood glucose increase from baseline for both the

intervention and control groups (2.3 and 3.18 mmol/L respectively), as did two hour glucose (2.53 and 4.78 mmol/L respectively).

Evidence statement 9:

Change in blood glucose

In the short-term (two to six years), both lifestyle and pharmacological interventions tended to show a slightly greater reduction in fasting blood glucose and two hour glucose than control groups. In the long-term, based on one study with a 20-year follow-up, the diet and exercise intervention had a slightly smaller increase in both fasting blood glucose and two hour glucose than the control group.

For diet only and exercise only interventions, these were based on one Chinese study Pan et al. 1997 ++). The diet combined with exercise intervention was based on five studies, one each from the following countries, Netherlands (Roumen et al. 2008 ++), Sweden (Lindahl et al. 2009 ++), Finland (Lindstrom et al. 2003 ++) and two Chinese studies (Li et al. 2008 -; Pan et al. 1997 ++). The pharmacological interventions was based on six studies, one each from the following countries, US (DeFronzo et al. 2011 +) Sweden (Torgerson et al. 2004 ++), Finland (Eriksson et al. 2006 ++), China (Li et al 1999 ++), India (Ramachandran et al. 2009 ++) and one multi country study (NAVIGATOR Study Group[b] 2010 ++).

Table 18: Change in blood glucose

Intervention	Study	Baseline		Follow-up		Length of follow-up	Mean change
		FG (mmol/L)	2 hour glucose (mmol/L)	FG (mmol/L)	2 hour glucose (mmol/L)		
Lifestyle							
Diet	Pan (Da Qing) 1997 intervention	5.56	9.03	5.94	10.54	6 year	FG (mmol/L) +0.38† 2 hour glucose (mmol/L) +1.51†
	Pan (Da Qing) 1997 control	5.52	9.03	7.59	12.99		FG (mmol/L) +2.07† 2 hour glucose (mmol/L) +3.96†
Exercise	Pan (Da Qing) 1997 intervention	5.56	8.83	6.83	10.34	6 year	FG (mmol/L) +1.27† 2 hour glucose (mmol/L) +1.51†
	Pan (Da Qing) 1997 control	5.52	9.03	7.59	12.99		FG (mmol/L) +2.07† 2 hour glucose (mmol/L) +3.96†
Diet & exercise	Roumen 2008 intervention	6.0	8.59	NR	NR	3 years	FG (mmol/L) +0.32 2 hour glucose (mmol/L) -0.05
	Roumen 2008 control	5.9	8.46	NR	NR		FG (mmol/L) +0.55 2 hour glucose (mmol/L) +0.89
	Li 2008 intervention	5.60	8.97	7.9	11.5	20 year	FG (mmol/L) +2.3† 2 hour glucose (mmol/L) +2.53†
	Li 2008 control	5.52	9.02	8.7	13.8		FG (mmol/L) +3.18† 2 hour glucose (mmol/L) +4.78†
	Lindahl 2009 intervention	5.84	7.90	6.4	9.7	5 years	FG (mmol/L) +0.56† 2 hour glucose (mmol/L) +1.8†
	Lindahl 2009 control	6.19	8.53	6.8	9.9		FG (mmol/L) +0.61† 2 hour glucose (mmol/L) +1.37†
	Lindstrom 2003 intervention	6.1	8.9	NR	NR	3 years	FG (mmol/L) 0.0 2 hour glucose (mmol/L) -0.5
	Lindstrom 2003 control	6.2	8.9	NR	NR		FG (mmol/L) +0.1 2 hour glucose (mmol/L) -0.1
	Pan (Da Qing) 1997 intervention	5.67	9.11	7.15	10.76	6 year	FG (mmol/L) +1.48† 2 hour glucose (mmol/L) +1.65†
	Pan (Da Qing) 1997 control	5.52	9.03	7.59	12.99		FG (mmol/L) +2.07† 2 hour glucose (mmol/L) +3.96†

Intervention	Study	Baseline		Follow-up		Length of follow-up	Mean change
		FG (mmol/L)	2 hour glucose (mmol/L)	FG (mmol/L)	2 hour glucose (mmol/L)		
Pharmacological							
Metformin	Li 1999 intervention	6.9	9.1	5.0	6.0	1 year	FG (mmol/L) -1.9† 2 hour glucose (mmol/L) -3.1†
	Li 1999 control	7.3	9.0	6.2	7.4		FG (mmol/L) -1.1† 2 hour glucose (mmol/L) -1.6†
Pioglitazone	Ramachandran 2009 intervention	5.6	8.8	5.8	9.2	3 years	FG (mmol/L) +0.24 2 hour glucose (mmol/L) +0.59
	Ramachandran 2009 control	5.7	8.9	5.9	9.5		FG (mmol/L) +0.19 2 hour glucose (mmol/L) +0.68
Glipzide	Erkisson 2006 intervention	5.3	7.9	5.3	7.0	18 months	FG (mmol/L) 0.0† 2 hour glucose (mmol/L) -0.9†
	Erkisson 2006 control	5.3	8.2	5.8	8.6		FG (mmol/L) +0.5† 2 hour glucose (mmol/L) +0.4†
Orlistat	XENDOS intervention	4.6	5.5	NR	NR	4 year	FG (mmol/L) +0.1 2 hour glucose (mmol/L) -0.4
	XENDOS control	4.6	5.5	NR	NR		FG (mmol/L) +0.2 2 hour glucose (mmol/L) -0.2

FG= Fasting Glucose NR=not reported †Calculated

Waist Circumference Change

Not every study reported and commented on the changes in waist circumference in the intervention and control groups at the end of the follow-up periods. Where changes were reported these have been included, where changes were not reported or commented on, but weight measurements for baseline and end of follow-up were in tables of characteristics, the change has been calculated.

Lifestyle interventions, diet combined with exercise

The study by Ramachandran did not report on waist circumference changes in detail (Ramachandran et al. 2006 ++), other than to say that the changes in waist circumference were not statistically significant in any group relative to the respective baseline values.

The study by Roumen did not report on the changes in waist circumference in the text of the paper (Roumen et al. 2008 ++). From information obtained from tables the published paper, waist circumference in the diet and exercise intervention group decreased by an average of 2.21 cm, and by 0.72 cm in the control group at the end of the 3-year follow-up period (p=0.505).

The study by Lindahl did not report on the changes waist circumference in the text, but gave the information in a table in the published paper, (Lindahl et al. 2009 ++). The average waist circumference in the diet and exercise intervention group decreased from 100.6 cm at baseline to an average of 99.4 cm, while in the control group, it decrease from an average of 99.9 cm to an average of 99.8 cm at the end of the 5-year follow-up period.

In the DPS study (Lindstrom et al. 2003 ++), it was reported in tables, the mean change in waist circumference for the intervention group from baseline to follow-up to follow-up of 3 years was -3.3 cm, and for the control group, the mean change was -1.2, this was statistically significant (p=0.0005).

Pharmacological interventions

In the XENDOS study (Torgerson et al. 2003 ++), it was reported in tables, the mean change in waist circumference for the intervention group from baseline to follow-up of 4 years was -6.4 cm, and for the control group, the mean change was -4.4, this was statistically significant ($p<0.01$).

Summary

Based on the limited evidence available, for lifestyle and pharmacological interventions, the mean reduction in waist circumference in the intervention groups was very slightly greater than the mean changes in the control groups.

Evidence statement 10:

Change in waist circumference

Both lifestyle and pharmacological interventions tended to show a slightly greater reduction waist circumference than control groups.

The diet combined with exercise intervention was based on four studies, one each from the following countries, Netherlands (Roumen et al. 2008 ++), Sweden (Lindahl et al. 2009 ++), Finland (Lindstrom et al. 2003 ++) and India (Ramachandran et al. 2006 ++) The pharmacological interventions was based on one study, from Sweden (Torgerson et al. 2004 ++).

Change in cholesterol

Some studies reported and commented on the changes in cholesterol in the intervention and control groups at the end of the follow-up periods, but most did not. Where changes were reported these have been included, where changes were not reported or commented on, but where cholesterol measurements for baseline and end of follow-up were in tables of characteristics, the change has been calculated.

Lifestyle interventions, diet combined with exercise

The study by Roumen reported on the changes in cholesterol in the text of the paper (Roumen et al. 2008 ++). Total cholesterol, high-density lipoprotein (HDL) and Low-density Lipoprotein (LDL) concentrations did not change over time and did not differ between groups (p for all > 0.05).

The study by Lindahl reported that, within the intensive intervention group, there was an increase in HDL cholesterol as compared to baseline at both 3- and 5-year follow-ups (p=0.0003 and p=0.003, respectively). Furthermore, on both occasions, the intensive intervention group had higher HDL cholesterol than the usual care group.

In the DPS study (Lindstrom et al. 2003 ++), it was reported in the text, that statistically significantly greater improvements were seen at year 1 in serum total cholesterol– to–HDL cholesterol ratio (-0.4 vs. -0.1), in the intervention group compared with the control group.

Pharmacological interventions

The Pan study in 2003 reported that acarbose had no significant effect on total, LDL or HDL cholesterol (Pan et al. 2003 ++), between intervention and control groups at the end of a 16 week follow-up.

In the XENDOS study (Torgerson et al. 2003 ++), it was reported in the text, that total and LDL cholesterol and the LDL-to-HDL cholesterol ratio decreased significantly more with orlistat than placebo, at both 1 and 4 years. Consistent with this, HDL cholesterol increased less with orlistat.

The Eriksson study in 2006 on glipizide reported that there was a statistically significant decrease in fasting insulin concentration and a significant increase in HDL cholesterol concentration in the glipizide group ($p \leq 0.05$) at the end of a 18 month follow-up (Eriksson et al. 2006 ++).

The DeFronzo study (Defronzo et al. 2011 +), reported that the change in HDL cholesterol was greater with pioglitazone (40±1 to 48±1 mg per deciliter [2.2±0.06 to 2.7±0.06 mmol per liter]) than with placebo (41±1 to 45.1±0.7 mg per deciliter [2.3±0.06 to 2.5±0.04 mmol per liter]) (p= 0.008 for the difference between groups). Neither pioglitazone nor placebo altered levels of low-density lipoprotein cholesterol.

Summary

Based on the limited evidence available, for lifestyle and pharmacological interventions, there was mixed evidence on the change in cholesterol in the intervention groups and the control groups.

Evidence statement 11:

Change in cholesterol

For both lifestyle and pharmacological interventions there was mixed evidence on the change in cholesterol in the intervention groups and the control groups.

The diet combined with exercise intervention was based on three studies, one each from the following countries, Netherlands (Roumen et al. 2008 ++), Sweden (Lindahl et al. 2009 ++) and Finland (Lindstrom et al. 2003 ++). The pharmacological interventions was based on four studies, one each from the following countries, Sweden (Torgerson et al. 2004 ++), China (Pan e tal. 2003 ++), US (DeFronzo et al. 2011 +) and Finland (Eriksson et al. 2006 ++).

5.2.7 Study duration

The RCTs included in this review are not consistent in reporting the various phases of each study (recruitment, baseline, active intervention, and follow up). For example, only 7 of 26 RCTs provide enough information to distinguish between the end of the intervention and the start of follow up (Eriksson et al. 2006 ++, Lindal et al. 2009 ++, Li et al. 1999 ++, Liao et al. 2002 +, Lindstrom et al. 2006 ++, Ramachandran et al. 2006 ++ and Li et al. 2008 -) thereby making each study's duration difficult to determine. Furthermore, the lack of data related to sample size with respect to follow up measurements makes analysing treatment effects over time within and between treatment arms tremendously difficult as well. Figure 11 displays how the various phases of a study's duration should be reported, and figure 12 displays how the phases of the studies included in this review are reported.

Figure 11: Schematic of study duration

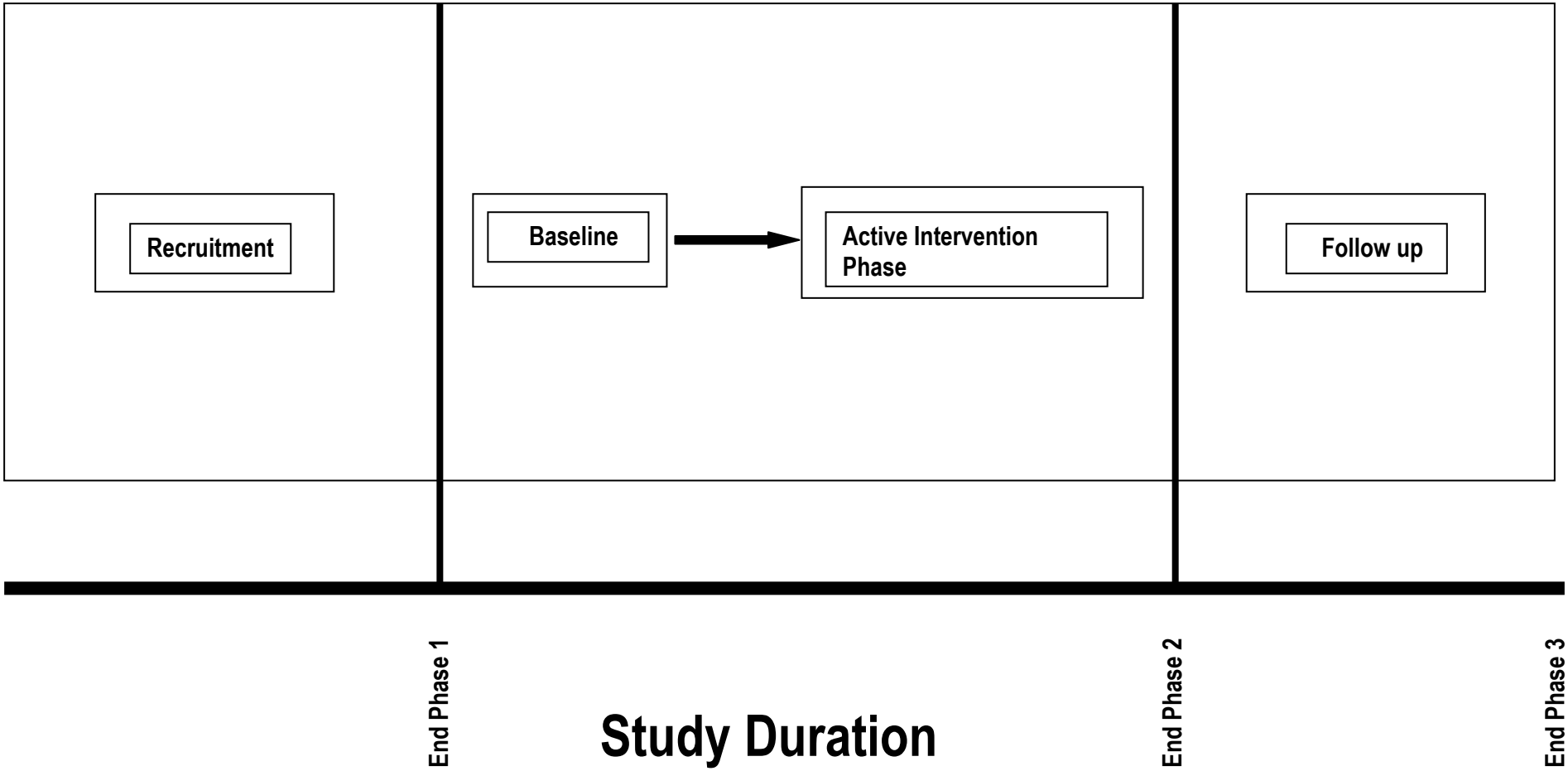
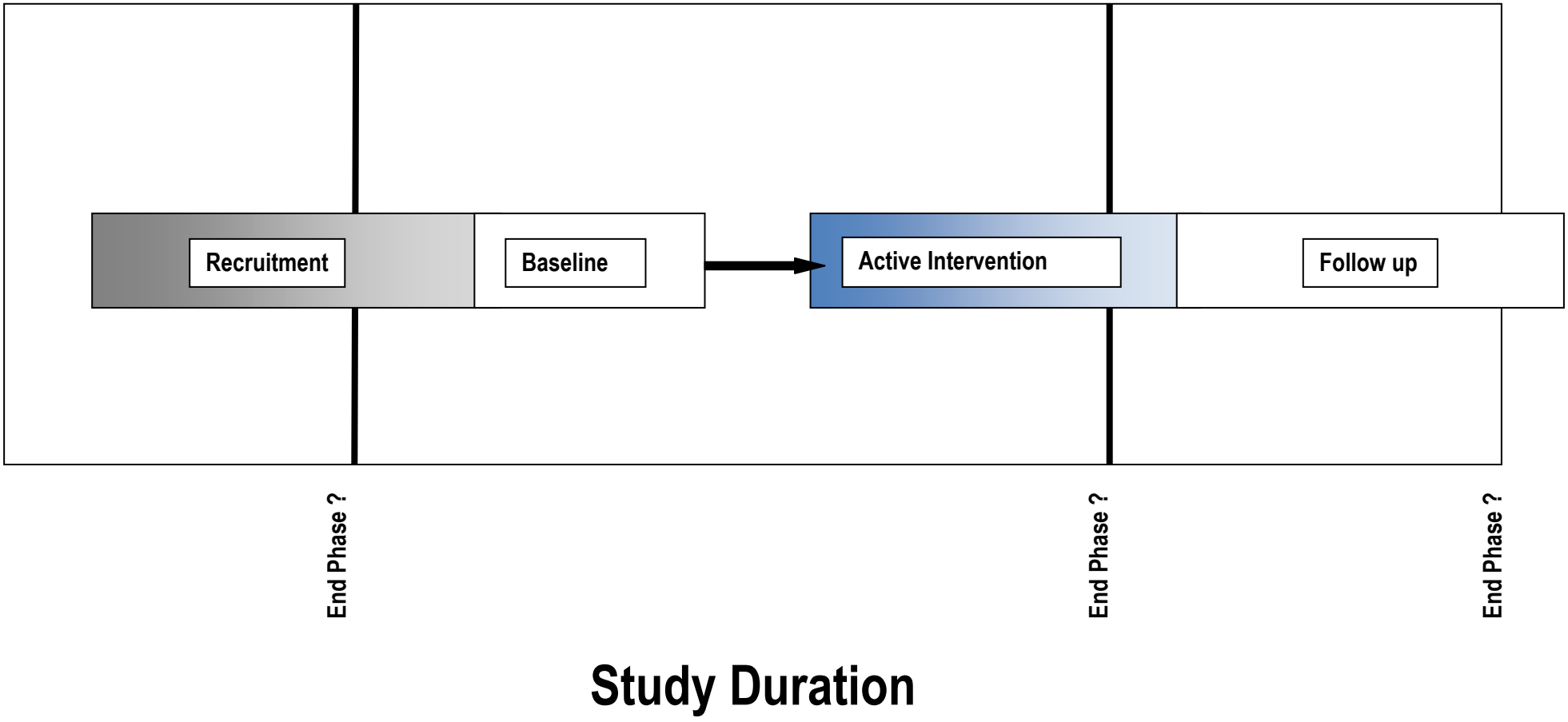


Figure 12: Schematic of included studies duration



6. DISCUSSION

6.1 Summary of findings

From an initial total of 5,601 references, 48 were examined at full paper stage with 37 being excluded (see appendix 4 for details), leaving a total of 12 papers of varying quality that met the inclusion criteria for the current review (appendix 5). Of the remaining papers, there were six additional papers published after the initial review and three papers detailing additional follow-up data, and updated data from these studies have been used to replace the original data. A further three papers were identified by PDG members, along with the included papers from the initial review, in total there were 26 papers identified for the current review. Fourteen of these papers were from the initial review (Gillies et al. 2007).

Pre-diabetes is an intermediate category between normal glucose tolerance and overt diabetes, and it can be identified by glucose tolerance test. Subjects with pre-diabetes have an increased risk of type 2 diabetes, and consequently many trials of interventions for the prevention of type 2 diabetes have focused on such individuals. Interventions to delay or even to prevent type 2 diabetes have a potential to improve the health of the population and reduce the burden of healthcare costs. The interventions assessed in this review have been diverse and include pharmacological and lifestyle interventions (diet, exercise, diet and exercise). Although the initial review also included a study on herbal remedies, this study was not included as it was a foreign language paper.

The RCTs included in this review have shown that lifestyle modification is an effective intervention in the prevention or delay of type 2 diabetes. For overweight and obese patients, a modest weight-loss goal of 5–10% (often < 10 kg) can substantially reduce the risk of diabetes. Moderate-intensity physical activity such as brisk walking also plays an important role in reducing diabetes risk, even in the absence of weight loss

Physical inactivity is an important risk factor for the development of type 2 diabetes, and the results of the 1997 Da Qing study (Pan et al. 1997 ++) show that increased physical activity is also associated with decreased rates of diabetes, although physical activity in combination with diet appears to has a greater effect.

The lifestyle interventions studies that appeared to be the most successful were those that had had prolonged frequent contacts, low attrition rates, and evidence of persisting behaviour change, which likely contributed to effectiveness, an example of theses are the DA Qing and DPP studies (Da Qing - Pan et al. 1997 ++; DPP - Knowler et al. 2002 ++).

It appears that lifestyle modification is the better strategy to prevent the progression of from IGT to type 2 diabetes. However, pharmacological trials also showed important results. When looking that the beneficial effects of pharmacological interventions, especially when there is a range of pharmacological agents, it is important to consider side affects associated with each pharmacological agent. Where adverse events have been reported, the have been classed as mild or moderate, and symptoms resolved with long-term treatment. The most often reported adverse event was gastrointestinal events, such as diarrhoea.

The available studies only permitted a limited analysis on key population sub-groups – such as by ethnic group. The overall pooled hazard ratio for the prevention of type 2 diabetes (0.58 96% CI 0.47 – 0.73) for diet combined with exercise interventions on south Asian populations with pre-diabetes was larger than the hazard ratio for all studies on diet combined with exercise interventions (0.47 95% CI 0.37- 0.59). A similar result was observed on the meta-analysis of pharmacological interventions, where for oral diabetes drugs, the overall pooled hazard ratio for the prevention of type 2 diabetes in south Asian populations was 0.72 (95% CI 0.52 – 0.99) compared to 0.47 (95% CI 0.37 – 0.99) for all population with pre-diabetes.

This review has reported where possible on the secondary outcomes such as BMI and weight, the authors of the DPP study reported in a separate paper the treatment effects in respect of secondary outcomes (DPP Research Group 2002). They reported that the lifestyle intervention was highly effective in all main secondary outcomes, although the study had inadequate power to assess the significance of effects within the subgroups. They further reported that the effect of metformin was less with a lower BMI or a lower fasting glucose concentration than with higher values for those variables. The advantage of the lifestyle intervention over metformin was greater in older persons and those with a lower BMI than in younger persons and those with a higher BMI. The Finnish Diabetes Prevention study group (Lindstrom et al. 2008), reported that the incidence of diabetes increased with increasing BMI and waist circumference in both intervention and control groups, but that the effect of the lifestyle intervention was of the same magnitude in all BMI groups.

Several large RCTs included in this review have shown that weight loss is a potentially important management strategy for overweight persons with pre-diabetes, as it may delay or prevent the progression to clinically defined type 2 diabetes.

Although the weight loss demonstrated in this review is small, this review demonstrated that some improvements in weight and in BMI appear achievable in populations with pre-diabetes.

The overall goal for diabetes prevention is to reach and maintain an active, healthy weight with a tendency toward a healthier diet. Evidence supports limiting total calories and fat (25% of caloric intake) and increasing dietary fibre (20 to 30 g/day) (Burnet et al. 2006). Essential skills include understanding portion sizes and reading food labels.

Information on change in blood glucose measurement was not always reported, even if measurements were routinely taken. Often the only reference to fasting blood glucose and two hour glucose measurements would be within the table of baseline characteristics. From the limited information available both lifestyle and pharmacological interventions have an effect in lowering fasting blood glucose and two hour glucose.

While the main focus of this review is on lifestyle interventions and pharmacological interventions compared to placebo or usual practice, the IDPP study (Ramachandran et al. 2006 ++) did examine the effect of a lifestyle intervention (diet combined with exercise) combined with a pharmacological intervention (metformin). The lifestyle and metformin group had a lower cumulative incidence of diabetes at the 3-year follow-up, when compared to the control group (39.5% vs. 55%).

The results in this review show that a lifestyle intervention as well as a pharmacological intervention can be effective in the prevention to diabetes in IGT subjects. A gap in the evidence base is the lack of studies evaluating use of lifestyle and drug together, and evaluating using a drug for those unable to make lifestyle changes and when lifestyle change hasn't been successful. To date this review authors are not aware of any study that examines whether a lifestyle in combination with a drug intervention is also effective.

Applicability and transferability of evidence to the UK

A total of two studies were carried out in the UK. The remaining 20 studies represent a range of populations from Europe, US, Australia, south and eastern Asia. Therefore caution is required when interpreting findings regarding the interventions carried out

in populations that may have different prevalence and risk for pre-diabetes, as well as the interventions having different durations and settings.

In terms of transferability to clinical practice, it should be remembered that the lifestyle interventions in the RCTs in this review were generally very intensive. Also patients were sometimes selectively recruited (baseline risk levels may differ from those identified by an NHS screening program), and patients may have been paid to participate in the RCTs resulting in a relatively high level of motivation and adherence.

7. CONCLUSIONS

The data derived from the trials show that both lifestyle and pharmacological interventions can reduce the risk of type 2 diabetes in people with pre-diabetes, and that lifestyle interventions seems to be at least as effective as pharmacological interventions. Lifestyle interventions, which aim to reduce obesity and increase physical activity, help in addressing directly these risk factors, and incur fewer and less serious side effects than drug treatment. As in pharmacological interventions, beneficial effects with lifestyle interventions may not be permanent, so advice on diet and exercise may need to be regularly reinforced in order to maintain behavioural changes. For pharmacological interventions, adverse effects need to be fully taken into account to enable the overall harms and benefits to be assessed.

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9. APPENDICES

Appendix 1: Search Strategy

The following audit table shows the searches undertaken by database and the results of these searches.

Audit Table

#	Source	Hits
1	Medline In Process and Other Non Indexed Citations and Medline 1950-Current	1548
2	Embase	2033
3	Cochrane Library DARE CENTRAL HTA	 36 1995 1
4	CINAHL	645
5	BNI	269
6	Science and Social Science Citation Indices	1264
7	PsycINFO	126

This table shows the ScHARR search strategy by individual databases searched.

Search Strategy by Database

Medline Search Strategy	Embase Search Strategy	PsycINFO Search Strategy
1. ((prevent* or avoid* or delay* or decreas* or reduc*) adj5 (type II diabetes or type 2 diabetes or T2D or DM or diabetes)).ti,ab. 2. Diabetes Mellitus, Type 2/ and Preventive Medicine/ 3. 1 or 2 4. *prediabetic state/ 5. (prediabetes or pre diabetes or raised glucose intolerance or impaired glucose level$ or impaired glucose tolerance or IGT or impaired fasting glucose or IFT or FPG or fasting plasma glucose or	1. ((prevent* or avoid* or delay* or decreas* or reduc*) adj5 (type II diabetes or type 2 diabetes or T2D or DM or diabetes)).ti,ab. 2. Diabetes Mellitus, Type 2/ and Preventive Medicine/ 3. 1 or 2 4. *prediabetic state/ 5. (prediabetes or pre diabetes or raised glucose intolerance or impaired glucose level$ or impaired glucose tolerance or IGT or impaired fasting glucose or IFT or FPG or fasting plasma glucose or	1. ((prevent* or avoid* or delay* or decreas* or reduc*) adj5 (type II diabetes or type 2 diabetes or T2D or DM or diabetes)).ti,ab. 2. Diabetes Mellitus/ and Preventive Medicine/ 3. 1 or 2 4. (prediabetes or pre diabetes or raised glucose intolerance or impaired glucose level$ or impaired glucose tolerance or IGT or impaired fasting glucose or IFT or FPG or fasting plasma glucose or impaired glucose

impaired glucose regulation or impaired glucose metabolism or raised glycated haemoglobin or raised glycated hemoglobin or high glycated Hb or hyperglycaemia or hyperglycemia).ti. 6. 4 or 5 7. 3 or 6 8. (gestational or pregnan$ or postpartum).ti,ab. 9. Pregnancy in Diabetics/ or Pregnancy/ 10. 8 or 9 11. 7 not 10 12. randomized controlled trial.pt. 13. controlled clinical trial.pt. 14. Randomized Controlled Trial/ 15. Random Allocation/ 16. Double-Blind Method/ 17. Single-Blind Method/ 18. clinical trial.pt. 19. Clinical Trial/ 20. clinical trial*.tw. 21. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw. 22. PLACEBOS/ 23. placebo$.tw. 24. random$.tw. 25. (clin$ adj5 trial$).ti,ab. 26. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27. 11 and 26 28. limit 27 to humans	impaired glucose regulation or impaired glucose metabolism or raised glycated haemoglobin or raised glycated hemoglobin or high glycated Hb or hyperglycaemia or hyperglycemia).ti. 6. 4 or 5 7. 3 or 6 8. (gestational or pregnan$ or postpartum).ti,ab. 9. Pregnancy in Diabetics/ or Pregnancy/ 10. 8 or 9 11. 7 not 10 12. Randomized Controlled Trial/ 13. Random Allocation/ 14. Double-Blind Method/ 15. Single-Blind Method/ 16. Clinical Trial/ 17. clinical trial*.tw. 18. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw. 19. PLACEBOS/ 20. placebo$.tw. 21. random$.tw. 22. (clin$ adj5 trial$).ti,ab. 23. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 24. 11 and 23 25. limit 24 to humans	regulation or impaired glucose metabolism or raised glycated haemoglobin or raised glycated hemoglobin or high glycated Hb or hyperglycaemia or hyperglycemia).ti. 5. 3 or 4 6. (gestational or pregnan$ or postpartum).ti,ab. 7. Pregnancy/ and Diabetes/ 8. 6 or 7 9. 5 not 8 10. Clinical Trials/ 11. Experimental Design/ 12. Clinical Trial/ 13. clinical trial*.tw. 14. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw. 15. Placebo/ 16. placebo$.tw. 17. random$.tw. 18. (clin$ adj5 trial$).ti,ab. 19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 20. 9 and 19

British Nursing Index	Cochrane Library	CINAHL
1. ((prevent* or avoid* or delay* or decreas* or reduc*) adj5 (type II diabetes or type 2 diabetes or T2D or DM or diabetes)).ti,ab. 2. Diabetes/ 3. 1 or 2	#1 ((prevent* or avoid* or delay* or decreas* or reduc*) NEAR/5 (type II diabetes or type 2 diabetes or T2D or DM or diabetes)):ti,ab,kw #2 MeSH descriptor Diabetes Mellitus, Type 2,	S31 S17 and S27 S30 S17 and S27 S29 S17 and S27 S28 S17 and S27 S27 S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26

4. (prediabetes or pre diabetes or raised glucose intolerance or impaired glucose level$ or impaired glucose tolerance or IGT or impaired fasting glucose or IFT or FPG or fasting plasma glucose or impaired glucose regulation or impaired glucose metabolism or raised glycated haemoglobin or raised glycated hemoglobin or high glycated Hb or hyperglycaemia or hyperglycemia).ti. 5. 3 or 4 6. (gestational or pregnan$ or postpartum).ti,ab. 7. Pregnancy/ and Diabetes/ 8. 6 or 7 9. 5 not 8 10. Clinical Trials/ 11. Clinical Trial/ 12. clinical trial*.tw. 13. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw. 14. Placebo/ 15. placebo$.tw. 16. random$.tw. 17. (clin$ adj5 trial$).ti,ab. 18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 19. 9 and 18	this term only #3 MeSH descriptor Preventive Medicine, this term only #4 (#2 AND #3) #5 (#1 OR #4) #6 MeSH descriptor Prediabetic State, this term only #7 (prediabetes or pre diabetes or raised glucose intolerance or impaired glucose level$ or impaired glucose tolerance or IGT or impaired fasting glucose or IFT or FPG or fasting plasma glucose or impaired glucose regulation or impaired glucose metabolism or raised glycated haemoglobin or raised glycated hemoglobin or high glycated Hb or hyperglycaemia or hyperglycemia):ti #8 (#6 OR #7) #9 (#5 OR #8) #10 (gestational or pregnan$ or postpartum):ti,ab,kw #11 MeSH descriptor Diabetes, Gestational, this term only #12 (#10 OR #11) #13 (#9 AND NOT #12) #14 (randomized controlled trial):pt #15 (controlled clinical trial):pt #16 MeSH descriptor Randomized Controlled Trials as Topic, this term only #17 MeSH descriptor Random Allocation, this term only #18 MeSH descriptor Double-Blind Method, this term only #19 MeSH descriptor Single-Blind Method, this term only #20 (clinical trial):pt #21 MeSH descriptor Clinical Trials as Topic, this term only	S26 TI clinical N5 trial$ S25 TX placebo$ or random$ S24 (MH "Placebos") S23 TX ((sing$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)) S22 TX clinical trial* S21 (MH "Double-Blind Studies") OR (MH "Single-Blind Studies") OR (MH "Triple-Blind Studies") S20 (MH "Random Assignment") S19 (MH "Clinical Trials") S18 PT controlled trial S17 S12 not S16 S16 S13 or S14 or S15 S15 (MH "Pregnancy") S14 (MH "Pregnancy in Diabetes") S13 TI gestational or pregnan$ or postpartum S12 S7 or S11 S11 S8 or S9 or S10 S10 TI raised glycated haemoglobin or TI raised glycated hemoglobin or TI high glycated Hb or TI hyperglycaemia or TI hyperglycemia S9 TI prediabetes or TI pre diabetes or TI raised glucose intolerance or TI impaired glucose level$ or TI impaired glucose tolerance or TI IGT or TI impaired fasting glucose or TI IFT or TI FPG or TI fasting plasma glucose or TI impaired glucose

	#22 (clinical trial*):ti,ab,kw #23 ((singl* or doubl* or trebl* or tripl*) and (mask* or blind*)):ti,ab,kw #24 MeSH descriptor Placebos, this term only #25 (placebo*):ti,ab,kw or (random*):ti,ab,kw #26 (clin* NEAR/5 trial*):ti,ab,kw #27 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25) #28 (#13 AND #27)	regulation or TI impaired glucose metabolism S8 (MH "Prediabetic State") S7 S3 or S6 S6 S4 and S5 S5 (MH "Preventive Health Care") S4 (MH "Diabetes Mellitus, Non-Insulin-Dependent") S3 S1 and S2 S2 TI type II diabetes or TI type 2 diabetes or TI T2D or TI DM or TI diabetes S1 TI prevent* or TI avoid* or TI delay* or TI decreas* or TI reduc*

Appendix 2: Criteria for pre-diabetes and diabetes

Impaired Glucose Tolerance (IGT) is defined as a fasting plasma glucose of <7.0mmol/l (126mg/dl) if measured, and a 2–hour plasma glucose (Venous plasma glucose 2–h after ingestion of 75g oral glucose load) ≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl) (WHO 2003).

Impaired Fasting Glucose (IFG) is defined as a fasting plasma glucose 6.1 to 6.9mmol/l (110mg/dl to 125mg/dl) (if measured) and 2–h plasma glucose <7.8mmol/l (140mg/dl) (WHO 2003).

In 1999 WHO adapted the recommended definition of Impaired Fasting Glucose (IFG) originally introduced by the American Diabetes Association Expert Committee. IFG thus describes the zone between the upper limit of normal fasting plasma glucose and the lower limit of the diabetic fasting plasma glucose, believed to be analogous to between the upper limit of a normal 2–h plasma glucose and the lower limit of the diabetic 2–h plasma glucose described by IGT.

IGT and IFG are risk factors for future diabetes and/or adverse outcomes rather than a clinical entity. Studies suggest that IGT is associated with muscle insulin resistance and defective insulin secretion, resulting in less efficient disposal of the glucose load during OGTT. IFG is associated with impaired insulin secretion and impaired suppression of hepatic glucose output (WHO 2006)

It is recognised that the term ‘pre-diabetes’ is not ideal, as not everyone with raised or impaired blood glucose levels will go on to develop type 2 diabetes. However, the term ‘pre-diabetes’ has been chosen because of its widespread use and recognition by a broad range of stakeholder groups and because of the lack of consensus on a suitable alternative.

HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement.

An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

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Appendix 3: Studies included in the Gillies et al. review

Studies in bold indicate inclusion in meta-analysis. The remaining studies were not included in the current meat-analyses due to being foreign language studies, or they were not included in the original Gilles meta-analyses.

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Appendix 4: Excluded studies

Studies excluded after review of full paper

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Author	Reason for exclusion
Cao 2004	Foreign language paper
Kawamori et al. 2009	Foreign language paper
Li 2008	Lack of reported details
Lindstrom & Uusitupa 2008	Lack of reported details
Mackerras 2003	Lack of reported details
Nissen et al. 2006	Lack of reported details
Pignone 2007	Lack of reported details
Bo et al. 2007	Incidence of/progression to diabetes not reported
Chiasson 2006	Incidence of/progression to diabetes not reported
Gruber & Nasser 2006	Incidence of/progression to diabetes not reported
Imai et al. 2008	Incidence of/progression to diabetes not reported
Kang et al. 2010	Incidence of/progression to diabetes not reported
Kulzer et al. 2009	Incidence of/progression to diabetes not reported
Mensink et al 2003(a)	Incidence of/progression to diabetes not reported
Mensink et al 2003(b)	Incidence of/progression to diabetes not reported
Parikh et al. 2010	Incidence of/progression to diabetes not reported
Ramachandran et al. 2007	Incidence of/progression to diabetes not reported
Tuomilehto et al. 2001	Incidence of/progression to diabetes not reported
Watanabe et al. 2003	Incidence of/progression to diabetes not reported
Conlon 2006	More recent data available
Laaksonen et al. 2005	More recent data available
Li et al. 2002	More recent data available
Lindstrom et al. 2003	More recent data available
Ratner 2006	More recent data available
Sjostrom 2006	More recent data available
The Diabetes Prevention Program Research Group 2005	More recent data available
Uusitupa et al. 2003	More recent data available
Uusitupa et al. 2000	More recent data available
Hu 2004	Not RCT
Agurs-Collins et al. 1997	Sample population included people with diabetes
Balducci et al. 2009	Sample population included people with diabetes
Castaneda 2002	Sample population included people with diabetes
Koyasu et al. 2010	Sample population included people with diabetes
Pradhan et al. 2009	Sample population included people with diabetes
Akhenizan 2007	Was a review paper
Steyn et al. 2009	Was a review paper
Torgerson 2004	Was a review paper
DREAM 2006	Drug withdrawn from market
Zinman 2010	Drug withdrawn from market

Appendix 5: Included studies

DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray, GA, Buchanan TA et al. Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance. *New England Journal of Medicine* 2011; 364(12):1104-1115.

Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *The Lancet* 2009; 374(9702):1677-1686.

DREAM T, I, Bosch J, Yusuf S, Gerstein HC, Pogue J, Sheridan P et al. Effect of ramipril on the incidence of diabetes. *New England Journal of Medicine* 2006; 355(15):1551-1562.

Kawamori R, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K et al. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* 2009; 373(9675):1607-1614.

Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008; 371(9626):1783-1789.

Lindahl B, Nilsson TK, Borch-Johnsen K, Roder ME, Soderberg S et al. A randomized lifestyle intervention with 5-year follow-up in subjects with impaired glucose tolerance: pronounced short-term impact but long-term adherence problems. *Scandinavian Journal of Public Health* 2009; 37(4):434-442.

Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemiö K et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006; 368(9548):1673-1679.

NAVITGATOR Study Group[a.] Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events. *New England Journal of Medicine* 2010; 362:1477-1490.

NAVITGATOR Study Group[b.] Effect of Nateglinidw on the Incidence of Diabetes and Cardiovascular Events. *New England Journal of Medicine* 2010; 362:1463-1476.

Penn LW. Prevention of type 2 diabetes in adults with impaired glucose tolerance: The European Diabetes Prevention RCT in Newcastle upon Tyne, UK. *BMC Public Health* 2009; 9, 2009. Article Number:342.

Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CK, Seeli AC et al. Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). *Diabetologia* 2009; 52(6):1019-1026.

Roumen C, Corpeleijn E, Feskens EJ, Mensink M, Saris WH, Blaak EE. Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. *Diabetic Medicine* 2008; 25(5):597-605.

Appendix 6: Hazard ratios for new studies

Table of intervention effect estimates

Study	$Baseline_{Tx}$	$Intervention_{Tx}$	HR	95% CI	Log_{HR}	SE_{LogHR}
DPPOS , 2009	Placebo	Lifestyle Intervention	0.34	(0.28-0.42)	-1.078	0.1077
	Placebo	Metformin (850 mg twice daily)	0.18	(0.12-0.28)	-1.714	0.2255
Ramachandran et al. 2009	Lifestyle modification + Placebo	Lifestyle modification + Pioglitazone (30mg)	0.984	(0.672-1.443)	-0.016	0.1949
Lindstrom et al. (DPS update) 2006	Placebo	Lifestyle Intervention	0.57	(0.43-0.76)	-0.562	0.1469
Roumen et al. 2008	Controls briefly informed about benefits of diet and exercise	Combined dietary and physical activity programme	0.42	(0.18-0.96)	-0.867	0.4219
Lindahl et al. 2009	Usual care	Intensive intervention programme of diet and exercise	0.30	(0.118-0.762)	-1.2039	0.4756
Li et al. 2008	No description of the control group provided	Diet and exercise intervention (6 year active intervention)	0.49	(0.33-0.73)	-0.713	0.2036
	No description of the control group provided	Diet and exercise intervention (20 year follow-up)	0.57	(0.41-0.81)	-0.562	0.1796
Penn et al. 2009	Usual care by physician	Diet and exercise intervention	0.45	(0.17-1.2)	-0.798	0.5
DREAM Trial Investigators 2006	Matching placebo	Ramipril (up to 15mg per day during year 1)	0.91	(0.80-1.03)	-0.094	0.0628
Kawamori et al. 2009	Standard exercise and diet + placebo	Standard exercise and diet + oral voglibose (0.2mg three times per day)	0.595	(0.433-0.818)	-0.519	0.1628

Appendix 7: Rosiglitazone

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial was designed to assess prospectively whether rosiglitazone can reduce the frequency of diabetes in individuals with impaired glucose tolerance or impaired fasting glucose, or both. In this study, 5,269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; n=2,365) or placebo (2,634) and followed for a median of 3 years. The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat.

The primary outcome of diabetes or death was seen in significantly fewer individuals in the rosiglitazone group than in the placebo group (hazard ratio [HR] 0.40, 95% CI 0.35–0.46; p<0 ·0001). There was no difference in the number of deaths (0.91, 0.55–1.49; p=0.7) and a large difference in the frequency of diabetes (0.38, 0.33–0.44; p<0.0001) between the two groups. The evidence table for this study is displayed after the text.

For adverse events, the study authors stated that one patient in the rosiglitazone group and three in the placebo group stopped because of hypoglycaemia.

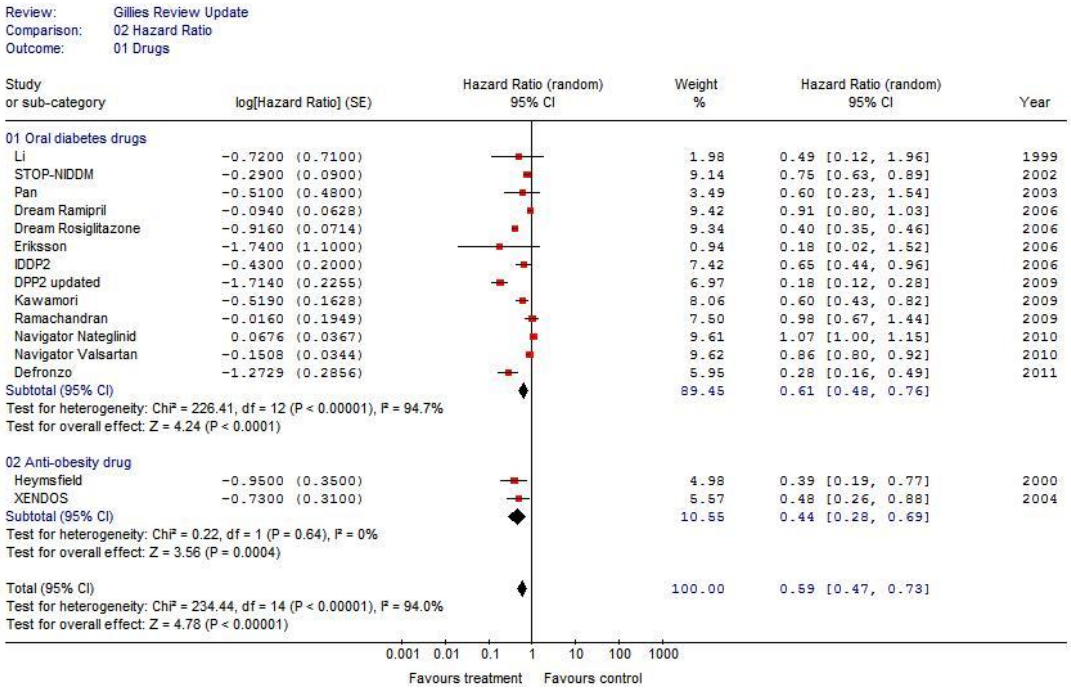
The meta-analysis with the addition of rosiglitazone is shown on the following page.

However, rosiglitazone was not included in the main results as the drug is suspended (European Medicines Agency website, accessed 19 April 2011) and will not be reinstated unless there is additional data to support its use in some specific subgroup. In the BMJ editorial it was stated that the best available evidence suggests limited benefit of intensified glycaemic control for patients with type 2 diabetes and that it may reduce the risk of myocardial infarction but does not reduce the risk of death from a cardiovascular event (Montori & Shah 2011). A recent systematic review (Loke, Kwok & Singh 2011) reported that compared with pioglitazone, the use of rosiglitazone was associated with a significantly increased odds of myocardial infraction (pooled odds ratio 1.16, 95% CI 1.07-1.24; p<0.001), congestive heart failure (pooled odds ratio 1.22, 95% CI 1.14-1.31; p<0.001) and death (pooled odds ratio 1.14, 95% CI 1.09-1.20; p<0.001). Thus, any recommendation that might be made based on the current evidence is immaterial

unless it is reinstated and the evidence is assess with respect to any subgroup that might be identified. Furthermore, rosiglitazone has been under investigation for some time and it is possible that the Dream 2006 trial is based on a different population given any previous restrictions on its use. It is possible that including the study would increase the heterogeneity in treatment effects between studies and any attempt to explain the heterogeneity would need to take into account the restrictions on its use that were known at the time.

The BMJ editorial in March 2011 states that the best available evidence suggests limited or no benefit of intensified glycaemic control for patients with type 2 diabetes, it greatly increases the risk of hypoglycaemia, and it may reduce quality of life as a result of the burden of treatment.

Meta-analysis with the addition of the rosiglitazone study



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Nissen SE, Herder C, Martin S, Kempf K, Rose B, Kolb H et al. The DREAM trial... The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006; 368(9552):2049-2051.

Study	ID: # 2978 Author: DREAM Trial Investigators Year : 2006 Country: Multiple countries Study design: RCT	Comments
Included in Gillies et al review?	No	
Intervention	Participants either received rosiglitazone (4 mg once daily for the first 2 months and then 8 mg once daily) or matching placebo. The dose of 8 mg per day was chosen to achieve maximum ability to identify whether the drug prevents diabetes and to ensure that a negative study would not be attributed to an inadequate dose. 15 Participants attended visits 2 months and 6 months after randomisation and every 6 months thereafter. At all visits, the importance of healthy diet and lifestyle was emphasised, drugs were dispensed, and adherence was assessed and reinforced.	
Comparator	Placebo	
Setting / Delivered by	191 sites in 21 countries, No additional details provided	
Randomisation method	Eligible patients were randomly assigned (stratified by site) by a concealed, computerised telephone randomisation system. Patients were concurrently randomly assigned to receive either ramipril (titrated to 15 mg once daily) or matching placebo with a 2×2 factorial design.	
Blinding	Not described	
Recruitment	5 269 adults aged 30 years or more with impaired fasting glucose or impaired glucose tolerance, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries.	
Population baseline characteristics	Sample: n= 5 269 Males: 41.7% (Intervention); 39.9% (Placebo) Mean age (yrs): 54.6±10.9 (Intervention); 54.8±10.9 (Placebo) Mean BMI (kg/m2): 30.8 (Intervention); 31.0 (Placebo) Waist circumference (cm): 101±14 (Intervention-Males) 102±13 (Placebo-Males) 96±14 (Intervention-Women); 96±14 (Placebo-Women) Other: Geographical distribution	
Sub-group	Age: <50 years 60+ years 50–59 years Geographical Location: North America South America Europe India Australia Ethnic group: SES group: Not reported	

	Obesity: Hip-to-waist ratio reported **Other: Drug use**	
Sub-groups identified (Y/N)	**Yes**	
Sub-group analysis (Y/N)	**Yes, but limited details reported in the paper**	
Criteria used for diagnosis of pre-diabetes	**A fasting plasma glucose concentration ≥6.1 mmol/L and <7.0 mmol/L and 2-h plasma glucose concentration <11.1 mmol/L during the oral glucose tolerance test) or impaired glucose tolerance (fasting plasma glucose concentration <7.0 mmol/L and 2-h plasma glucose concentration ≥7.8 mmol/L and <11.1 mmol/L).**	
Criteria used for diagnosis of diabetes	**Diabetes was diagnosed if (1) a locally measured fasting plasma glucose concentration of 7.0 mmol/L or greater or 2-h plasma glucose concentration of 11.1 mmol/L or greater during a 75 g oral glucose tolerance test was confirmed by a second test on a different day; (2) a single test was consistent with diabetes, no confirmatory test was done, and the masked adjudicator had no reason to reject the diagnosis; or (3) a physician diagnosed diabetes outside the study and the diagnosis was supported by the prescription of an anti-diabetic agent and either a fasting plasma glucose concentration of 7.0 mmol/L or greater or any glucose concentration of 11.1 mmol/L or more. Diabetes status and date of diagnosis were established by masked adjudication of all relevant data.**	
Primary findings	**The primary outcome of diabetes or death was seen in significantly fewer individuals in the rosiglitazone group than in the placebo group (hazard ratio [HR] 0.40, 95% CI 0.35–0.46; p<0・0001). There was no difference in the number of deaths (0.91, 0.55–1.49; p=0.7) and a large difference in the frequency of diabetes (0.38, 0.33–0.44; p<0.0001) between the two groups. Effects on the primary outcome were much the same irrespective of the glycaemic abnormality that was present at the time of randomisation. Thus, an HR for the primary outcome of 0.30 (0.19–0.49) was recorded in individuals with isolated impaired fasting glucose, of 0.45 (0.36–0.55) in those with isolated impaired glucose tolerance, and 0.36 (0.29–0.43) in those with combined impaired fasting glucose tolerance and impaired glucose tolerance (p value for heterogeneity 0.14). When analysed on the basis of the fasting plasma glucose alone, participants with any impaired fasting glucose tolerance had an HR of 0.35 (0.29–0.42) for the primary outcome. If impaired fasting glucose is defined as a fasting plasma glucose of 5.6 mmol/L to 6.9 mmol/L18 the hazard for these participants was 0.41 (0.30–0.55).**	
Secondary findings	**The effect of rosiglitazone was much the same in all regions of the world, different ethnic groups, in both sexes, and across all ages. Rosiglitazone was also effective irrespective of baseline weight or fat distribution, albeit to a different degree. Whereas increasing baseline weight or waist-to-hip ratio predicted a higher frequency of diabetes in individuals in the placebo group, this relation was not seen in those in the rosiglitazone group.**	
Follow up	**Participants were followed for a median of 3.0 years (range 2.5–4.7). During the trial 992 (18.8%) individuals experienced the primary outcome: 63 (1.2%) people died and 938 (17.8%) people developed diabetes on the basis of either study-related glucose concentrations (n=786) or other criteria (152). Of the remaining participants, 3961 completed a final visit, 218 provided a verbal report of their diabetes status, and 98 did not respond. Vital status could not be ascertained in 105 (2.0%) people by the end of the trial; in these individuals, vital status was known for 2 years or more in 56 people, in 22 for 1–2 years, and in 27 for less than 1 year. In surviving participants for whom adherence to study drug was recorded by the research staff (2604 individuals assigned rosiglitazone and 2600 assigned placebo), 1868 (71.7%) in the rosiglitazone group and 1952 (75.1%) in the placebo group were at least 80% adherent at the end of the study; two**	

	individuals in the rosiglitazone group and one in the placebo group were taking 4 mg daily; four receiving rosiglitazone and 16 receiving placebo were taking open-label rosiglitazone. 752 (28.5%) participants in the rosiglitazone group and 641 (24.3%) in the placebo group stopped taking their assigned treatment at any time; and 602 (23.6%) people assigned to receive rosiglitazone and 517 (20.2%) assigned to receive placebo were not taking the allocated drug at their last visit. The most common reasons for stopping rosiglitazone and placebo included participant refusal (503 [18.9%] in the rosiglitazone group and 439 [16.7%] in the placebo group); oedema (439 [4.8%] and 41 [1.6%]), physician's advice (50 [1.9%] and 39 [1.5%]), and weight gain (50 [1.9%] and 15 [0.6%]).	
Intention to Treat analysis	**All results were analysed on the basis of intention to treat. Cox's proportional hazards models were used to estimate the effect of rosiglitazone on the hazard of the primary and other outcomes (stratified by ramipril allocation) and the significance of the effect. Interaction of the effect of rosiglitazone and ramipril on the primary outcome was assessed by including an interaction term in the Cox model. Individuals for whom diabetes status was unavailable at the end of the study were censored at the time of their last glucose measurement. Kaplan-Meier curves for the primary and secondary outcome were constructed for rosiglitazone and placebo and compared with stratified log-rank tests. Statistical heterogeneity of treatment effects within key subgroups was also assessed.**	
Adverse events	**One patient in the rosiglitazone group and three in the placebo group stopped because of hypoglycaemia.**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**Rosiglitazone at 8 mg daily for 3 years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.**	
Quality Assessment	**Jadad=3** **NICE ++**	

Appendix 8: Evidence Tables for included studies

Lifestyle interventions		
Study	**Author: Da Qing Study** **Year 1997** **Country: China** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Diet group. In clinics assigned to the diet-only intervention, participants with BMI <25 kg/m^2 were prescribed a diet containing 25-30 kcal/kg body wt (105-126 kJ/kg), 55-65% carbohydrate, 10-15% protein, and 25-30% fat. These participants were encouraged to consume more vegetables, control their intake of alcohol, and reduce their intake of simple sugars. Subjects with BMI >or= to 25 were encouraged to reduce their calorie intake so as to gradually lose weight at a rate of 0.5-1.0 kg per month until they achieved a BMI of 23. Individual goals were set for total calorie consumption and for daily quantities of cereals, vegetables, meat, milk, and oils. This was accomplished by providing a list to each individual of the recommended daily intake of commonly used foods and a substitution list to allow exchange within food groups. Patients received individual counselling by physicians concerning daily food intake. In addition, counselling sessions (in small groups) were conducted weekly for 1 month, monthly for 3 months, and then once every 3 months for the remainder of the study.** **Exercise group. Participants in clinics assigned to the exercise group were taught and encouraged to increase the amount of their leisure physical exercise by at least one unit per day (such as slow walking for 30 minutes, fast walking for 20 minutes etc) and by two units per day if possible for those <50 years of age with no evidence of cardiovascular disease or arthritis. As in the diet group, counselling sessions were conducted weekly for one month, monthly for three months, and then once every three months for the remainder of the study. The rate of increase and type of exercise recommended depended on age, past exercise patterns, and the existence of health problems other than IGT. Appropriate indoor activities were suggested for winter.** **Diet-plus-exercise group. Participants from clinics assigned to this group received instructions and counselling for both diet and exercise interventions that were similar to those for the diet-only and the exercise-only intervention groups**	
Comparator	**Subjects from clinics assigned to the control group were exposed to general information about diabetes and IGT. Clinic physicians also dispensed informational brochures with general instructions for diet and/or increased leisure physical activities to control group subjects, but no individual instruction or formal group counselling sessions were conducted.**	
Setting / Delivered by	**Local physicians, nurses and technicians.**	
Randomisation method	**Intervention was provided by 33 local health clinics associated with the oil factory communities that are dispersed throughout the city. The number of subjects attending each of these clinics ranged from 5 to 33.**	

	Each clinic, rather than each subject, was randomized to carry out the intervention on each of the eligible subjects attending that clinic according to one of the four specified intervention protocols. Study participants in each clinic were categorized according to BMI, with 208 individuals categorized as lean (BMI <25) and 322 as overweight (BMI >or= to 25).	
Blinding	**None**	
Recruitment	**1986, the population of Da Qing included 281,589 people over the age of 25, all of whom received health care in designated clinics located throughout the city. Half of these clinics, which served 126,715 people over the age of 25, were selected to participate in a screening study. Between June and December 1986, most (87.3%) of the target population (110,660 total: 55,391 men and 55,269 women) underwent screening at nearby hospitals. 577 people had for IGT agreed to participate in the study.**	
Population baseline characteristics	**Sample: n= 577** **Males: 59/130 Diet group, 81/141 Exercise group, 70/126 Diet & Exercise group, 73/133 Control group** **Mean age: 44.7 years ± 9.4 Diet group, 44.2 years ± 8.7 Exercise group, 44.4 years ± 9.2 Diet & Exercise group, 46.5 years ± 9.3 Control group** **Mean BMI: 25.3 ± 3.8 Diet group, 23.0 ± 3.7 Exercise group, 26.3 ± 3.9 Diet & Exercise group, 26.2 ± 3.9 Control group** **Waist circumference:** **Other:**	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**Yes all sample was Chinese**	
Sub-group analysis (Y/N)	**Yes all sample was Chinese**	
Criteria used for diagnosis of pre-diabetes	**1985 World Health Organisation criteria**	
Criteria used for diagnosis of diabetes	**1985 World Health Organisation criteria**	
Primary findings	**Among individual subjects in the control group, the incidence of diabetes was 15.7/100 person-years (95% CI, 12.7-18.7%). In each of the three intervention groups, the incidence of diabetes was significantly lower than in the control group (10.0 [95% CI, 7.5-12.5], 8.3 [6.4-10.3], and 9.6 [7.2-12.0] per 100 person-years in the diet, exercise, and diet-plus-exercise groups, respectively) (P < 0.05 for all) (Table 2). Incidence rates did not differ significantly among the three intervention groups (P > 0.05). The incidence of diabetes by group was 57/130 in the Diet group, 58/141 in the Exercise group, 58/126 in the Diet & Exercise group and 90/133 in the Control group.**	
Secondary findings	**-**	

Follow up	**Six years**	
Intention to Treat analysis	**No**	
Adverse events	**None reported**	
Other properties	**-**	
Cost Effectiveness	**-**	
Reviewer comments		
Authors conclusions	**Diet and/or exercise interventions led to a significant decrease in the incidence of diabetes over a six year period among those with IGT.**	
Quality Assessment	**Jadad 2 (Gillies)** **NICE ++**	
Study	**Author: Diabetes Prevention Program Research Group** **Year 2002** **Country: US** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Metformin at a dose of 850 mg taken orally once a day for first month, then increased to 850 mg twice a day.** **Or** **Lifestyle intervention, where participants were encouraged to follow a Food Guide Pyramid and the equivalent of a National Cholesterol Education Program Step 1 diet, to reduce their weight and increase their physical activity. Self-reported levels of leisure physical activity were assessed annually using a Modifiable Activity Questionnaire.**	
Comparator	**Placebo**	
Setting / Delivered by	**Clinical center (n=27)**	
Randomisation method	**Random treatment assignments were stratified according to the clinical center.**	
Blinding	**Assignments to metformin and placebo were double-blinded**	
Recruitment	**Unclear**	
Population baseline characteristics	**Sample: n= 3,234 persons with elevated fasting and post-load plasma glucose concentrations** **Males: 1,043 (32.3%)** **Mean age**: **51 years** **Mean BMI**: **Waist circumference:** **Other**:	

Sub-group	**Age: 25-44 years, 1,000 (30.9%)** **45-59 years, 1,586 (49.0%)** **≥ 60 years, 648 (20.0%)** **Ethnic group: Asian, 142 (4.4%)** **SES group**: **Obesity**: **BMI 22 - <30, 1.045 (32.3%)** **BMI 30- <35, 995 (30.8%)** **BMI >35 1,194 (36.9%)** **Other**:	
Sub-groups identified (Y/N)	**Yes ethnicity and BMI**	
Sub-group analysis (Y/N)	**Yes, partial by BMI (see secondary findings)**	
Criteria used for diagnosis of pre-diabetes	**1997 criteria of the American Diabetes Association.**	
Criteria used for diagnosis of diabetes	**Diabetes was diagnosed on the basis of an annual oral glucose tolerance test or a semi-annual fasting plasma glucose test, according to the 1997 criteria of the American Diabetes Association. The diagnosis required confirmation by a second test carried out usually within six weeks using the same criteria.**	
Primary findings	**Incidence of diabetes was 11.0 cases per 100 person years in placebo group, 7.8 cases per 100 person years in Metformin group and 4.8 cases per 100 person years in the lifestyle group.** **Lifestyle interventions reduced the incidence of diabetes by 58% (95% CI 48%-66%) and metformin by 31% (95% CI 17%-43%) compared to placebo. The lifestyle intervention was more effective than metformin.** **The estimated cumulative incidence of diabetes at three years was 28.9% in the placebo group, 21.7% in the metformin group and 14.4% in the lifestyle intervention group.**	
Secondary findings	**The advantage of the lifestyle intervention over metformin was greater in older persons and those with a lower BMI than in younger persons and those with a higher BMI.** **Half (50%) of the participants in the lifestyle intervention group had achieved the goal of a 7% or more weight loss by the end of 24 weeks, and 38% had a weight loss of at least 7% percent at the time of the most recent visit.** **Participants in the lifestyle intervention group had a greater weight loss and a greater increase in leisure activity than the participants in the metformin and placebo groups.** **The average weight loss was 0.12 kg in the placebo group, 2.1 kg in the metformin group and 5.6 kg in the lifestyle intervention group.**	
Follow up	**Average follow-up of 2.8 years**	
Intention to Treat analysis	**Yes. To prevent one case of diabetes during a period of three years, 6.9 persons would have to participate in the lifestyle intervention program and 13.9 would have to receive metformin.**	
Adverse events	**The rate of gastrointestinal symptoms was highest in the metformin group, and the rate of musculoskeletal symptoms was highest in the lifestyle intervention group. Hospitalisation and mortality rates were unrelated**	

	to treatment, no deaths were attributed to the study interventions.	
Other properties		
Cost Effectiveness	**Not reported**	
Reviewer comments		
Authors conclusions	**Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin.**	
Quality Assessment	**Jadad 2 (by Gillies)** **NICE ++**	
Study	**Author: Finnish Diabetes Prevention Study Group** **Year 2003** **Country: Finland** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**The participants in the intervention group had face-to-face consultation sessions (from 30 minutes to one hour) with the study nutritionist at weeks 0, 1–2, and 5–6 and at months 3, 4, 6, and 9, (altogether seven sessions during the first year and every 3 months thereafter). The first year sessions had a pre-planned topic (e.g., diabetes risk factors, saturated fat, fibre, physical activity, and problem solving), but the discussions were individualised, focusing on specific individual problems. Printed material was used to illustrate the message and to serve as a reminder at home. In addition, there were voluntary group sessions, expert lectures, low-fat cooking lessons, visits to local supermarkets, and between-visit phone calls and letters. The subjects in the intervention group were individually guided to increase their overall level of physical activity. This was done by the nutritionist during the dietary counselling sessions and highlighted by the study physicians at the annual visits. Endurance exercise was recommended to increase aerobic capacity and cardio respiratory fitness. Supervised, progressive, individually tailored circuit type moderate intensity resistance training sessions to improve the functional capacity and strength of the large muscle groups of the upper and lower body were also offered free of charge. As a means for improving motivation, an "exercise competition" between the five study centers was organized twice during the study period. Voluntary group walking and hiking were also organized.**	
Comparator	**At baseline, the control group was given general information about lifestyle and diabetes risk. This was done either individually or in one group session (30 minutes to one hour), and some printed material was delivered. The message to reduce weight, increase physical activity, and make qualitative changes in diet was the same as for the intervention group subjects, but counselling was not individualized.**	
Setting / Delivered by	**A multi-center study with five participating centers in Helsinki, Kuopio, Turku, Tampere, and Oulu. Each study center employed a physician, study nurse, and nutritionist (MSc in nutrition) on a part-time basis. Either an exercise instructor/ physiotherapist was a member of the study team or these services were provided commercially.**	
Randomisation method	**At the first study visit after the screening phase, the subjects were randomly allocated to the intervention group or the usual care control group. Randomization was stratified by center, sex, and two hour plasma glucose value.**	

Blinding	**No**	
Recruitment	**Study subjects were recruited mainly by screening high-risk groups such as first-degree relatives of type 2 diabetes patients who voluntarily responded to local advertisements or were identified in earlier epidemiological surveys. The inclusion criteria were 1) age 40–64 years at screening, 2) BMI >25 kg/m^2 at screening, and 3) the mean value of two 75-g oral glucose tolerance tests in the impaired glucose tolerance range based on 1985 World Health Organization criteria.**	
Population baseline characteristics	**Sample: n=** 522 **Males: 172** **Mean age**: **55** ± 7 **Mean BMI**: **31.4 ± 4.5 (intervention group), 31.1 ± 4.5 (control group)** **Waist circumference: 102.0 cm ± 11.0 (intervention group), 100.5 cm ± 10.9 (control group)** **Other**:	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**1985 World Health Organization criteria**	
Criteria used for diagnosis of diabetes	**Not stated but assume the 1985 World Health Organization criteria**	
Primary findings	**During the first three years of the study, 22 subjects (9%) in the intervention group and 51 (20%) in the control group developed diabetes (P = 0.0001, χ^2 test)**	
Secondary findings	**Not applicable**	
Follow up	**Three year follow up.**	
Intention to Treat analysis	**No**	
Adverse events	**None reported**	
Other properties		
Cost Effectiveness		

Reviewer comments		
Authors conclusions	**The intensive lifestyle intervention produced long-term beneficial changes in diet, physical activity, and clinical and biochemical parameters and reduced diabetes risk. This type of intervention is a feasible option to prevent type 2 diabetes and should be implemented in the primary health care system.**	
Quality Assessment	**Jadad 1 (by Gillies)** **NICE ++**	
Study	**Author: Diabetes Prevention Program Research Group** **Year: 2009** **Country: USA** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Participants were randomly assigned centrally to one of three interventions: intensive lifestyle (aimed to help participants to achieve and maintain 7% weight loss and 150 min or more per week of moderate-intensity physical activity); metformin 850 mg twice per day; or placebo.**	
Comparator	**Metformin and Placebo**	
Setting / Delivered by	**Clinic**	
Randomisation method	**Randomisation procedure not described**	
Blinding	**The metformin and placebo groups were masked (double blind) to treatment. Masked treatment was discontinued in July, 2001, after it was established that lifestyle intervention reduced incidence of diabetes by 58% and metformin by 31% compared with placebo during an average of 2.8 years in the DPP. After participants were informed of the main results from DPP, those in the metformin and placebo groups entered into a 1–2 week drug washout study to identify whether treatment of fasting glucose accounted for the diabetes risk reduction with metformin. They were then unmasked to their treatment assignments, and placebo was stopped.**	
Recruitment	**All 3150 surviving DPP participants who had not withdrawn consent were eligible, irrespective of whether they had developed diabetes. Enrolment started in September, 2002, and was largely completed within 1 year, by which time 2665 participants (85%) had enrolled. By Aug 27, 2008, 2766 (88%) had enrolled.**	
Population baseline characteristics	**Sample: n= 2766** **Males: 888** **Mean age (years): 55.2 $\pm$ 10.3** **Mean BMI (kg/m2): 31.1 $\pm$ 5.9 (Men); 34.2 $\pm$ 7.2 (Women)** **Waist circumference: Not reported** **Other: Not reported**	
Sub-group	**Age (years): 25-44; 45-59; 60 and older** **Ethnic group: SES group: White (n=1506); African-American (n=559); Hispanic (n=424); American Indian (n=153); Asian American or Pacific Islander (n=124)** **Obesity: Not reported**	

	Other: Not reported	
Sub-groups identified (Y/N)	**Yes**	
Sub-group analysis (Y/N)	**Yes**	
Criteria used for diagnosis of pre-diabetes	**Not reported in the paper**	
Criteria used for diagnosis of diabetes	**The primary outcome, as in the DPP, was development of diabetes according to American Diabetes Association criteria—fasting plasma glucose 7·0 mmol/L or higher measured every 6 months, or 2-h plasma glucose 11·1 mmol/L or higher after a 75 g oral glucose load, measured yearly. A provisional diagnosis by either test needed confirmation with a repeat test.**	
Primary findings	**During DPPOS, diabetes incidence rates did not significantly differ between groups. Incidence rates were stable in the lifestyle group, but fell in the placebo and metformin groups during the DPPOS. During the combined DPP, bridge, and DPPOS periods, the incidence rate of the lifestyle group was reduced by 34% (95% CI 24–42) and metformin by 18% (7–28) compared with placebo. The lifestyle effect was greatest in participants aged 60–85 years at randomisation (49% rate reduction), in whom metformin had no significant effect. The median delay to onset of diabetes was approximately 4 years by lifestyle and 2 years by metformin, compared with placebo. At the most recent yearly examination, 23% in the lifestyle, 19% in the metformin, and 19% of participants in the placebo groups had become normoglycaemic by criteria defined and reported previously (fasting glucose <6.1 mmol/L, 2-h glucose <7.8 mmol/L, and no previous diagnosis of diabetes.**	
Secondary findings	**The lifestyle group participants initially lost the most weight (a mean of 7 kg by 1 year), but gradually regained, although still weighing about 2 kg less than they did at randomisation. The metformin group lost a mean of 2.5 kg during DPP and maintained most of that weight loss. The placebo group's mean weight loss was less than 1 kg from DPP entry. Thus, the groups' mean weights differed at the start of DPPOS—90.6 kg for lifestyle, 92.0 kg for metformin, and 93.4 kg for placebo (p=0.0158). The lifestyle group subsequently regained about 1 kg, whereas the metformin and placebo groups initially lost and then regained weight back to their respective levels at DPPOS baseline. Participants younger than 45 years at randomisation had less sustained weight loss from randomisation throughout the DPPOS than did those aged 45 years and older. Participants in both the metformin and placebo groups who were aged 60–85 years at DPP randomisation lost weight. Every age-group in the lifestyle intervention gained weight, on average, during the DPPOS.**	
Follow up	**10 years after DPP randomisation**	
Intention to Treat analysis	**Pair-wise comparisons of diabetes incidence in the three intervention groups were performed. The intention-to-treat analysis compared each intervention with placebo on a modified product-limit life-table distribution with a log-rank test statistic. Treatment groups and periods during the study were also compared with incidence per 100 person-years. Cases were new confirmed diagnoses of diabetes. Person-years were the sum of time under follow-up for all participants in a group before diagnosis of diabetes or end of follow-up if diabetes did not develop during the time of interest.**	

Adverse events	**Not reported**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**During follow-up after DPP, incidences in the former placebo and metformin groups fell to equal those in the former lifestyle group, but the cumulative incidence of diabetes remained lowest in the lifestyle group. Prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.**	
Quality Assessment	**Jadad =2** **NICE ++**	
Study	**Author: Indian Diabetes Prevention Programme** **Year 2006** **Country: India** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Group 2 subjects followed lifestyle modification (LSM), subjects who were involved in physical labour or who had to walk or cycle for >30 minutes per day or were performing exercises regularly were asked to continue their routine activities. Subjects engaged in sedentary or light physical activity, as assessed in the initial were advised and regularly motivated to walk briskly for at least 30 minutes each day.** **Group 3 subjects were treated with metformin (MET), subjects received metformin tablets and were given diaries to record their daily consumption of tablets, particularly whether any doses were missed. Three months' supply was provided, and leftover tablets were counted to assess the compliance. The initial dose of 250 mg twice daily was increased to 500 mg twice daily in the first 50 patients after 2 weeks (26 and 24 in the MET and LSM + MET groups, respectively).** **Group 4 subjects were given LSM plus MET**	
Comparator	**Group 1 subjects were given standard health care advice**	
Setting / Delivered by	**Community based no further details.**	
Randomisation method	**Unclear**	
Blinding	**Not reported**	
Recruitment	**The study subjects were recruited from the middle-class population working in service organisations and also from their families. They were identified by work-place announcements and circulars. Non-diabetic subjects with no major illness aged 35–55 years and of both sexes, were screened from March 2001 to July 2002. At the time of recruitment and during the interim six monthly follow-up, screening was carried out using a 2 hour post-glucose capillary glucose measurement and confirmatory diagnosis was based on a standard OGTT (75 g glucose load) using plasma glucose values.**	

Population baseline characteristics	**Sample: n=** 531 **Males: 420** **Mean age**: **Group 1 (control) 45.2 years ± 5.7** **Group 2 (LSM) 46.1 years ± 5.7** **Group 3 (MET) 45.9 years ± 5.9** **Group (LSM + MET) 46.3 years ± 5.7** **Mean BMI**: **Group 1 (control) 26.3± 3.7** **Group 2 (LSM) 25.7 ± 3.3** **Group 3 (MET) 25.6 ± 3.7** **Group (LSM + MET) 25.6 ± 3.3** **Waist circumference: Group 1 (control) 90.8 cm ± 7.5** **Group 2 (LSM) 89.0 cm ± 7.9** **Group 3 (MET) 89.7 cm ± 9.5** **Group (LSM + MET) 90.2 cm ± 7.6** **Other**:	
Sub-group	**Age:** **Ethnic group: All sample was Asian Indians** **SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**All sample was a sub-group**	
Sub-group analysis (Y/N)	**Yes**	
Criteria used for diagnosis of pre-diabetes	**1999 World Health Organization criteria, (fasting glucose <7.0 mmol/l [<126 mg/dl]; 2-h glucose 7.8–11.0 mmol/l [140–199 mg/dl])**	
Criteria used for diagnosis of diabetes	**Diabetes, as indicated by either a fasting plasma glucose of ≥7.0 mmol/l (≥126 mg/dl) and/or a 2-h plasma glucose concentration of ≥11.1 mmol/l (≥200 mg/dl) during either a six-monthly or an annual follow-up which was confirmed by an OGTT.**	
Primary findings	**44.4% of 502 subjects had developed diabetes, group 1 (control) 55% (n=133), group 2 (LSM) 39.3% (n=120), group3 (MET) 40.5% (n=128) and group 4 (LSM + MET) 39.5% (n=121)**	
Secondary findings		
Follow up	**36 months median follow-up of 30 months**	
Intention to Treat analysis	**No**	

Adverse events	**There were 11 cases of cardiovascular events: two in controls, four in LSM and five in LSM + MET. In the control group, one subject died following surgery for a cerebrovascular accident. In the LSM group, one subject died of hepatic encephalopathy and in the LSM + MET group one subject died during the postoperative period after thyroid surgery. There were 25 other cases of hospitalisation for various surgeries. All the subjects involved recovered uneventfully. In the MET and LSM + MET groups symptoms of hypoglycaemia were reported by 22 subjects in the MET and LSM + MET groups when they were receiving metformin 500 mg twice a day. The symptoms were relieved after eating food. Five cases had gastrointestinal symptoms with this dose of metformin. The symptoms did not recur when the dose was reduced to 250 mg twice a day.**	
Other properties		
Cost Effectiveness		
Reviewer comments		
Authors conclusions	**Progression of IGT to diabetes is high in native Asian Indians. Both LSM and MET significantly reduced the incidence of diabetes in Asian Indians with IGT; there was no added benefit from combining them.**	
Quality Assessment	**Jadad 2 (Gillies)** **NICE ++**	
Study	**Author: Jarrett** **Year 1979** **Country: UK** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Group 3 recommended 120g/day carbohydrate diet + 50mg. phenformin S. A. once daily.** **Group 4 recommended to 'limit sucrose intake' and 50 mg phenformin S. A. once daily.**	
Comparator	**Group 1 was recommended 120g/day carbohydrate diet + placebo capsule.** **Group 2 recommended to 'limit sucrose (i. e. table sugar) intake' + placebo capsule.**	
Setting / Delivered by	**Clinics**	
Randomisation method	**At the first visit subjects were allocated at random to one of four treatment groups:**	
Blinding	**The diet part of the trial was not 'blind' so that periodic reinforcement of dietary advice could be given. The drug trial was 'double-blind' and was planned to run for the first five years of the ten year study. Follow-up examinations were at approximately six month intervals.**	
Recruitment	**All but eighteen of the subjects were recruited between 1968 and 1970 from the Whitehall Survey, a screening study of 20,000 male Civil Servants working in London. The others were recruited during the pilot phase of the Survey, which was carried out using the same screening techniques, amongst Post Office employees.**	
Population baseline characteristics	**Sample: n=** 204 **Males: 204** **Mean age**: **Mean BMI**: **Waist circumference:**	

	Other:	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**Borderline diabetics were defined on the basis of the following criteria of impaired glucose tolerance:** **(a) Survey blood sugar 6.1-11.0 mmol/1 (110 and 199 mg/dl); and, at standard GTT,** **(b) Peak blood sugar >10 mmol/l (180 mg/dl) and two hour blood sugar 6.7-11.0 mmol/1 (120-199 mg/dl) and/or two values exceeding 10.0 mmol/1 (180 mg/dl) and/or mean 2 hour blood sugar (Survey and G.T.T.) ~ 6.7 mmol/1 (120 mg/dl).**	
Criteria used for diagnosis of diabetes	**The arbitrary criteria for determining this "worsening to diabetes" were:** **(1) two successive two-hour post glucose blood sugars > 11.1 mmol/1 (200 mg/dl).** **(2) three non-successive two-hour blood sugars > 11.1 mmol/l (200 rng/dl).** **(3) the development of unequivocal symptoms or signs of diabetes mellitus.** **(4) a two-hour blood sugar > 11.1 mol/l (200mg/dl) at a standard afternoon oral glucose tolerance test carried out at the 10th visit (i. e. 5 years), whether or not previous two-hour values were also elevated.**	
Primary findings	**13.3% (6/45) of group 2, 18.4% (9/49) of group 4, 18.2% (8/44) in group 1 and 9.3% (4/43) in group 2 worsen to diabetes.**	
Secondary findings	**-**	
Follow up	**Five years**	
Intention to Treat analysis	**No**	
Adverse events	**None reported**	
Other properties	**-**	
Cost Effectiveness	**-**	
Reviewer comments		
Authors conclusions	**'Worsened to diabetes' was not significantly influenced by treatment with carbohydrate restriction with or without a daily dose of 50 mg phenformin.**	
Quality Assessment	**Jadad 3** **NICE +**	
Study	**Author: Kosaka** **Year 2005** **Country: Japan** **Study design: RCT**	**Comments**

Included in Gillies et al review?	**Yes**	
Intervention	**Subjects with a BMI ≥22 kg/m^2 were informed of their desirable body weight (calculated on the basis of their height so that the BMI = 22 kg/m^2) individually. We told them to weigh themselves at least once a week at home and advised them to reduce their weight to the desirable level at a rate of 0.5–1.0 kg/month. Those with a BMI less than 22 kg/m^2 were advised to maintain their present weight and not gain weight. To achieve the body weight objective, the following questions and instructions were repeated every 3–4 months at each hospital visit.** **(1) First, the subjects were asked about their usual diet in terms of the amount and kinds of food they ate. If there were no major deviations in nutrient balance, they were advised to reduce the amount of each food by about 10% and recommended consuming a large amount of vegetables. Special instructions were given to subjects who could not maintain good dietary habits, such as to use a smaller rice bowl, to ask for the cooperation of the family members in reducing the size of servings, and to take breakfast and the evening meal together with the family as much as possible.** **(2) When fat intake was judged to exceed 50 g, it was explained to them, the kinds of food that are rich in fat, and the subjects were advised to consume less of such foods.** **(3) If alcohol intake was judged to be excessive (more than 350 ml of sake, about 50 g alcohol, a day) and consuming alcoholic beverages seemed to be associated with excessively large meals, the subjects were advised to stop consuming alcoholic beverages or to reduce the amount by half.** **(4) It was recommended that they eat out no more than once a day.** **(5) Special instructions were given individually with regard to intake of snacks and fruits. For these instructions on diet described above, ''Food Exchange Lists, Dietary Guidance for Persons with Diabetes'' by the Japan Diabetes Society, which provides a rough gauge of the amount of energy and of each nutrient contained in each food, as the basis for instructions on diet was used.** **(6) Current physical activity was assessed by interview, and inclusion of moderate exercise, such as walking 30–40 minutes a day, was recommended. Realistic ways of increasing physical activity was discussed individually, for example, to use a staircase instead of an elevator or an escalator as much as possible, 30-minute bicycle riding in weekends, getting off the bus before the destination and walk one bus-stop distance, and so forth. About 15% of the subjects were already performing that amount of exercise, and it was recommended that they maintain their present level of activity in these cases.** **These means of intervention were repeatedly explained at hospital visits every 2–3 months to measure FPG, HbA1c, and body weight, and every 6 months for an OGTT.**	
Comparator	**Subjects with a BMI ≥24 kg/m^2 were advised to take 5–10% smaller meals than they had been taking, and to increase their physical activity. They were encouraged to lose weight. Subjects with a BMI <24 kg/m^2 were told to avoid gaining weight by dieting and exercise. These objectives were repeatedly explained every 6 months when the subjects came to the hospital.**	
Setting / Delivered by	**Subjects seen in an ordinary outpatient clinic**	
Randomisation method	**One of every five subjects was randomly selected for allocating to the intensive intervention group, and the others were assigned to the standard intervention (control) group.**	
Blinding	**None**	
Recruitment	**Subjects with a fasting plasma glucose (FPG) value below 140 mg/dl and a 2-h plasma glucose (2hPG) value**	

	after a 100 g glucose load of between 160 and 239 mg/dl on 100 g OGTTs from among examinees in 1990–1992 were randomly selected. Only men were selected for the present study, as in the author's previous long-term follow-up experience there were more dropouts among the women than among the men in a similar setting. Exclusion criteria were: (1) previous history of diabetes; (2) diagnosed or suspected malignant neoplasm; (3) diagnosed or suspected disease of the liver, pancreas, endocrine organs, or kidney; (4) ischemic heart disease or cerebrovascular disease or a history of such disease.	
Population baseline characteristics	**Sample: n= 458 (356 control, 102 intervention)** **Males: 458** **Mean age**: **Mean BMI**: **23.8 ± 2.1 (control group), 24.0 ± 2.3 (intervention group)** **Waist circumference:** **Other**:	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**All sample was Japanese males**	
Sub-group analysis (Y/N)	**Yes All sample was Japanese males**	
Criteria used for diagnosis of pre-diabetes	**1980 World Health Organisation criteria**	
Criteria used for diagnosis of diabetes	**Diabetes was determined by FPG and it was judged to have developed when FPG reached or exceeded 140 mg/dl on two consecutive tests performed at an interval of 2 weeks or less.**	
Primary findings	**The cumulative incidence of diabetes in the intervention group during the 4 years was 3.0% (3/102), and in the control group 9.3% (33/356)**	
Secondary findings	**Change in body weight, -0.39 kg in control group, - 2.18 kg in intervention group.**	
Follow up	**Four years**	
Intention to Treat analysis	**No**	
Adverse events	**None reported**	
Other properties		
Cost Effectiveness		
Reviewer comments		
Authors conclusions	**A lifestyle intervention designed to achieve and maintain ideal body weight (BMI <22 kg/m^2) is an effective means of reducing incidence of type 2 diabetes in Japanese males with IGT detected in regular health-screening examinations. Reduction in the incidence by lifestyle intervention was successfully carried out in a clinical outpatient setting for diabetic patients. The incidence of diabetes was positively correlated and the improvement in glucose tolerance was negatively associated with the change in body weight. A higher**	

	FPG and low insulinogenic index at baseline increased the risk of developing diabetes.	
Quality Assessment	**Jadad 2 (Gillies)** **NICE ++**	
Study	**Author: Li, G et al** **Year: 2008** **Country: China** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Adults with impaired glucose tolerance at 33 clinics in Da Qing city, China, were recruited and randomised by clinic into either a control group or one of three lifestyle interventions: diet, exercise, or diet plus exercise. The goal of the diet intervention was to increase participants' vegetable intake and lower their alcohol and sugar intake. Those who were overweight or obese were also encouraged to lose weight by reducing their total calorie intake. The goal of the exercise intervention was to increase leisure time physical activity. The effect of the intervention was assessed at 2-yearly intervals. In 1992, after a 6-year intervention, participants were informed of the final results and asked to continue with normal medical care.**	
Comparator	**Control group; No description of the control condition reported**	
Setting / Delivered by	**Clinics**	
Randomisation method	**The study adopted a randomised cluster design, randomising participants on the basis of the clinics where they received their usual medical care. No further description of the randomization process was reported.**	
Blinding	**No description reported**	
Recruitment	**In 1986, 577 adults with impaired glucose tolerance at 3 clinics in Da Qing city, China, were recruited and randomised by clinic into either a control group or one of three lifestyle interventions. No further description was provided.**	
Population baseline characteristics	**Sample: n= 577** **Males: 233 (Intervention); 79 (Control)** **Mean age: 44.7±0.4 (Intervention); 46.6±0.8 (Control)** **Mean BMI: 25.7 ±0.2 (Intervention); 26.2 ±0.3 (Control)** **Waist circumference: Not reported** **Other: Not reported**	
Sub-group	**Age: Not reported** **Ethnic group: SES group: Not reported** **Obesity: Not reported** **Other: Not reported**	
Sub-groups identified (Y/N)	**No**	

Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**Not reported**	
Criteria used for diagnosis of diabetes	**Diabetes status was defined by self-reported diagnosed diabetes plus evidence of raised glucose levels in the medical record, taking hypoglycaemic medications, or fasting glucose and oral glucose tolerance tests, done every 2 years during the active intervention period (1986–1992) and at the end of follow-up (2006), and interpreted using 1985 WHO criteria for diabetes.**	
Primary findings	**Of the 577 participants in 1986, 435 had developed diabetes by the end of follow-up. 265 cases were identified by oral glucose tolerance tests during the active intervention phase, 145 were identified by report from the patient or relative, with additional evidence of either use of hypoglycaemic medication or raised glucose level recorded in the medical record at time of diagnosis during the post-intervention period. Finally, 25 cases were identified by oral glucose tolerance tests at the end of the study. The diabetes status of 14 participants was unknown. During the active intervention, the cumulative diabetes incidence was 43% in the intervention group and 66% in the control group, and the number needed to treat to prevent a case of diabetes was five people. During the 20 year follow-up, the cumulative diabetes incidence was 80% in the intervention group and 93% in the control group, and the number needed to treat to prevent a case of diabetes was six people. Participants in the intervention group had an average of 3.6 fewer years with diabetes. In people with diabetes, comparing the active intervention group to the controls at the end of follow-up, fewer were on insulin (26% [82 of 314] *vs.* 34% [41 of 121]) and they had lower average haemoglobin A_1C levels (7.34% *vs.* 7.76%), but these differences were not significant (p=0.11 and p=0.07, respectively).**	
Secondary findings	**In multivariate analyses that controlled for age and clustering by clinic, participants in the combined intervention group had a 43% lower incidence of diabetes than those in the control group (HRR 0.57; 95% CI 0.41−0.81). Over 20 years, the yearly estimated HRRs ranged from 0.51 to 0.64, with intervention participants having a lower diabetes incidence throughout the study (data not shown). In a sub-analysis of the effects of diet, exercise, and diet plus exercise versus control, the randomisation groups for the original study, the 20-year HRRs for diabetes were 0.58 (0.38−0.89), 0.51 (0.31−0.83), and 0.66 (0.41−1.09), respectively.**	
Follow up	**Of the original 577 CDQDPS participants, one could not be traced at the end of the active intervention in 1992. By 2006, 142 (25%) had died and 426 (74%) were alive on Dec 31, 2006. Eight could not be traced and were lost to follow-up. For 26, only data from the active intervention period or from medical records during the post-intervention period were obtained. For the remainder (400), 293 were interviewed and examined at the Da Qing First Hospital and 79 were interviewed at home, of whom 58 were examined. For those living outside the Da Qing area (28), the interview was done by phone, and 21 of these participants were examined by their health providers. Of the 426 living participants, 372 (87%) had the interview and had a clinical examination. The medical records of 396 alive and 64 deceased participants were obtained. At the end of follow-up, 153 people were eligible for oral glucose tolerance tests, but only 128 received the test and 25 had a fasting plasma glucose test at their homes. Of the 577 CDQDPS participants, valid follow-up information was obtained for 98% (563) for diabetes, 94% (542) for any CVD events, and 98% (568) for CVD and all-cause mortality. The total number of person-years of follow-up was 5268 for the diabetes outcome (range 1−20, median 6, IQR 11, mean 9·4 years), 8817 for the CVD-event outcome (range 1−20, median 20, IQR 7, mean 16.3 years), and 9699 for the CVD and all-cause mortality outcome (range 0.2−20, median 20, IQR 2, mean 17.9 years).**	

Intention to Treat analysis	**Diabetes was not included in the post-intervention analyses since 265 patients had already developed diabetes by the end of the active intervention period, thus greatly truncating and biasing the available sample entering the post-intervention period. The analyses were based on intention to treat and were done with the NLMIXED procedure in SAS version 9.1.2. Multilevel discrete time survival models to estimate a time-varying HRR between treated and control groups were used. The HRR was treated as a random effect and separate ratios for each follow-up year were estimated. Clinic was included in these models as a random effect, but age was not, since its inclusion results in data too sparse for fitting these models. Because of the randomised design, these comparisons are valid without adjusting for covariates. These time-varying HRR models were fit using WinBUGS.**	
Adverse events	**No adverse events were recorded.**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**Group-based lifestyle interventions over 6 years can prevent or delay diabetes for up to 14 years after the active intervention. However, whether lifestyle intervention also leads to reduced CVD and mortality remains unclear.**	
Quality Assessment	**Jadad=2** **NICE -**	
Study	**Author: Liao** **Year 2002** **Country: US** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Endurance exercise training and a dietary prescription. For the first 6 months, exercise sessions were directed by an exercise physiologist. Subjects performed endurance exercise (walk/jog) on a treadmill three times a week for one hour at each session. Exercise began with a 10 minute warm-up period and ended with a 10 minute cool down period. Initially, exercise was designed to attain 50% of heart rate reserve [0.5 times (maximum heart rate – resting heart rate) - resting heart rate]. Heart rate reserve was estimated from the maximum and resting heart rates observed at the baseline VO2max for each individual. The exercise was gradually increased at two week intervals over a period of three months until subjects were exercising at a goal of 70% of heart rate reserve. Pulse rates were electronically monitored during exercise. The treatment group was also prescribed an isocaloric American Heart Association (AHA) step 2 diet comprising <30% of total calories as fat (<7% as saturated fat), 55% as carbohydrate, the balance as protein, and <200 mg cholesterol daily.**	
Comparator	**Stretching exercises three times a week for one hour (each session under staff supervision) and control group participants were prescribed an isocaloric AHA step 1 diet comprising 30% of total calories as fat (10% as saturated fat), 50% as carbohydrate, 20% as protein, and <300 mg cholesterol daily.**	
Setting / Delivered by	**Exercise physiologist**	
Randomisation method	**Adaptive randomisation**	
Blinding	**No**	

Recruitment	**Unclear**	
Population baseline characteristics	**Sample: n= 64** **Males: 12 (37%) Intervention group, 17 (53%) Control group** **Mean age: 55.8 years ± 1.8 (Intervention group) 52.2 years ± 1.8 (Control group)** **Mean BMI: 25.6 ± 0.8 (Intervention group) 26.6 ± 0.8 (Control group)** **Waist circumference: 80.9 cm ± 2.0 (Intervention group) 87.2 cm ± 2.2 (Control group)** **Other:**	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**All sample was Japanese American**	
Sub-group analysis (Y/N)	**Yes, all sample was Japanese American**	
Criteria used for diagnosis of pre-diabetes	**Not stated**	
Criteria used for diagnosis of diabetes	**Not stated**	
Primary findings	**At six months – one person in each group had developed diabetes.** **At 12 months - one person from the intervention group had diabetes (1/32, 3.1%), and two from the control group had diabetes (2/32, 6.3%)**	
Secondary findings	**At six months - the treatment group showed significantly greater reduction in BMI (-1.1 ± 0.2 vs. –0.4 ± 0.1, p= 0.0006).** **At 24 months - the treatment group showed significantly greater reduction in BMI (-0.7 ± 0.2 vs. 0.2 ± 0.2, p= 0.0023).**	
Follow up	**Three, six, nine, 12 and 24 month follow-up**	
Intention to Treat analysis	**No**	
Adverse events	**None reported**	
Other properties	**-**	
Cost Effectiveness	**-**	
Reviewer comments	**Study was not designed to demonstrate prevention of diabetes.**	
Authors conclusions	**Diet and endurance exercise improved BMI, body composition, and body fat distribution and, thus, may delay or prevent type 2 diabetes in Japanese Americans with IGT.**	
Quality Assessment	**Jadad 2 (Gillies)** **NICE +**	
Study	**Author: Lindahl et al** **Year: 2009**	**Comments**

	Country: Sweden Study design: RCT	
Included in Gillies et al review?	**No**	
Intervention	**The intensive intervention group was divided into two halves, and 50 individuals were simultaneously admitted on each occasion. This residential programme was implemented during a 1-month stay with full boarding at Sorsele (n=20) and Vindeln (n=30) wellness centres, owned by the Vasterbotten County Council. The intervention programme included approximately 140 h of scheduled activities. Aerobic physical activity of moderate intensity was performed daily for 2.5 h, e.g. brisk walks, gymnastics, bicycling and swimming. The diet served during the stay contained approximately 20% of the energy in the form of fat and had a high fibre content. Consumption of alcohol was not allowed, and all current smokers were offered group treatment for smoking cessation. The behavior change process was facilitated by teaching goalsetting, self-monitoring and problem-solving techniques, together with stress management and relapse prevention. The examination protocol with additional learning sessions was repeated during a 4-day follow-up 12 months later. They were also offered the same examination protocol as the usual care group at 3 and 5 years.**	
Comparator	**A health survey was performed, including a physical examination, a 2-h OGTT and blood sampling. The survey was followed by a 30–60-min counseling session, where the participants were given both oral and written advice. The same examination protocol was repeated after 1, 3 and 5 years.**	
Setting / Delivered by	**Wellness centres**	
Randomisation method	**Each subject was allotted a uniformly distributed random number. The subjects were then sorted according to this random number, and 100 subjects were invited into each treatment arm. The rest of the subjects were used as possible substitutes. At the start of the study, 100 participants were enlisted in the intensive intervention group but only 94 in the usual care group. This difference between groups (n=6) was due to a logistic error. The randomization procedure was carried out by a statistician employed by Vasterbotten County Council but otherwise not involved in the study.**	
Blinding	**The study was blinded for researchers performing laboratory analyses, but not for participants or professionals involved in the treatment.**	
Recruitment	**Since 1985, there has been an ongoing community intervention programme on CVD and diabetes in the province of Vasterbotten in northern Sweden – the Vasterbotten Intervention Programme (VIP). By the end of 1994, 28,000 subjects had participated, of whom a majority also donated blood to the bio-bank for future research purposes. Subjects who fulfilled the inclusion criteria of having a 2-h glucose concentration during an oral glucose tolerance test (OGTT) in the range of IGT and a body mass index above 27 kg/ m2 (n=650) were invited by mail to participate in a randomized clinical trial, and 345 individuals accepted.**	
Population baseline characteristics	**Sample: n=301** **Males: 25 (Intervention) ; 33 (Control)** **Mean age: 52.2 ±9.0 (Intervention); 53.5 ± 8.4 (Control)** **Mean BMI: 31.2 ± 3.1(Intervention); 30.2 ±3.4 (Control)** **Waist circumference: 100.6±7.8 (Intervention); 99.9 ±8.6 (Control)** **Other: Smoking**	
Sub-group	**Age: Not reported** **Ethnic group: SES group: Not reported** **Obesity: Not reported**	

	Other: Not reported	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**Not reported**	
Criteria used for diagnosis of diabetes	**Diabetes was defined as having known diabetes (questionnaire) or a fasting plasma glucose concentration ≥7.0 mmol/l.**	
Primary findings	**At 1 year, five subjects in the intensive intervention group and 20 in the usual care group developed diabetes (7% vs. 25%, p=0.003). The relative risk reduction between groups was 70%. At 3-year follow-up, 12 (17%) vs. 20 (25%) new cases were discovered. The relative risk reduction was 40%. At 5-year follow-up, there were 17 (24%) vs. 23 (29%) new cases. The relative risk reduction was 25%. The risk reductions at 3 and 5 years were not significant.**	
Secondary findings	**At 3- and 5-year follow-ups, most of the beneficial effects on cardiovascular and metabolic risk factors seen in the intensive intervention group at 12-month follow-up had disappeared. However, within the intensive intervention group, there was an increase in HDL cholesterol as compared to baseline at both 3- and 5-year follow-ups (p=0.0003 and p=0.003, respectively).**	
Follow up	**One hundred and sixty eight individuals, 83 in the intensive intervention group and 85 in the usual care group, completed the whole study period and formed the basis of the present study. The participation rate at 5-year follow-up was 83% in the intensive intervention group and 90% in the usual care group.**	
Intention to Treat analysis	**A complementary intention-to-treat (ITT) analysis was conducted. The database for the ITT analysis was created by imputation of missing values in subjects still on treatment as well as in dropouts. The principle chosen was to carry the baseline value forward, i.e. to use the assumption that the treatments, intensive or usual care, had no effect. If the baseline value was missing, it was replaced by the mean of the whole study group. For many of the variables, there were occasional (one or two subjects) missing values in the baseline measurement. For waist and hip circumference, there were more missing data (n=18), all in the usual care group. Finally, in the completed ITT database, all individuals included in the study (n=194) had either a measured or an imputed value in all variables at all points of time.**	
Adverse events	**Not reported**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**The intervention affected several important cardio-metabolic risk variables beneficially, and reduced the risk for type 2 diabetes, but the effects persisted only as long as the new lifestyle was maintained. Increased physical activity seemed to be the behaviour that was most easy to preserve.**	
Quality Assessment	**Jadad=1** **NICE ++**	
Study	**Author: Lindstrom et al.** **Year 2006** **Country: Finland** **Study design: RCT**	**Comments**

Included in Gillies et al review?	**No**	
Intervention	**The main goals of the intervention were: weight reduction of 5% or more; less than 30% of the daily energy intake from fat; less than 10% of the daily energy intake from saturated fat; fibre intake 15 g per 1000 kcal or more; and moderately intense physical activity 30 min per day or more. The duration of intervention ranged from less than 1 year (indicating withdrawal before the first yearly visit) up to 6 years, with median length of 4 years. The implementation of the intervention programme has been previously reported. Briefly, the participants in the intervention group were given detailed and individualised counselling to achieve the lifestyle goals. They had seven personal counselling sessions with the study nutritionist during the first year and every 3 months thereafter. The median number of dietary counselling sessions per participant was 20 thus indicating excellent compliance with the study protocol. The participants were also advised to increase their level of physical activity, and were offered free of charge, supervised, individually tailored circuit-type moderate-intensity resistance training sessions to improve the functional capacity and strength of the large muscle groups of the upper and lower body.**	
Comparator	**The participants in the control group were given general verbal and written health behaviour information at baseline without specific individualised advice. At the last intervention period visit all the participants were given a summary of their laboratory test results during the intervention period, including the glucose values, and they were also told about the findings of the randomised trial.**	
Setting / Delivered by	**A multi-center study with five participating centers in Helsinki, Kuopio, Turku, Tampere, and Oulu. Each study center employed a physician, study nurse, and nutritionist (MSc in nutrition) on a part-time basis. Either an exercise instructor/ physiotherapist was a member of the study team or these services were provided commercially.**	
Randomisation method	**Originally, 522 men and women in five study centres were randomised at the baseline visit to one of the two treatment modalities, the intervention group with intensive diet-exercise counselling (n=265, the proportion of women 66%) or the control group (n=257, the proportion of women 69%).**	
Blinding	**Not reported**	
Recruitment	**All individuals who participated in the Diabetes Prevention Study were invited to take part in the post-intervention follow-up. During this follow-up, all study participants had a yearly visit with the study nurse. The visits included the same procedures as during the intervention period, and were similar for all participants irrespective of their former randomisation group. No specific diet or exercise counselling was provided.**	
Population baseline characteristics	**Sample: n= 522** **Males: 172** **Mean age: 55 ± 7** **Mean BMI: 31.4 ± 4.5 (intervention group), 31.1 ± 4.5 (control group)** **Waist circumference: 102.0 cm ± 11.0 (intervention group), 100.5 cm ± 10.9 (control group)** **Other:**	
Sub-group	**Age:** **Ethnic group: SES group:** **Obesity:** **Other:**	

Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**WHO 1985 criteria**	
Criteria used for diagnosis of diabetes	**The development of type 2 diabetes was the primary endpoint. Since the study was started before the current criteria for diabetes were introduced, diabetes was defined according to WHO 1985 criteria, ie, either fasting plasma glucose of 7·8 mmol/L or more, or 2-hour post-challenge plasma glucose of 11·1 mmol/L or more. The diagnosis of diabetes was confirmed by a second oral glucose tolerance test.**	
Primary findings	**The total number of cases of diabetes diagnosed during the overall follow-up of 7 years was 75 in the intervention group and 110 in the control group. The incidence rates were 4·3 (95% CI 3·4–5·4) and 7·4 (6·1–8·9) per 100 person-years in the intervention and control group, respectively (p=0·0001 log-rank test). The corresponding hazard ratio was 0·57 (0·43–0·76). The cumulative incidence of diabetes at year 6 was 23% in the intervention group and 38% in the control group, with an absolute risk reduction of 15% (7·2–23·2). The number of people needed to be treated to prevent one case of type 2 diabetes by lifestyle intervention was 22 for 1 year. In the intervention and the control group, respectively, 10% and 27% of the participants did not achieve any of the predefined goals by the 3-year examination, whereas 14% and 6% achieved four or five goals (p<0·0001 for Fisher's exact test). There was a strong inverse correlation between the success score and the incidence of diabetes during the total follow-up. Incidence rate per 100 person-years ranged from 8·4 (95% CI 6·2–11·3) in the participants who did not achieve any of the goals at the 3-year visit, to 2·0 (1·0–4·3) in those who achieved four or five of the goals. The hazard ratios were 1·00, 0·85 (0·57–1·28), 0.66 (0·40–1·09), 0·69 (0·38–1·26), and 0·23 (0·10–0·52) for success score from 0, 1, 2, 3, to 4–5, respectively (test for trend p=0·0004).**	
Secondary findings	**Univariate hazard ratios (95% CI) were 0·45 (0·31–0·64) for weight reduction from baseline, 0·65 (0·45–0·95) for intake of fat, 0·59 (0·31–1·13) for intake of saturated fat, 0·69 (0·49–0·96) for intake of fibre, and 0·62 (0·46–0·84) for physical activity, comparing those who did or did not achieve the respective goal. When all five success score components were simultaneously included in the Cox model, the multivariate-adjusted hazard ratios for diabetes (95% CI) were 0·43 (0·30–0·61) for weight reduction, 0·80 (0·48–1·34) for intake of fat, 0·55 (0·26–1·16) for intake of saturated fat, 0·97 (0·63–1·51) for intake of fibre, and 0·80 (0·57–1·12) for physical activity. Furthermore, weight change from baseline was significantly associated with the achievement of each of the other four lifestyle goals, and consequently, success score was strongly and inversely correlated with weight reduction. The 3-year weight reduction was 0·5%, 2·1%, 4·3%, 4·7%, and 8·7% for success score from 0, 1, 2, 3, to 4–5, respectively (test for trend p<0·0001). Additionally, all the dietary goals (total fat, saturated fat, and fibre) were significantly associated with each other (p for all <0·0001). Achievement of the fat intake goal or the fibre intake goal was associated also with the physical activity goal (p=0·0019 and p<0·0001, respectively). Univariate hazard ratios (95% CI) for diabetes incidence during the post-intervention follow-up were 0·55 (0·30–1·02) for achieving the weight reduction goal, 0·74 (0·44–1·27) for achieving the fat intake goal, 1·01 (0·54–1·89) for achieving the saturated fat intake goal, 0·72 (0·40–1·30) for achieving the fibre intake goal, and 0·62 (0·36–1·06) for achieving the physical activity goal, compared with those who did not achieve the respective goal at the first post-intervention follow-up examination. When all five variables for lifestyle goals were simultaneously analysed, the adjusted hazard ratios were 0·52 (0·28–0·96) for weight reduction from baseline, 0·67 (0·35–1·31) for the intake of fat, 1·62 (0·68–3·85) for the intake of saturated fat, 0·77 (0·38–1·57) for the intake of fibre, and 0·82 (0·46–1·48) for physical activity.**	

Follow up	**The median post-intervention follow-up time was 3 years, and the number of incident new cases of type 2 diabetes was 31 in the intervention group of 221 people at risk, and 38 in the control group of 185 people at risk. The corresponding incidence rates were 4·6 and 7·2 per 100 person-years, respectively (log-rank test p=0·0401), ie, 36% relative risk reduction**	
Intention to Treat analysis	**Kaplan-Meier survival curves were calculated to estimate the probability of remaining free of diabetes in the two groups. Participants who were lost during follow-up were treated as censored observations. The difference between the survival curves was tested with the log-rank test. The Cox proportional hazards model was used to estimate the hazard ratio for development of diabetes. The proportionality assumption of the model was assessed with graphical methods (ie, the log-log plot). All comparisons of the endpoints were based on the intention-to-treat principle.**	
Adverse events	**None reported**	
Other properties		
Cost Effectiveness		
Reviewer comments		
Authors conclusions	**Lifestyle intervention in people at high risk for type 2 diabetes resulted in sustained lifestyle changes and a reduction in diabetes incidence, which remained after the individual lifestyle counselling was stopped.**	
Quality Assessment	**Jadad 1** **NICE ++**	
Study	**Author: Roumen** **Year: 2008** **Country: Netherlands** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**No**	
Intervention	**The intervention programme consisted of a dietary and physical activity part. Dietary recommendations were based on the Dutch guidelines for a healthy diet (Dutch Nutrition Council). After consideration of a 3 day food diary, every 3 months a skilled dietician gave personal dietary advice during a 1-h counselling session. In addition, subjects received individual advice on how to increase their level of physical activity to at least 30 min a day for at least 5 days a week. A body weight loss of 5–7% was the objective. Dietary intake and physical activity were documented in 3-day records and new goals were set and documented for future reference. Furthermore, subjects were encouraged to participate in a combined aerobic and resistance exercise programme in which subjects participated at an intensity of at least 70% of their VO 2 max. Three times a year subjects were asked to participate in the exercise programme using a heartbeat watch to validate the exercise intensity. Control subjects were only briefly informed about the beneficial effects of a healthy diet and physical activity, whereas no individual advice was provided.**	
Comparator	**Control group**	
Setting / Delivered by	**Not reported**	
Randomisation method	**Subjects were randomized with stratification for sex and mean 2-h plasma glucose concentration to the intervention group (INT: 74 subjects; 38 male, 36 female) or the control group (CON: 73 subjects; 37 male, 36 female).**	
Blinding	**Not reported**	
Recruitment	**Subjects with an increased risk for glucose intolerance were selected from a cohort in the area of Maastricht, the Netherlands and invited to undergo a capillary standard OGTT. Those subjects with a 2-h**	

	blood glucose concentration > 7.8 mmol/l were invited for a second venous OGTT. For inclusion, mean 2-h glucose concentration of both OGTTs had to be between 7.8 and 12.5 mmol/l and fasting glucose concentration < 7.8 mmol/l. Data obtained during the second (venous) OGTT were used as baseline values.	
Population baseline characteristics	**Sample: n=147** **Males: 28 (Intervention); 30 (Control)** **Mean age: 54.2 ± 5.8 (Intervention); 58.4 ± 6.8 (Control)** **Mean BMI: 29.6 ± 3.8 (Intervention); 29.2 ± 3.3 (Control)** **Waist circumference: 103.2 ± 10.6 (Intervention); 102.4 ± 9.2 (Control)** **Other: Weight (kg): 87.5 ± 13.7 (Intervention); 83.0 ± 11.7 (Control)**	
Sub-group	**Age: Not reported** **Ethnic group: SES group: Not reported** **Obesity: Not reported** **Other: Not reported**	
Sub-groups identified (Y/N)	**Yes**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**The MetS (metabolic syndrome) was defined according to the National Cholesterol Education Program (NCEP) criteria as having three or more of the following conditions: waist circumference > 102 cm in men and > 88 cm in women; fasting serum triglyceride levels ≥ 1.7 mmol/l; high-density lipoprotein (HDL) cholesterol level < 1.03 mmol/l in men and < 1.30 mmol/l in women; blood pressure ≥ 130/85 mmHg; and fasting glucose ≥ 6.2 mmol/l. Subjects using anti-hypertensive drugs or lipid-lowering medication were classified positive for the respective criterion.**	
Criteria used for diagnosis of diabetes	**The incidence of Type 2 diabetes was determined by one OGTT according to World Health Organization (WHO) criteria of 1999.**	
Primary findings	**In the analysis of the subjects who completed the full 3 years of the study, the cumulative incidence of diabetes was 18% (8/44) in the intervention group and 38% (18/47) in the control group. The *P*-value of the log-rank test was 0.025, and the relative risk was 0.42 [95% confidence interval (CI) 0.18–0.96]. In the intention-to-treat analysis, the cumulative incidence of diabetes in the intervention group was 18% (11/61) compared with 32% (19/60) in the control group. The *P*-value from the log-rank test was 0.07 and the relative risk 0.52 (95% CI 0.25–1.10).**	**The authors noted that incidence of diabetes was not the primary outcome of the study and although it was examined, the results have to be interpreted with caution because the study was underpowered for those analyses.**
Secondary findings	**Multiple linear regression analysis revealed that a decrease in body weight correlated with a decrease in 2 h glucose levels (β=0.257 kg, *P*=0.020) and a decrease in 2-h glucose levels correlated with an improvement in VO2 max (β=−0.220 l/min, *P*=0.048), although not independent of body weight loss (β=−0.174 kg, *P*=0.117). No differences were observed in fasting plasma glucose and HbA1c in the completers analysis, whereas the change in fasting glucose did become significantly different between groups in the intention-to-treat analysis (*P*=0.04).**	
Follow up	**Data analyses of the 3-year results include those subjects still participating in the study (completers, *n*= 106: 52 INT subjects and 54 CON subjects). Forty-one subjects (22 INT, 19 CON) were unable to adhere to the study for 3 years; of those 28 subjects (14 INT and 14 CON) completed the first year. Thirty-two**	

	subjects discontinued the study (16 INT, 16 CON), as a result of medical reasons in 10 cases, lack of time in seven, lack of motivation in seven, dissatisfaction in three instances, no response in one case, no transportation in one case, unknown reasons in two cases and death in one case. Nine subjects did not attend all annual measurements.	
Intention to Treat analysis	**All available data of all 147 subjects was analysed, including those who dropped out before the 3-year examination, on an intention-to-treat basis. Insulin, serum lipids and FFA concentrations were not normally distributed and were ln-transformed. Data are presented as mean ± SD. Differences between groups were tested by Student's *t* -test for independent samples or by a $\chi 2$-test when applicable. Changes over time between groups were assessed using ANOVA for repeated measures for the completers analysis and with MIXED linear models for the intention-to-treat analysis. A *P* -value of less than 0.05 was considered statistically significant. All tests were two-sided.**	
Adverse events	**One death was reported.**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**The lifestyle intervention showed a sustained beneficial effect on 2-h glucose concentrations, insulin resistance and 2-h FFA, even after 3 years. The lifestyle intervention is effective, but for implementation more information is needed about factors influencing adherence.**	
Quality Assessment	**Jadad=2** **NICE ++**	
Study	**Author: Penn et al** **Year: 2009** **Country: UK** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**No**	
Intervention	**Dietary intervention consisted of advice and counselling, with an aim of achieving: >50% total dietary energy intake from carbohydrate, reduced total and saturated fat intake with <30% total dietary energy from fat, increased fibre intake and weight loss to achieve a BMI<25 kgm^{-2}. Physical activity intervention was designed to encourage participation in increased physical activity equivalent to 30 minutes of moderate physical activity per day.**	
Comparator	**Control group**	
Setting / Delivered by	**EDIPS centres; no description provided.**	
Randomisation method	**Participants were randomly allocated to intensive behavioural interventions to promote dietary modification and increased physical activity or to a minimal intervention Control group. Eligible participants with IGT were randomly allocated to the Intervention or Control group using randomisation lists, prepared independently by the EDIPS co-ordinating centre in Helsinki. Randomisation was stratified by sex and by 2 hour plasma glucose value.**	
Blinding	**Blinding of participants and intervention staff was not possible. Data collection staff were blinded to the extent that this was possible given participants' knowledge of their allocation.**	
Recruitment	**Recruitment was by referral from primary care physicians who identified eligible people likely to be at risk of impaired glucose regulation (using the criteria: aged over 40 and overweight (BMI > 25 kgm^{-2})) from their primary care databases and invited them to participate.**	

Population baseline characteristics	**Sample: n= 102** **Males: 21 (41.2%-Intervention group); 20 (39.2%-Control group)** **Mean age: 56.8 (Intervention group); 57.4 (Control group)** **Mean BMI: 34.1 kgm^{-2} (Intervention group); 33.5 kgm^{-2} (Control group)** **Waist circumference: 104.6 cm (Intervention group); 104.3 cm (Control group)** **Other: 2 hour fasting glucose: 8.7mmol/l (Intervention group); 8.9 mmol/l (Control group)** **Weight: 93.4 kg (Intervention group); 90.6 kg (Control group)**	
Sub-group	**Age: Not reported** **Ethnic group: SES group: Not reported** **Obesity: Not reported** **Other: Not reported**	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**Participants were identified to be at risk of impaired glucose regulation (using the criteria: aged over 40 and overweight (BMI > 25 kgm^{-2}))**	
Criteria used for diagnosis of diabetes	**A diabetic value in the second OGTT was an exclusion criterion, even if the mean value was in the IGT range. People with previous diagnosis of diabetes, or with chronic illness that would make participation in moderate physical activity impossible, or on a special diet for medical reasons were excluded.**	
Primary findings	**T2D was diagnosed in a total of 16 participants (I = 5, C = 11). The absolute incidence of T2D was 32.7 (95% CI: 10.7 to 74.6) per 1000 person years of follow-up in the Intervention group and 67.1 (95% CI: 34.2 to 117.5) per 1000 person years of follow-up in the Control group. The relative risk of T2D in the Intervention group, compared with the Control group was 0.45 (95% CI: 0.2 to 1.2). After year two of follow-up, there were no further incidences of T2D in the Intervention group. Thus, overall the cumulative incidence of diabetes was 55% less in the Intervention group compared with the Control group.**	
Secondary findings	**There were no significant differences in mean values for secondary outcome measures between the Intervention and Control groups at baseline or at annual follow-up in any year. Analysis of difference from baseline value in these secondary outcome measures showed a significant difference between Intervention and Control groups in weight loss at year 1 follow-up only (mean weight change: Intervention group = -2.3 kg, Control group = 0.01 kg; mean difference -2.5 (95% CI: -4.2 to 0.7)kg, p = 0.007). Only three participants achieved BMI < 25 kgm^{-2}.**	
Follow up	**Mean duration of follow up was 3.11 years (range 0 to 5). In the first year 19 participants (I = 11, C = 8) left the study. The mean age of those who left in the first year was 54.8(95% CI: 49.3 to 60.4) years compared with 57.2 years (95% CI: 55.5 to 59.8) for those who stayed in the study.**	
Intention to Treat analysis	**Pragmatic (intention-to-treat) analysis of the primary endpoint was conducted using Kaplan-Meier survival analysis to determine the difference in relative risk of cumulative incidence of diabetes between the Intervention and Control groups.**	
Adverse events	**Not reported**	
Other properties	**Not reported**	

Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**The results are consistent with other diabetes prevention trials. This study was designed as part of a larger study and although the sample size limits statistical significance, the results contribute to the evidence that T2D can be prevented by lifestyle changes in adults with IGT. In explanatory analysis small sustained beneficial changes in weight, physical activity or dietary factors were associated with reduction in T2D incidence.**	
Quality Assessment	**Jadad=2** **NICE ++**	
Study	**Author: Wein** **Year 1999** **Country: Australia** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**All participants (both control and intervention groups) were reminded of the need for regular exercise (e.g. brisk walking for 30 minutes three times per week). The group randomised to active follow-up contact was given the same dietary advice but, in addition, telephone contact with the dietician was arranged three-monthly.**	
Comparator	**All participants (both control and intervention groups) were reminded of the need for regular exercise (e.g. brisk walking for 30 minutes three times per week). The control group were given dietary questionnaires and the standard diet advice sheet ('TARGET ON HEALTHY EATING' recommended by the Health Department Foundation (SA) and the Food and Nutrition Project (Victoria))**	
Setting / Delivered by	**Unclear**	
Randomisation method	**Not stated**	
Blinding	**No**	
Recruitment	**During the period November, 1989 to July, 199 I , all women who were diagnosed as having impaired glucose tolerance and who could communicate directly or through translation were randomized to one of two forms of follow-up. The study was continued until 100 women were enrolled in each arm of the study. All participants (both control and intervention groups) were reminded of the need for regular exercise (e.g. brisk walking for 30 minutes three times per week).**	
Population baseline characteristics	**Sample: n= 200** **Males: no males, all female sample** **Mean age: 39.5 years (95% CI 38.2 to 40.8) intervention group, 37.8 years (95% CI 36.5 to 39.0) Control group** **Mean BMI: 25.2 (95% CI 24.1 to 26.4) intervention group, 25.6 (95% CI 24.5 to 26.8) Control group** **Waist circumference:** **Other:** **Weight: 64.9 kg (95% CI 61.8 to 68.1) intervention group, 66.4 kg (95% CI 63.2 to 69.6) Control group**	
Sub-group	**Age:**	

	Ethnic group: SES group: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**1985 World Health Organisation criteria**	
Criteria used for diagnosis of diabetes	**1985 World Health Organisation criteria**	
Primary findings	**There were 796.4 women-years of follow-up, with diabetes mellitus being diagnosed in 53 women, giving an overall incidence of diabetes of 6.7 cases per 100 women-years. At the final follow-up test, after a median length of follow-up of 51 months, there was no significant difference between the intervention and control groups in the prevalence of diabetes (26/97 [26.8%] Intervention group, 27/96 [28.1%] Control group). However the intervention group had a significantly longer median length of follow-up than the control group - 58.6 months (range 1 1.7-8 I . 1) versus 47.9 (range 7.1 -78.0), p = 0.02 1 . Because of this longer follow-up, the intervention group had more opportunity to develop diabetes, so a comparison of the annual rates of conversion to diabetes needed to be made. The annual incidence rates of diabetes mellitus for the 2 groups were 6.1 % (intervention) and 7.3% (control), an incident rate ratio of 0.83, 95% confidence interval 0.47- 1.48, p ~0.50.**	
Secondary findings	**-**	
Follow up	**796.4 woman-years of follow-up**	
Intention to Treat analysis	**No**	
Adverse events	**None reported**	
Other properties	**-**	
Cost Effectiveness	**-**	
Reviewer comments		
Authors conclusions	**In women with impaired glucose tolerance, this randomized controlled study showed no significant benefit in women given dietary guidelines reinforced with continued, regular contact with a dietician, compared with those given dietary guidelines alone. However, compared with the Da Qing study, the results in the control group were encouraging, and combined with the results of other trials, suggest that dietary intervention is warranted in individuals with impaired glucose tolerance.**	
Quality Assessment	**Jadad 2 (Gillies)** **NICE -**	
Pharmacological interventions		
Study	**Author: DeFronzo et al** **Year 2011** **Country: USA**	**Comments**

	Study design: RCT	
Included in Gillies et al review?	**No**	
Intervention	**After eligibility for the study was ascertained, participants underwent randomization according to center and sex and received 30 minutes of dietary instruction consistent with the goals of the Diabetes Prevention Program, which was reinforced on follow-up visits. Once enrolled, participants were asked to fast overnight before undergoing an oral glucose-tolerance test at 8 a.m. the next day. Samples were collected every 15 minutes for 2 hours for measurements of glucose, insulin, and C-peptide. Additional baseline assessments included measurements of blood pressure, height, weight, waist circumference, and level of HbA1c; a lipid profile; screening blood tests; urinalysis, with calculation of the ratio of microalbumin to creatinine; and electrocardiography. Participants initially received 30 mg of pioglitazone per day or placebo. One month after randomization, the dose of pioglitazone was increased to 45 mg per day. Participants returned at 2, 4, 6, 8, 10, and 12 months during the first year of the study and once every 3 months thereafter. Fasting plasma glucose was also measured at each follow-up visit. The levels of HbA1c, alanine aminotranferase, and aspartate aminotransferase were measured every 6 months, and the oral glucose-tolerance test was repeated annually. All measurements obtained at baseline were repeated at the end of the study.**	
Comparator	**Placebo**	
Setting / Delivered by	**Clinic-based**	
Randomisation method	**Participants were randomised according to center and sex. Method not described.**	
Blinding	**Not described**	
Recruitment	**Male and female patients who were 18 years of age or older and had impaired glucose tolerance (defined as a 2-hour glucose level of 140 to 199 mg per deciliter [7.8 to 11.0 mmol per liter] during a single oral glucose-tolerance test)15 and a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 25 or more were recruited for participation in the study. Patients were eligible for enrollment if they had a fasting plasma glucose level between 95 and 125 mg per deciliter (5.3 and 6.9 mmol per liter) and at least one other risk factor for diabetes. During the course of recruitment, the glycemic inclusion criteria were modified to include patients with a fasting plasma glucose level between 90 and 125 mg per deciliter (5.0 and 6.9 mmol per liter) if their 2-hour plasma glucose level during the oral glucose-tolerance test was between 170 and 199 mg per deciliter (9.4 and 11.1 mmol per liter); the change was made in recognition of the high risk of diabetes in such persons. The first participant was recruited in January 2004, with the screening ultimately including 1827 potentially eligible patients with impaired glucose tolerance. The enrollment of 602 participants was completed in March 2006. Participants were followed until they reached the primary end point of diabetes, withdrew from the study, were lost to follow-up, or completed the end of the study.**	
Population baseline characteristics	**Sample: n= 602** **Males: 42%** **Mean age: 52.3±0.5 years** **Mean BMI: 34.5±0.4** **Waist circumference:** **Other:**	

Sub-group	**Age:** **Pioglitazone (%) — Placebo (%)** **18–39 yr 36 42** **40–59 yr 32 28** **≥60 yr 32 30** **Ethnic group:** **Pioglitazone (N) — Placebo (N)** **Hispanic 79 75** **White 156 171** **Black 57 44** **Other 11 9** **SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**Yes**	
Sub-group analysis (Y/N)	**Yes, but data not provided in the paper**	
Criteria used for diagnosis of pre-diabetes	**Diagnosis of pre-diabetes not repôrted.**	
Criteria used for diagnosis of diabetes	**The primary outcome was the development of diabetes (defined as a fasting plasma glucose level ≥126 mg per deciliter [≥7.9 mmol per liter] or a 2-hour glucose level ≥200 mg per deciliter [11.1 mmol per liter]); an oral glucose-tolerance test was performed to confirm the diagnosis. If the diagnosis was not confirmed, patients continued with their assigned therapy.**	
Primary findings	**Diabetes was not confirmed but was considered to have developed in five patients receiving pioglitazone and five patients receiving placebo. At the final visit, six patients had a single oral glucose-tolerance test with results that met the diagnostic criteria for diabetes; four of the six were started on antidiabetic medication by their physician. The annual average incidence of diabetes, calculated on the basis of person-years, was 7.6% in the placebo group and 2.1% in the pioglitazone group (P<0.001). The hazard ratio for development of diabetes in the pioglitazone group was 0.28 (95% confidence interval, 0.16 to 0.49; P<0.001). Adjustment for baseline characteristics did not alter the hazard ratio. The number of people who would need to be treated to prevent one case of diabetes was 8 for 2.2 years of the trial and 18 for 1 year. Protection from diabetes with pioglitazone was of similar magnitude (with no significant heterogeneity) in subgroups defined by sex, age, weight, race or ethnic group, and fasting glucose level, as well as in patients**	

	with both impaired glucose tolerance and impaired fasting glucose and those with isolated impaired glucose tolerance. There was no evidence of heterogeneity of the response according to the baseline level of HbA1c.	
Secondary findings	**Greater reductions in fasting and 2-hour glucose levels were achieved in the pioglitazone group than in the placebo group (P<0.001 for both comparisons), with a between-group difference of 3.5±1.1 mg per deciliter (0.2±0.06 mmol per liter) and 14±3 mg per deciliter (0.8±0.17 mmol per liter), respectively, at the end of the study. Levels of HbA1c differed between the groups throughout the study (P<0.001), increasing by 0.20±0.02% in the placebo group, with no change in the pioglitazone group. Body weight, BMI, and body fat increased in the placebo group (96.7±1.2 to 97.3±1.3 kg, 34.5±0.4 to 34.7±0.4, and 39.0±0.7 to 39.3±0.7%, respectively) and in the pioglitazone group (94.9±1.2 to 98.7±1.3 kg, 34.1±0.4 to 35.5±0.4, and 40.0±0.8 to 41.9±0.7%, respectively), but the increments were greater with pioglitazone (P<0.001 for all comparisons). Systolic blood pressure declined slightly in both groups, but the difference in decline between the groups was not significant. Diastolic blood pressure was consistently lower in the pioglitazone group (P = 0.01).**	
Follow up	**During a median follow-up period of 2.4 years (mean, 2.2), diabetes developed in 50 of the 299 patients in the placebo group (16.7%) and in 15 of the 303 patients in the pioglitazone group (5.0%). Among the patients who completed the study, 103 of those in the pioglitazone group (48%) and 65 of those in the placebo group (28%) had normal glucose tolerance (P<0.001). A total of 161 patients did not complete the study (71 in the placebo group and 90 in the pioglitazone group). The median follow-up time for these patients was 7.6 months. Baseline characteristics of the patients who did not complete the study were similar to those of the 441 patients who completed the study (i.e., those who had conversion to type 2 diabetes mellitus during the study or who completed the oral glucose tolerance test at the end of the trial). Reasons for not completing the study included weight gain (in 9 patients in the pioglitazone group and 3 in the placebo group); patients also left for reasons unrelated to the study medication.**	
Intention to Treat analysis	**Not reported**	
Adverse events	**Adverse events occurred in 121 patients in the placebo group and 151 patients in the pioglitazone group (P = 0.03). Edema increased at some point during the trial in 19 patients receiving placebo (6.4%) and 39 patients receiving pioglitazone (12.9%) (P = 0.007). Events related to the cardiovascular system numbered 23 in the placebo group (7.7%) and 26 in the pioglitazone group (8.6%), with 1 case of congestive heart failure in each group (0.3%). One unexplained sudden death occurred in the placebo group, and three deaths occurred in the pioglitazone group (one unexplained sudden death, one death from biliary carcinoma, and one death from a carcinoid tumor). Nine fractures occurred in 8 of the patients receiving pioglitazone (3%) and eight fractures occurred in 7 of the patients receiving placebo (2.6%)**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**As compared with placebo, pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes mellitus by 72% but was associated with significant weight gain and edema.**	
Quality Assessment	**Jadad = 2** **NICE +**	
Study	**Author: The DREAM Trial Investigators** **Year: 2006** **Country: Multi-country** **Study design: RCT**	**Comments**

Included in Gillies et al review?	**No**	
Intervention	**Eligible participants entered a 17-day, single blind, double-placebo run-in period. If they showed adherence to their study medications during that period, participants were randomly assigned to receive either ramipril (5 mg daily for the first 2 months, with an increase to 10 mg at the 2-month visit and 15 mg after 1 year) or matching placebo (and rosiglitazone or matching placebo) (4 mg once daily for the first 2 months and then 8 mg thereafter). Visits were scheduled 2 months and 6 months after randomisation and then every 6 months until the common termination window between February and April 2006. Alanine aminotransferase levels were measured every 2 months during the first year. At each visit, study drugs were dispensed, and adherence was assessed and reinforced, as was a healthy diet and lifestyle. Electrocardiograms were recorded at baseline, at 2 years, and at the end of the study. If diabetes was diagnosed during the study and required pharmacologic therapy, the study medications were continued and antihyperglycemic agents other than thiazolidinediones could be prescribed. Participants who had not received a diagnosis of diabetes by the end of the study entered a single-blind placebo washout period and underwent a glucose-tolerance test (2 hours after an oral glucose load) 2 to 3 months later.**	
Comparator	**Matching placebo and rosiglitazone or matching placebo (4 mg once daily for the first 2 months and then 8 mg thereafter).**	
Setting / Delivered by	**Multiple sites; 191 centres in 21 countries**	
Randomisation method	**In a 2-by-2 factorial design, patients were randomly assigned to a study group with the use of a concealed, computerized telephone randomization system, stratified according to center, with a permuted block size of 8.**	
Blinding	**Single blinded**	
Recruitment	**A total of 24 592 participants were screened at 191 centers in 21 countries. Of those screened, 5808 entered the run-in phase of the trial. The most common reasons for exclusion were ineligibility (94.2%) and refusal to participate (3.0%). Of those entering the run-in phase, 5 269 participants were randomly assigned to treatment (739 had impaired fasting glucose levels alone and 4 530 had impaired glucose tolerance with or without impaired fasting glucose levels).**	
Population baseline characteristics	**Sample: n= 5 269 enrolled in the trial** **Males: 40.3% (Treatment); 41.3% (Placebo)** **Mean age: 54.7 ± 10.9 (Treatment and Placebo groups)** **Mean BMI: 30.9 ± 5.6 (Treatment); 30.9 ± 5.7 (Placebo)** **Waist circumference: Not reported** **Other: Waist-to-hip ratio (Men): 0.96 ± 0.07 (Treatment and Placebo groups); Waist-to-hip ratio (Women): 0.86 ± 0.08 (Treatment); 0.87 ± 0.08 (Placebo)**	
Sub-group	**Age: Not reported** **Ethnic group: SES group: Not reported** **Obesity: Not reported** **Other: Not reported**	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	

Criteria used for diagnosis of pre-diabetes	**Persons 30 years of age or older who had impaired fasting plasma glucose levels (at least 110 mg per deciliter [6.1 mmol per liter] but less than 126 mg per deciliter [7.0 mmol per liter]) or impaired glucose tolerance (a plasma glucose level of at least 140 mg per deciliter [7.8 mmol per liter] but less than 200 mg per deciliter [11.1 mmol per liter] 2 hours after an oral glucose load).**	
Criteria used for diagnosis of diabetes	**At the 2-year and final visits, a glucose-tolerance test was performed 2 hours after a 75-g oral glucose load in participants in whom diabetes had not developed. At other annual visits, fasting plasma levels of glucose and glycated haemoglobin were measured locally, and an oral glucose-tolerance test was performed if the fasting plasma glucose level was 126 mg per deciliter (7.0 mmol per liter) or higher, to confirm or refute the diagnosis of diabetes, or if the fasting plasma glucose level exceeded 95 mg per deciliter (5.3 mmol per liter) and the glycated hemoglobin value exceeded 93% of the upper limit of the normal range for the assay.**	
Primary findings	**Diabetes or death occurred in 475 participants (18.1%) in the ramipril group, as compared with 517 (19.5%) in the placebo group (hazard ratio, 0.91; 95% confidence interval [CI], 0.81 to 1.03; P = 0.15). There were 31 deaths in the ramipril group and 32 in the placebo group, whereas diabetes developed in 449 participants in the ramipril group (17.1%) and in 489 in the placebo group (18.5%; hazard ratio, 0.91; 95% CI, 0.80 to 1.03). The effect of ramipril on the development of diabetes was consistent, even after controlling for the use of diuretics, beta-blockers, or angiotensin-receptor blockers. The results for the primary outcome were similar among participants with impaired fasting glucose levels and in those with impaired glucose tolerance.**	
Secondary findings	**By the end of the study, 1 116 participants (42.5%) receiving ramipril, as compared with 1 012 participants (38.2%) receiving placebo, had normal fasting plasma glucose levels (less than 110 mg per deciliter [6.1 mmol per liter]) and normal 2-hour plasma glucose levels (less than 140 mg per decilitre [7.8 mmol per liter]) (hazard ratio, 1.16; 95% CI, 1.07 to 1.27; P = 0.001). These results were unchanged after adjustment for the use of diuretics or beta-blockers. At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group (102.7 mg per deciliter [5.70 mmol per liter]) than in the placebo group (103.4 mg per deciliter [5.74 mmol per liter], P = 0.07). The median 2-hour post-load plasma glucose level was significantly lower in the ramipril group (135.1 mg per deciliter [7.50 mmol per liter]) than in the placebo group (140.5 mg per deciliter [7.80 mmol per liter], P = 0.01). Alanine aminotransferase levels decreased more in the ramipril group than in the placebo group — by 3.4 U per liter and 2.3 U per liter, respectively (P = 0.004) — during the first year of the trial.**	
Follow up	**Participants were followed for a median of 3.0 years. At 1 year, 86.6% of participants randomly assigned to receive ramipril and 89.9% of those randomly assigned to receive placebo were still taking the study medication. The corresponding proportions at 2 years were 81.3% and 84.8%; at 3 years, 75.4% and 80.9%; and at the end of the study, 72.7% and 78.0%. Throughout the study, the most common reasons for the discontinuation of study medications among participants in the ramipril group and those in the placebo group were the participant's decision to stop taking the medication (17.4% and 17.7%, respectively), cough (9.7% and 1.8%), advice from a physician (2.3% and 2.5%), and peripheral edema (1.0% and 1.1%).**	
Intention to Treat analysis	**All data were collected and analyzed with the use of an intention-to-treat approach, under the supervision of the steering committee. Data for participants whose diabetes status was unavailable at the end of the study were censored at the time of the last glucose assessment. Kaplan–Meier curves for the primary outcome as well as regression to normoglycemia were constructed for the treatment and placebo groups and were compared with the use of logrank tests. The outcome of regression was based on available values. If glucose levels were not available, it was assumed that glycemic status had not changed since the last known value. Cox proportional hazards models were used to estimate the effect of ramipril on the hazard ratio for the primary and secondary outcomes. Interaction between the ramipril and rosiglitazone treatments was assessed with the inclusion of an interaction term in the model.**	

Adverse events	**The numbers of cardiovascular events were similar in the two groups (67 events in the ramipril group and 63 in the placebo group, P = 0.68). The numbers of hospitalizations for all events were also similar (497 in the ramipril group and 489 in the placebo group, P = 0.67). Angioedema occurred in three participants receiving ramipril (0.1%) and in four participants receiving placebo (0.2%).**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**Among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of ramipril for 3 years does not significantly reduce the incidence of diabetes or death but does significantly increase regression to normoglycemia.**	
Quality Assessment	**Jadad =3** **NICE ++**	
Study	**Author: Eriksson** **Year 2006** **Country: Finland** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Glipizide 2.5 mg once daily for six months.**	
Comparator	**Matching placebo for six months.**	
Setting / Delivered by	**One of four clinics**	
Randomisation method	**Stratified according to age and BMI.**	
Blinding	**double blinded**	
Recruitment	**All participants had, 12 months prior to being randomised into the present study, glucose concentrations fulfilling the diagnostic criteria for Impaired Glucose Tolerance (IGT). A repeat Oral Glucose Tolerance Test (OGTT) was performed 12 months later, at the study baseline, and if it confirmed the IGT diagnosis, they were entered into the study.**	
Population baseline characteristics	**Sample: n= 34** **Males: 25** **Mean age**: **59 years ± 2 (intervention group), 54 years ± 3 (control group)** **Mean BMI**: **27.9 ± 1.5 (intervention group), 28.8 ± 1.3 (control group)** **Waist circumference:** **Other**:	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	

Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**World Health Organisation criteria (years not specified) for IGT on two consecutive OGTTs**	
Criteria used for diagnosis of diabetes	**Not stated**	
Primary findings	**At 18 months five of control group (n=16) had developed type 2 diabetes and one of the intervention group (n=16) had developed type 2 diabetes.**	
Secondary findings	**Not applicable**	
Follow up	**Eighteen months.**	
Intention to Treat analysis	**No**	
Adverse events	**A similar number of subjects in both groups reported hypoglycaemic symptoms (e.g. hunger, fatigue, palpitations, tremor) during the study; the numbers were 41% in the glipizide group and 32% in the placebo group. One subject in the glipizide treatment group discontinued the study early due to hypoglycaemic symptoms. All other side effects were mild.**	
Other properties		
Cost Effectiveness		
Reviewer comments		
Authors conclusions	**Short-term treatment with glipizide improves glucose and insulin metabolism in subjects with IGT primarily by improving insulin sensitivity mediated by lowering glucose toxicity, thereby providing the beta cells rest. Larger studies are needed to establish whether these effects are sufficient to prevent progression to manifest type 2 diabetes and associated cardiovascular morbidity in subjects at increased risk of developing type 2 diabetes.**	
Quality Assessment	**Jadad 4 (Gillies)** **NICE ++**	
Study	**Author: Heymsfield** **Year 2000** **Country: US and European** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Orlistat, 120 mg 3 times a day, for 104 weeks**	
Comparator	**A placebo 3 times a day, for 104 weeks**	
Setting / Delivered by	**Subjects were recruited, evaluated, and monitored at 39 clinical research centers in the United States and Europe between 1992 and 1995.**	
Randomisation method	**Unclear**	
Blinding	**Three two-year, double-blind, randomized, placebo-controlled clinical trials.**	
Recruitment	**Entry criteria included age greater than 18 years, BMI of 30 to 43, adequate contraception in women of childbearing potential, and absence of weight loss (.4 kg) in the previous three months. Subjects were excluded if they had stopped smoking within the past 6 months; had significant cardiac, renal, hepatic, gastrointestinal, psychiatric, or endocrine disorders; had drug-treated type 2 diabetes; had a history or**	

	presence of substance abuse; had excessive intake of alcohol; or concomitantly used medications that alter appetite or lipid levels.	
Population baseline characteristics	**Sample: n= 675 (359 intervention group, 316 control group** **Males: 118 (69 in intervention group, 49 in control group).** **Mean age**: 43.9 **years ± 0.6 (intervention group), 44.3 years ± 0.7 (control group)** **Mean BMI: 35.6 ± 0.1 (intervention group), 36.0 ± 0.9 (control group)** **Waist circumference:** **Other**: **Mean weight (kg) 99.0 ± 0.6 (intervention group), 99.8 ± 0.9 (control group)**	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**1985 World Health Organisation Criteria**	
Criteria used for diagnosis of diabetes	**1985 World Health Organisation Criteria**	
Primary findings	**Subjects with impaired glucose tolerance at baseline progressed to diabetic status in the orlistat (3.0%) vs. placebo (7.6%) group.**	
Secondary findings	**Obese subjects in the orlistat group achieved a weight loss of 6.72±0.41 kg over the study period (i.e., from week −4) compared with a weight loss of 3.79±0.38 kg for obese subjects in the placebo group (P,.001). Expressed as percentage of weight change from initial body weight, the orlistat group lost significantly more weight than the placebo group (6.8%±0.4% vs. 3.9%±0.4%; P,.001). Analysis of the frequency distribution of weight loss indicated that 52.9% of subjects in the orlistat group lost 5% or more of initial body weight and 30.1% lost 10% or more of initial weight, while 37.7% of subjects in the placebo group lost 5% or more of initial body weight and 16.5% lost 10% or more of initial weight (P,.001 for orlistat vs. placebo for both $5% and $10% weight loss).**	
Follow up	**104 weeks**	
Intention to Treat analysis	**Yes**	
Adverse events	**None reported**	
Other properties		
Cost Effectiveness		
Reviewer comments		
Authors conclusions	**The addition of orlistat to a conventional weight loss regimen significantly improved oral glucose tolerance and diminished the rate of progression to the development of impaired glucose tolerance and type 2 diabetes.**	

Quality Assessment	**Jadad 2 (Gillies)** **NICE ++**	
Study	**Author: Kawamori et al** **Year : 2009** **Country: Japan** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**No**	
Intervention	**Eligible individuals randomly allocated to voglibose 0.2mg or an identical looking placebo three times per day before meals. 4–8 weeks before the start of treatment, each person was given advice about appropriate nutrition and exercise programmes (interview, survey of lifestyle, and individualised guidance on future lifestyle habits based on intensity of daily activity categories defined by the Japanese Ministry of Health and Labour) and adherence to these was assessed at each visit.**	
Comparator	**Placebo**	
Setting / Delivered by	**Multicentre**	
Randomisation method	**Randomisation was done with a stratified allocation procedure designed to balance the two treatment groups in each institution with respect to the number of risk factors (≤2 or ≥3), which were hypertension or high normal blood pressure, dyslipidaemia, obesity, a family history of diabetes, and a 2hPG greater than 9.4 mmol/L (a concentration associated with an increased risk of developing type 2 diabetes in Japan) to 11.0 mmol/L. An independent statistician computer-generated the random sequence and this was maintained securely until the study was unmasked. Allocation was concealed with sealed opaque envelopes.**	
Blinding	**Double-blinded**	
Recruitment	**Individuals were recruited from 103 Japanese institutions, mainly through assessment of high-risk populations, and in particular from first-degree relatives of patients with type 1 or 2 diabetes.**	
Population baseline characteristics	**Sample: n= 4582 men and women screened; 1 780 randomised into treatment or control groups** **Males: 1 071** **Mean age: 55.7 (Treatment group); 55.7 (Control group)** **Mean BMI: 25.76 (Treatment group); 25.89 (Control group)** **Waist circumference: Not reported** **Other: Not reported**	
Sub-group	**Age: Not reported** **Ethnic group: SES group: Not reported** **Obesity: 502 (Treatment group); 500 (Control group)** **Other: Smoker, Hypertension,**	
Sub-groups identified (Y/N)	**Yes**	
Sub-group analysis (Y/N)	**Yes, not reported in the paper**	
Criteria used for diagnosis of pre-diabetes	**Individuals were eligible for the trial if they had a fasting plasma glucose concentration of less than 6.9 mmol/L, a 2 h plasma glucose concentration during OGTT (2hPG) of between 7.8 mmol/L and 11.0 mmol/L, HbA1c less than 6.5%, and at least one of the following risk factors for type 2 diabetes: high normal blood**	

	pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg) or were being treated for hypertension; dyslipidaemia (concentrations of total cholesterol ≥5.7 mmol/L, triglyceride ≥1.7 mmol/L, or HDL cholesterol <1.04 mmol/L); obesity (body-mass index ≥25 kg/m2); and a family history of diabetes (in a first-degree or second-degree relative).	
Criteria used for diagnosis of diabetes	**Type 2 diabetes was defined as an HbA1c level of at least 6.5%, and, on two separate occasions, at least one of the following: a 2hPG of at least 11.1 mmol/L, fasting plasma glucose concentration of at least 7.0 mmol/L, or random plasma glucose concentration of at least 11.1 mmol/L. The secondary endpoint was the number of people who achieved normoglycaemia (i.e., 2hPG <7.8 mmol/L and a fasting plasma glucose concentration <6.1 mmol/L). Diagnosis of type 2 diabetes and normoglycaemia was made by the principal investigator in compliance with the standards of the Japan Diabetes Society.**	
Primary findings	**The cumulative number of cases that progressed to diabetes at the end of the study was 50 of 897 in the voglibose group versus 106 of 881 in the placebo group. The HR was 0.595 (95% CI 0.433–0.818), showing that voglibose-treated individuals had a 40.5% lower risk of developing type 2 diabetes than did placebo-treated individuals (p=0.0014). The cumulative progression rate to type 2 diabetes after 48 weeks was 9.4% (7.1–11.8) for placebo and 3.6% (2.0–5.2) for voglibose. After 96 weeks, the corresponding rates were 23.5% (18.5–28.5) and 12.1% (6.9–17.3), respectively, and after 144 weeks they were 36.2% (27.7–44.8) and 30.2% (19.5–41.0), respectively.**	
Secondary findings	**Voglibose was associated with a 39.3% risk reduction (HR 0.607, 95% CI 0.428–0.863; p=0.0053) compared with placebo in individuals with at least three risk factors (41 *vs.* 87 cases), whereas the difference was not significant in individuals with at most two risk factors (9 *vs.* 19 cases, 0.544, 0.258–1.147; p=0.1098).**	
Follow up	**The risk of an individual developing type 2 diabetes was reduced (HR 0.512, 95% CI 0.360–0.727; p=0.0002) in the voglibose group compared with the placebo group when adjustments were made for multivariables, including age, sex, obesity, dyslipidaemia, hypertension, family history, 2hPG, insulinogenic index, homoeostasis model assessment for insulin resistance (HOMA-R), and intensity of daily activity in a Cox regression analysis.**	
Intention to Treat analysis	**Not reported**	
Adverse events	**Gastrointestinal symptoms were the most common and more frequent in the voglibose group than in the placebo group. However, they were generally thought to be mild to moderate in severity. The rate of serious adverse effects was low. No deaths occurred in the placebo group versus six in the voglibose group (two accidents, and one each of suicide, possible self-intoxication with insecticide resulting in heart failure, lung cancer, and myocardial infarction); none of the deaths were thought to be related to the drug treatment.**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**Voglibose, in addition to lifestyle modification, can reduce the development of type 2 diabetes in high risk Japanese individuals with impaired glucose tolerance**	
Quality Assessment	**Jadad =4** **NICE ++**	
Study	**Author: Li** **Year 1999** **Country: China** **Study design: RTC**	**Comments**
Included in Gillies et al review?	**Yes**	

Intervention	**Metformin at a dosage of 250 mg three times daily for a duration of 12 months**	
Comparator	**Placebo three times daily for a duration of 12 months**	
Setting / Delivered by	**Clinic (unspecified)**	
Randomisation method	**Not specified**	
Blinding	**People meeting the entry criteria were randomized under double-blind conditions to receive either placebo or metformin.**	
Recruitment	**Twenty-nine thousand, nine-hundred and thirty-eight subjects were investigated using a 75-g oral glucose tolerance test (OGTT). People with pre-existing diabetes were excluded. The authors found a prevalence of IGT of 4.19%, the total number of people with IGT being 1165. In 1994, these people with IGT were re-examined using 75-g OGTT. Those whose test results showed IGT in both 1992 and 1994 were eligible for the study. Males and females aged 30±60 years were eligible. Patients with a history of ischaemic heart disease or renal or hepatic disorders were excluded, as were patients who had previously been treated with metformin.**	
Population baseline characteristics	**Sample: n= 90** **Males: 50** **Mean age**: **49.0 years ± 1.3 (intervention group), 50.0 years ± 1.1 (control group)** **Mean BMI**: **Waist circumference:** **Other**:	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**All sample was Chinese**	
Sub-group analysis (Y/N)	**Yes**	
Criteria used for diagnosis of pre-diabetes	**1985 World Health Organisation criteria**	
Criteria used for diagnosis of diabetes	**1985 World Health Organisation criteria**	
Primary findings	**Six of 37 patients on placebo converted to frank diabetes (16.2%) and this compared to one of 33 patients (3.0%) on metformin (P = 0.011)**	
Secondary findings	**-**	
Follow up	**12 months**	
Intention to Treat analysis	**Yes, Six of 43 patients on placebo converted to frank diabetes (14.0%) and this compared to three of 42 patients (7.1%) on metformin, P = 0.091.**	
Adverse events	**No significant changes were observed for blood pressure, cholesterol or triglyceride during the course of the study. Three patients reported mild diarrhoea and nausea when starting metformin, but the symptoms**	

	resolved with long-term treatment. Six patients reported mild nausea on placebo but the symptoms remitted with duration of treatment. One placebo-treated patient developed raised liver enzymes and required treatment.	
Other properties		
Cost Effectiveness		
Reviewer comments		
Authors conclusions	**Metformin can improve glucose metabolism in IGT patients and may be a treatment option in the management of IGT subjects.**	
Quality Assessment	**Jadad 3 (Gillies)** **NICE ++**	
Study	**Author: NAVIGATOR Study Group (Valsartan)** **Year 2010** **Country: Multi Country** **Study design: RCT**	**Comments**
Study	**Author: The NAVIGATOR Study Group** **Year 2010b** **Country: Multiple sites** **Study design: RCT**	
Included in Gillies et al review?	**No**	
Intervention	**Patients were randomised into Valsartan or matching placebo group. Valsartan was started at a dose of 80 mg once daily, with an increase after 2 weeks to 160 mg once daily; dose reduction or interruption because of adverse events or for other clinical reasons was permitted. All patients were required to participate in a study specific lifestyle-intervention program that was designed to reduce the risk of diabetes. The objective of the intervention was to help patients achieve and maintain a 5% weight loss, reduce intake of saturated and total dietary fat, and increase physical act ivit y to 150 minutes weekly. Site personnel were trained to administer this program and provided materials designed to facilit ate adherence at each clinic visit, with reinforcement and monitoring by telephone between study visits.**	
Comparator	**Matching placebo**	
Setting / Delivered by	**Clinic-based intervention conducted at 806 centres in 40 countries.**	
Randomisation method	**A computerized, interact ive voice-response telephone randomization system involving concealed study-group assignments was used to randomly assign patients to valsartan or matching placebo (and nateglinide or matching placebo) in a 2-by-2 factorial design. Randomization was stratified according to center, with a block size of eight within each center.**	
Blinding	**Study described as double-blind.**	
Recruitment	**From January 2002 through January 2004, we recruited patients at 806 centers in 40 countries. All eligible patients had impaired glucose tolerance, a fasting plasma glucose level of at least 95 mg per deciliter (5.3 mmol per liter) but less than 126 mg per deciliter (7.0 mmol per liter), and one or more cardiovascular risk factors (if 55 years of age or older) or known cardiovascular disease (if 50 years of age or older). A screening glucose-tolerance test was performed 2 hours after a 75-g oral glucose load to determine study eligibility. Impaired glucose tolerance was defined as a post-load plasma glucose level of at least 140 mg per deciliter (7.8 mmol per liter) but less than 200 mg per deciliter (11.1 mmol per liter). Exclusion criteria were laboratory abnormalities or conditions that could interfere with assessment of the safety or efficacy of**	

	a study drug, the use of an ACE inhibitor or ARB for the treatment of hypertension (although ACE inhibitors were allowed for other indications), and the use of an antidiabetic medication within the previous 5 years.The trial was approved by each center's ethics committee. All patients provided written informed consent.	
Population baseline characteristics	**Sample: n=9306** **Males: 50.0% (Intervention group); 48.7% (Placebo group)** **Mean age: 63.7 ± 6.8 (Intervention group); 63.8 ± 6.9 (Placebo group)** **Mean BMI: 30.4 ± 5.5 (Intervention group), 30.6 ± 5.3 (Placebo group)** **Waist circumference: 104 cm ± 13 (Males Intervention group), 104 cm ± 12 (Males Placebo group)** **98 cm ± 14 (Females Intervention group), 98 cm ± 14 (Females Placebo group)** **Other:**	
Sub-group	**Age: Not reported** **Ethnic group:** **(Intervention Group) (Placebo Group)** **White 3849 (83.1) 3885 (83.1)** **Black 113 (2.4) 123 (2.6)** **Asian 298 (6.4) 315 (6.7)** **Other 371 (8.0) 352 (7.5)** **SES group:** **Obesity:** **Other:**	
Sub-groups identified (Y/N)	**Yes**	
Sub-group analysis (Y/N)	**Yes. Subgroup analyses were performed for patients with and without established CHD at baseline, male and female patients, by race, age group, low and high body mass index, low/high fasting glucose at baseline, and low/high post-prandial glucose at baseline, patients taking ACE-inhibitors at baseline, and patients with hypertension at baseline. However, the results were not provided in the paper.**	
Criteria used for diagnosis of pre-diabetes	**Not reported**	
Criteria used for diagnosis of diabetes	**Diabetes was defined as a fasting plasma glucose level of 126 mg per deciliter (7.0 mmol per liter) or more or a plasma glucose level of 200 mg per deciliter (11.1 mmol per liter) or more as measured 2 hours after an oral glucose load, confirmed within 12 weeks by a glucose tolerance test. The date of onset of diabetes was defined as the date of the first diagnostic glucose value. An independent committee whose members were not aware of study-group assignments adjudicated the small number of cases in which patient s received a diagnosis of diabetes or were started on an antidiabetic drug without undergoing the study specified**	

	laboratory investigations.	
Primary findings	**Diabetes mellitus developed in 1532 patients (33.1%) in the valsartan group and 1722 patients (36.8%) in the placebo group. The hazard ratio for this outcome in the valsartan group, as compared with the placebo group, was 0.86 (95% CI, 0.80 to 0.92; P<0.001 in both one-sided and two-sided tests). The effect of valsartan on progression to diabetes was consistent across all prespecified subgroups. The proportion of patients who were taking an antidiabetic medication at their last study visit was smaller in the valsartan group than in the placebo group (P<0.001).** **When added to lifestyle intervention, a single daily dose of valsartan (up to 160 mg) reduced the risk of diabetes but not of cardiovascular events in patients with impaired glucose tolerance and established cardiovascular disease or risk factors. The relative reduction of 14% in the risk of diabetes in the valsartan group would translate into 38 fewer cases of diabetes per 1000 patients treated for 5 years, a reduction that was consistent across all subgroups that were examined.**	
Secondary findings	**During the study, the fasting plasma glucose level was reduced by a mean of 0.59 mg per deciliter (95% CI, 0.16 to 1.02) (0.03 mmol per liter [95% CI, 0.01 to 0.06]) in the valsartan group, as compared with the placebo group (P<0.01). The plasma glucose level 2 hours after a glucose load was reduced by a mean of 3.15 mg per deciliter (95% CI, 1.58 to 4.72) (0.17 mmol per liter [95% CI, 0.09 to 0.26]) in the valsartan group (P<0.001).** **The extended cardiovascular outcome occurred in 672 patients (14.5%) in the valsartan group and 693 patients (14.8%) in the placebo group. The hazard ratio for this outcome in the valsartan group, as compared with the placebo group, was 0.96 (95% CI, 0.86 to 1.07; P=0.22 in a one-sided test; P=0.43 in a two-sided test). The core cardiovascular outcome occurred in 375 patients (8.1%) in the valsartan group and 377 patients (8.1%) in the placebo group (hazard ratio, 0.99; 95% CI, 0.86 to 1.14; P=0.42 in a one-sided test; P=0.85 in a two-sided test). The neutral effect of treatment was consist ent for both outcomes across all pre-specified subgroups.** **There was no significant difference between the study groups with respect to any of the components of the extended cardiovascular outcome or the prespecified exploratory outcomes. The numbers of deaths were 295 (6.4%) in the valsartan group and 327 (7.0%) in the placebo group (P=0.17) .**	
Follow up	**Among surviving patients who had not withdrawn consent and had not received a clinical diagnosis of diabetes, 80% underwent measurement of fasting plasma glucose or plasma glucose 2 hours after an oral glucose load at the close-out visit or during the final 6 months of the study. The rate of loss to follow-up (including withdrawal of consent) was 12.7% in the valsartan group (588 patients) and 13.3% in the placebo group (623 patients). Because many discontinuations occurred late in the study, informat ion on vital status was available for 96% of possible follow-up time in the two study groups. The median follow-up was 6.5 years for vital status, 6.4 years for the core cardiovascular outcome, 6.3 years for the extended cardiovascular outcome, and 5.0 years for the incidence of diabetes.**	
Intention to Treat analysis	**Log-rank tests, stratified according to the presence or absence of a history of cardiovascular disease and to randomized assignment to valsartan or placebo, were used to compare the nateglinide and placebo groups with respect to the time to the first event in the extended or core cardiovascular outcome. A Cox discrete-time proportional-odds model was used to assess incident diabetes, given the fixed-time schedule for glucose measurements. Predefined analyses of the components of the composite cardiovascular outcome, exploratory outcomes (the time to death from all causes and the time to cardiovascular-related**	

	hospitalization), indexes of hyperglycemia, and body weight were also preformed. In addition, a possible interaction between valsartan and nateglinide for each reported outcome was tested. The effects of the study treatment were evaluated in prespecified subgroups.	
Adverse events	**An independent committee whose members were unaware of study-group assignments adjudicated the occurrence of death, hospitalization, and potential cardiovascular events that occurred in patients who were not hospitalized. Nasopharyngitis, back pain, and arthralgia were the most commonly reported individual adverse events. There was no excess of renal dysfunction or hyperkalemia in the valsartan group, but hypotension-related adverse events were more common in the valsartan group (occurring in 42.4% of patients) than in the placebo group (35.9%) (P<0.0 01). During the course of the study, 556 patients (12.0%) in the valsartan group and 531 (11.4%) in the placebo group discont inued the study drug because of an adverse event (P=0.33).**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**Among patients wit h impaired glucose tolerance and cardiovascular disease or risk factors, the use of valsartan for 5 years, along with lifestyle modification, led to a relative reduction of 14% in the incidence of diabetes but did not reduce the rate of cardiovascular events.**	
Quality Assessment	**Jadad 3** **NICE ++**	
Study	**Author: NAVIGATOR Study Group (Nateglinide)** **Year 2010** **Country: Multi Country** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**No**	
Intervention	**Participants were randomly assigned, to nateglinide, at a dose of 60 mg taken before meals three times daily, or placebo and, in a 2-by-2 factorial design, to valsartan or placebo. Nateglinide was initially dispensed at a dose of 30 mg, with an increase to the full dose of 60 mg after 2 weeks. Reductions in the dose were permitted if there were side effects. All patients were required to participate in a study specific lifestyle-intervention program that was designed to reduce the risk of diabetes. The objective of the intervention was to help patients achieve and maintain a 5% weight loss, reduce intake of saturated and total dietary fat, and increase physical act ivit y to 150 minutes weekly. Site personnel were trained to administer this program and provided materials designed to facilit ate adherence at each clinic visit, with reinforcement and monitoring by telephone between study visits.**	
Comparator	**Matching placebo**	
Setting / Delivered by	**Clinic-based intervention conducted at 806 centres in 40 countries.**	
Randomisation method	**A computerized, interact ive voice-response telephone randomization system involving concealed study-group assignments was used to randomly assign patients to valsartan or matching placebo (and nateglinide or matching placebo) in a 2-by-2 factorial design. Randomization was stratified according to center, with a block size of eight within each center.**	
Blinding	**Both the participants and the investigators were unaware of the treatment assignments.**	
Recruitment	**From January 2002 through January 2004, we recruited patients at 806 centers in 40 countries. All eligible patients had impaired glucose tolerance, a fasting plasma glucose level of at least 95 mg per deciliter (5.3**	

	mmol per liter) but less than 126 mg per deciliter (7.0 mmol per liter), and one or more cardiovascular risk factors (if 55 years of age or older) or known cardiovascular disease (if 50 years of age or older). A screening glucose-tolerance test was performed 2 hours after a 75-g oral glucose load to determine study eligibility. Impaired glucose tolerance was defined as a post-load plasma glucose level of at least 140 mg per deciliter (7.8 mmol per liter) but less than 200 mg per deciliter (11.1 mmol per liter). Exclusion criteria were laboratory abnormalities or conditions that could interfere with assessment of the safety or efficacy of a study drug, the use of an ACE inhibitor or ARB for the treatment of hypertension (although ACE inhibitors were allowed for other indications), and the use of an antidiabetic medication within the previous 5 years. The trial was approved by each center's ethics committee. All patients provided written informed consent.	
Population baseline characteristics	**Sample: n=9306** **Males: 49.0% (Intervention group); 49.7% (Placebo group)** **Mean age: 63.7 ± 6.8 (Intervention group); 63.8 ± 6.9 (Placebo group)** **Mean BMI: 30.5 ± 5.4 (Intervention group), 30.5 ± 5.4 (Placebo group)** **Waist circumference: 104 cm ± 12 (Males Intervention group), 104 cm ± 13 (Males Placebo group)** **98 cm ± 14 (Females Intervention group), 98 cm ± 14 (Females Placebo group)** **Other:**	
Sub-group	**Age: Not reported** **Ethnic group:** **(Intervention Group) (Placebo Group)** **White 3854 (83.0) 3880 (83.2)** **Black 120 (2.6) 116 (2.5)** **Asian 310 (6.7) 303 (6.5)** **Other 361 (7.8) 362 (7.8)** **SES group:** **Obesity:** **Other:**	
Sub-groups identified (Y/N)	**Yes**	
Sub-group analysis (Y/N)	**Yes. Subgroup analyses were performed for patients with and without established CHD at baseline, male and female patients, by race, age group, low and high body mass index, low/high fasting glucose at baseline, and low/high post-prandial glucose at baseline, patients taking ACE-inhibitors at baseline, and patients with hypertension at baseline.**	
Criteria used for diagnosis of pre-diabetes	**Not reported**	
Criteria used for diagnosis of diabetes	**Diabetes was considered to be present if the participant had a fasting plasma glucose level of 126 mg per deciliter or more or a glucose level of 200 mg per deciliter (11.1 mmol per liter) or more 2 hours after a glucose challenge — confirmed by an oral glucose-tolerance test within 12 weeks after the elevated glucose**	

	value was recorded.	
Primary findings	**Diabetes developed in 1674 participants in the nateglinide group (36.0%) and in 1580 participants in the placebo group (33.9%) (hazard ratio with nateglinide, 1.07; 95% confidence interval [CI], 1.00 to 1.15; P = 0.05). The effect of nateglinide on the progression of impaired glucose tolerance to diabetes was consistent across all prespecified subgroups except for subgroups specified according to sex and fasting plasma glucose level.**	
Secondary findings	**The extended composite cardiovascular outcome occurred in 658 participants in the nateglinide group (14.2%) and in 707 participants in the placebo group (15.2%) (hazard ratio with nateglinide, 0.93; 95% CI, 0.83 to 1.03; P = 0.16. The core composite cardiovascular outcome occurred in 365 participants in the nateglinide group (7.9%) and in 387 participants in the placebo group (8.3%) (hazard ratio with nateglinide, 0.94; 95% CI, 0.82 to 1.09; P = 0.43). During the course of the study, participants in the nateglinide group had lower mean fasting plasma glucose levels than did those in the placebo group; the mean difference was 0.47 mg per deciliter (95% CI, 0.05 to 0.90) (0.03 mmol per liter [95% CI, 0.003 to 0.05]) (P = 0.03). However, glucose levels 2 hours after a glucose challenge were higher in the nateglinide group than in the placebo group; the mean difference was 4.37 mg per deciliter (95% CI, 2.80 to 5.93) (0.24 mmol per liter [95% CI, 0.16 to 0.33]) (P<0.001). In the two conducted exploratory analyses, incident diabetes defined on the basis of fasting plasma glucose levels and adjudicated outcomes alone occurred in 775 of the participants in the nateglinide group (16.7%) and 877 of the participants in the placebo group (18.8%) (hazard ratio with nateglinide, 0.87; 95% CI, 0.79 to 0.96; P = 0.005). In contrast, incident diabetes defined on the basis of plasma glucose levels 2 hours after a glucose challenge and adjudicated outcomes alone occurred in 981 of the participants in the nateglinide group (21.1%) and 819 of the participants in the placebo group (17.6%) (hazard ratio with nateglinide, 1.24; 95% CI, 1.13 to 1.36; P<0.001). Mean (±SD) glycated hemoglobin levels, measured at the time the diagnosis of diabetes was made, were lower in the nateglinide group than in the placebo group (6.1±0.6% vs. 6.3±0.6%, P<0.001).** **There was a reduction in mean body weight during the study, with 10.1% of participants losing 5% of their baseline weight by 6 months, but the mean body weight was higher among participants in the nateglinide group than among those in the placebo group throughout the course of the study (mean difference, 0.35 kg; 95% CI, 0.22 to 0.48; P<0.001). Mean waist circumference was also higher in the nateglinide group than in the placebo group. No significant between group differences were seen in systolic or diastolic blood pressure**	
Follow up	**The fasting plasma glucose level or the plasma glucose level 2 hours after a glucose challenge was measured at the closeout visit or during the final 6 months of the study in 80% of the surviving participants who had not withdrawn consent and in whom diabetes had not developed. A total of 609 participants in the nateglinide group (13.1%) and 602 in the placebo group (12.9%) were lost to follow-up or withdrew from the study; however, because many of these participants were lost to follow-up or withdrew consent late in the study, information on vital status was available for 95.7% of the possible follow-up time in both groups. The median follow-up time for data on vital status was 6.5 years, and the median follow-up times for data on the diabetes, extended cardiovascular, and core cardiovascular outcomes were 5.0, 6.3, and 6.4 years, respectively.**	
Intention to Treat analysis	**Log-rank tests, stratified according to the presence or absence of a history of cardiovascular disease and to randomized assignment to valsartan or placebo, were used to compare the nateglinide and placebo groups with respect to the time to the first event in the extended or core cardiovascular outcome. A Cox discrete-time proportional-odds model was used to assess incident diabetes, given the fixed-time schedule for**	

	glucose measurements. Predefined analyses of the components of the composite cardiovascular outcome, exploratory outcomes (the time to death from all causes and the time to cardiovascular-related hospitalization), indexes of hyperglycemia, and body weight were also preformed. In addition, a possible interaction between valsartan and nateglinide for each reported outcome was tested. The effects of the study treatment were evaluated in prespecified subgroups.	
Adverse events	**A total of 520 participants in the nateglinide group (11.2%) and 485 in the placebo group (10.4%) discontinued the study drug owing to an adverse event (P = 0.23). Rates of adverse events did not differ significantly between the groups, except that more participants in the nateglinide group reported hypoglycemia (mostly mild events) (911 participants [19.6%], vs. 527 [11.3%] in the placebo group; P<0.001).**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**Among persons with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors, assignment to nateglinide for 5 years did not reduce the incidence of diabetes or the coprimary composite cardiovascular outcomes.**	
Quality Assessment	**Jadad 3** **NICE ++**	
Study	**Author: Pan** **Year 2003** **Country: China** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**Acarbose 50 mg t.i.d. for a period of 16 weeks. Administration of acarbose was started at 50 mg per day for one week followed by two weeks at 50 mg b.i.d. to minimize gastrointestinal side effects; subjects then received 50 mg t.i.d. for the remainder of the study. Patients were instructed to take one tablet with the first mouthful of their main meals.**	
Comparator	**Placebo 50 mg t.i.d. for a period of 16 weeks.**	
Setting / Delivered by	**Unclear**	
Randomisation method	**All eligible individuals were randomly assigned within a centre in blocks of six to either acarbose or matching placebo.**	
Blinding	**Double blinded**	
Recruitment	**Subjects were recruited by five centres in the mainland of China; after obtaining written informed consent, the subjects were screened using the oral glucose tolerance test (75 g glucose) to determine if IGT**	
Population baseline characteristics	**Sample: n= 252 (125 Intervention group, 127 Control group)** **Males: 39.2% Intervention group, 40.9% Control group** **Mean age: 53.4 years ± 8.63 (Intervention group) 55.6 years ± 8.31 (Control group)** **Mean BMI: .25.6 ± 2.99 (Intervention group) 25.8 ± 3.22 (Control group)** **Waist circumference:** **Other:** **Weight: 67.6 kg ± 10.33 (Intervention group) 68.2kg ± 11.55 (Control group)**	
Sub-group	**Age:** **Ethnic group: SES group**:	

	Obesity: **Other**:	
Sub-groups identified (Y/N)	**All sample was Chinese**	
Sub-group analysis (Y/N)	**Yes, all sample was Chinese**	
Criteria used for diagnosis of pre-diabetes	**World Health Organisation criteria, two hour postprandial plasma glucose ±140 mg/dl <200 mg/dl and fasting plasma glucose <125 mg/dl.**	
Criteria used for diagnosis of diabetes	**American Diabetes Association criteria**	
Primary findings	**Nineteen individuals (7.54%) converted to Type 2 diabetes during the study period: 12 subjects in the placebo (9.45%) and seven in the acarbose arm (5.6%). The comparison between treatments showed no significant difference (p=0.245).**	
Secondary findings	**Body weight 64.6 kg ± 9.96 (Intervention group) 66.4 kg ± 11.2 (Control group), difference of -1.34 kg (95% CI, -1.95 to -0.74, p=0.0001)**	
Follow up	**16 weeks**	
Intention to Treat analysis	**Yes**	
Adverse events	**Drug-related adverse events with a 'possible' or 'probable' relation to the study drug were reported by 35.7% of acarbose subjects compared to 18.2% patients on placebo. The difference between the treatment arms primarily resulted from the higher frequency of gastrointestinal events in the acarbose group. The most frequently reported events were flatulence (15.9% acarbose versus 6.1% placebo), abdomen enlarged (13.5 vs. 3.8%) and diarrhoea (9.5 vs. 2.3%); all were mild to moderate in intensity. Five subjects (two acarbose and three placebo) were prematurely withdrawn from the study because of adverse events and all study medication was permanently discontinued. No fatalities occurred. Four subjects experienced serious adverse events: one in the placebo group (tenosynovitis) and three on acarbose medication (cerebral infarction, hepatitis and glaucoma). Relation to the study medication was considered to be remote or none.**	
Other properties	**-**	
Cost Effectiveness	**-**	
Reviewer comments		
Authors conclusions	**The study showed that acarbose was efficacious and safe in the reduction of hyperglycaemia and hyperinsulinaemia in IGT subjects, indicating a potential benefit for the delay or prevention of onset of Type 2 diabetes.**	
Quality Assessment	**Jadad 3 (Gillies)** **NICE ++**	
Study	**Author: Ramachandran et al** **Year: 2009** **Country: India** **Study design: Community-based; placebo-controlled design**	**Comments**
Included in Gillies et al review?	**No**	
Intervention	**Lifestyle modification with pioglitazone or lifestyle modification with placebo.**	
Comparator	**Placebo**	
Setting / Delivered by	**The team members included a physician, three laboratory technicians, a dietician, a social worker and a**	

	helper. The measurements were repeated by the same members throughout the study, to eliminate inter-observer variations.	
Randomisation method	**Participants were not randomized. Participants with persistent IGT were assigned to group A (tablet A) and B (tablet B) in sequential order.**	
Blinding	**The participants and investigators were blinded to the group allocation. The principal investigators, field staff and the study participants, were not aware which the active drug was. The code was unblinded at the closure of the study in April 2008 by the advisory committee after reviewing preliminary analysis of the results in March 2008.**	
Recruitment	**Men and women of 35 to 55 years were selected among employees, and their families, of service organisations such as the railways and electricity board who responded to workplace announcements, and were identified from areas not included in IDPP-1**	
Population baseline characteristics	**Sample: n= Screening of 6,644 non-diabetic participants identified 407 participants with persistent IGT** **Males: 353 (86.7)** **Mean age (years): 45.1±6.1 (Intervention group); 45.5±6.3 (Control group)** **Mean BMI (kg/m2): 26.0±3.5 (Intervention group); 26.2±3.3 (Control group)** **Waist circumference (cm): 91.2±8.0 (Intervention group-Men); 91.3±7.2 (Control group-Men)** **89.2±9.4 (Intervention group-Women); 89.8±8.0 (Control group-Women)** **Other: Smoking 18.1% (Intervention group); 23.2% (Control group)**	
Sub-group	**Age: Not reported** **Ethnic group: SES group: Not reported** **Obesity: Not reported** **Other: Not reported**	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**WHO criteria for IGT (2 h value ≥7.8 to <11.1 mmol/l)**	
Criteria used for diagnosis of diabetes	**WHO criteria for diabetes (fasting ≥7.0 and/or 2 h ≥11.1 mmol/l)**	
Primary findings	**The cumulative incidence of diabetes at 36 months, corrected for the confounding variables such as age, sex, BMI and family history using the Kaplan–Meier survival test, was similar in both groups (pioglitazone=29.8% and placebo= 31.6%; unadjusted HR for placebo vs. pioglitazone 1.084 [CI 0.753–1.560], p=0.665); adjusted HR 0.984 [CI 0.672–1.443], p=0.93.**	
Secondary findings	**Reversal to normoglycaemia occurred in 40.9% of participants receiving pioglitazone and in 32.3% receiving placebo; the difference was not statistically significant (χ2 1.602, p=0.109). Analysis of the incidence of diabetes in relation to categories of baseline BMI (<25, 25–29 and >29 kg/m2) showed a respective distribution of 33.8%, 25.3% and 43.1%. The differences were statistically nonsignificant (trend χ2 6.77, p=0.149). Cox's proportional hazard model showed that only baseline 2 h plasma glucose (per mmol) had a significant contribution to the conversion to diabetes with HR 1.014 (95% CI 1.002–1.026; β=0.014), p=0.024.**	

	The result was similar when either BMI or waist circumference was entered as an independent variable. BMI × drug interaction was non-significant (β=−0.59, p=0.672).	
Follow up	**At year 3, the overall response rate was 90.2% (n=367): 88.7% (n=181) in the pioglitazone group and 91.6% (n=186) in the placebo group. Participants lost to follow-up numbered 21 in the pioglitazone group and 16 in the placebo group.**	
Intention to Treat analysis	**It was assumed that the cumulative incidence of diabetes in 3 years would be 40% in the control group with lifestyle modification and placebo and 25% in the group receiving lifestyle modification and pioglitazone. The sample sizes required in each of the two groups were 165 with a type 1 error of 5%, with 80% power. Higher numbers were recruited (204 in group A and 203 in group B) to allow for drop out. The intention-to-treat approach was used.**	
Adverse events	**In the pioglitazone group, cardiac problems accounted for two deaths and two non-fatal hospital admissions. There were two cases of cardiac disease in the placebo group. More participants in the placebo group than in the pioglitazone group were hospitalised for other reasons such as bone fractures, infectious diseases and treatment for renal stones. Of the four participants with elevated transaminases, three were in the placebo group. None of these individuals had values greater than 120 U/l.**	
Other properties	**Not reported**	
Cost Effectiveness	**Not reported**	
Reviewer comments	**None**	
Authors conclusions	**Despite good adherence to lifestyle modification and drug therapy, no additional effect of pioglitazone was seen above that achieved with placebo. The effectiveness of the intervention in both groups was comparable with that of lifestyle modification alone, as reported from the Indian Diabetes Prevention Programme-1. The results are at variance with studies that showed significant relative risk reduction in conversion to diabetes with pioglitazone in Americans with IGT. An ethnicity-related difference in the action of pioglitazone in non-diabetic participants may be one explanation.**	
Quality Assessment	**Jadad=1** **NICE ++**	
Study	**Author: STOP-NIDDM Trial Research Group** **Year 2002** **Country: Canada and Europe** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**100 mg acarbose three times daily, taken with the first bite of a meal. To keep the known gastrointestinal side-effects of acarbose (flatulence, diarrhoea, or abdominal cramps) to a minimum, the drug was started at 50 mg per day, and increased gradually to a maximum of 100 mg three times daily or to the maximum tolerated dose.**	
Comparator	**Placebo**	
Setting / Delivered by	**Clinics in Canada and Europe.**	
Randomisation method	**A computer program was used to generate the random allocation sequence, which was stratified by centre. Randomisation was done in blocks of four and six. Numbered drug containers were used to implement the random allocation process. Patients were randomised sequentially at each centre since the random code was stratified by centre. Random codes were concealed in a three-part container label that was separated from the box and stored in the event that investigators needed to know the randomisation status of the**	

	patient. An independent statistician, who was a member of the data safety and quality review committee, generated the allocation sequence; enrolment and randomisation was handled at the sites.	
Blinding	**Double-blind, placebo-controlled trial.**	
Recruitment	**Patients were recruited mainly through screening of high-risk populations, and in particular from first-degree relatives of patients with type 2 diabetes. Men and women aged between 40 and 70 years with a body-mass index of between 25 and 40 were screened. Patients were eligible for the study if they had impaired glucose tolerance**	
Population baseline characteristics	**Sample: n= 1,368 (682 Intervention group, 686 Control group)** **Males: 48% (329/682) Intervention group and 50% (344/686) Control group** **Mean age: 54.3 years (SD 7.9) Intervention group and 54.6 years (SD 7.9) Control group** **Mean BMI: 31.0 (SD 4.3) Intervention group and 30.9 (SD 4.2) Control group** **Waist circumference:** **Other:** **Weight: 87.6 kg (SD 15.3) Intervention group and 87.1 kg(SD 14.1) Control group**	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	
Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**1985 World Health Organisation criteria.**	
Criteria used for diagnosis of diabetes	**Not stated but assume same as above.**	
Primary findings	**Based on one abnormal plasma glucose concentration two hours after 75 g glucose load, cumulative incidence of diabetes was 221 (32·4%) in the acarbose-treated group versus 285 (41·5%) in the placebo group. Incidence of the disorder was 101 cases per 1000 person-years in the acarbose group and 121 cases per 1000 person-years in the placebo group, with a risk difference of 9·1% over 3·3 years.**	
Secondary findings	**Mean bodyweight decreased from 87.6 kg (SD 15.2) to 87.1 kg (15.3) during the study in patients given acarbose and increased from 87.0 kg (14.1) to 87.3 kg (15.2) in those on placebo (difference 0.77 kg [95% CI 0.01–1.54], p=0.0184).**	
Follow up	**Mean follow-up time was 3.3 years**	
Intention to Treat analysis	**Yes**	
Adverse events	**Almost a quarter of patients discontinued early, of whom almost a half (48%) discontinued during the first year. The commonest single cause of early discontinuation was gastrointestinal side-effects (93 patients in the Intervention group and 18 in the Control group).**	
Other properties	**-**	
Cost Effectiveness	**-**	
Reviewer comments		

Authors conclusions	**Acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of type 2 diabetes in patients with impaired glucose tolerance.**	
Quality Assessment	**Jadad 3 (Gillies)** **NICE ++**	
Study	**Author: Torgerson** **Year 2004** **Country: Sweden** **Study design: RCT**	**Comments**
Included in Gillies et al review?	**Yes**	
Intervention	**During the entire study period, all patients were prescribed a reduced-calorie diet (800 kcal/day deficit) containing 30% of calories from fat and not more than 300 mg of cholesterol per day. The prescribed energy intake was readjusted every 6 months to account for any weight lost during the preceding months. Participants received dietary counselling every two weeks for the first 6 months and monthly thereafter. Patients were also encouraged to walk at least 1 extra kilometer a day in addition to their usual physical activity. All patients kept physical activity diaries. The intervention group received orlistat 120 mg with breakfast, lunch, and dinner.**	
Comparator	**During the entire study period, all patients were prescribed a reduced-calorie diet (800 kcal/day deficit) containing 30% of calories from fat and not more than 300 mg of cholesterol per day. The prescribed energy intake was readjusted every 6 months to account for any weight lost during the preceding months. Participants received dietary counselling every two weeks for the first 6 months and monthly thereafter. Patients were also encouraged to walk at least 1 extra kilometer a day in addition to their usual physical activity. All patients kept physical activity diaries. The control group received placebo t.i.d. with breakfast, lunch, and dinner.**	
Setting / Delivered by	**Clinic visits**	
Randomisation method	**Not stated**	
Blinding	**Yes, double blinding**	
Recruitment	**Eligible patients were 30–60 years of age, with a BMI ≥30. Patients were required to have non-diabetic glucose tolerance as assessed by a 75-g oral glucose tolerance test (OGTT) performed at baseline. Exclusion criteria included diabetes and ongoing and active cardiovascular and gastrointestinal disease.**	
Population baseline characteristics	**Sample: n= 3,277 (1,640 Intervention group, 1,637 Control group** **Males: 735 (44.8%) Intervention group, 732 (55.3%) Control group** **Mean age: 43.0 years ± 8.0 Intervention group, 43.7 years ± 8.0 Control group** **Mean BMI: 37.3 ± 4.2 Intervention group, 37.4 ± 4.5 Control group** **Waist circumference: 115.0 cm ± 10.4 Intervention group, 115.4 cm ± 10.4 Control group** **Other:** **Weight: 110.4 kg ± 16.3 Intervention group, 110.6 kg ± 16.5 Control group**	
Sub-group	**Age:** **Ethnic group: SES group**: **Obesity**: **Other**:	

Sub-groups identified (Y/N)	**No**	
Sub-group analysis (Y/N)	**No**	
Criteria used for diagnosis of pre-diabetes	**1994 World Health Organization criteria**	
Criteria used for diagnosis of diabetes	**Diagnosis of type 2 diabetes was based on a single two hour whole blood glucose measure ≥10 mmol/l.**	
Primary findings	**During four years of treatment, orlistat plus lifestyle changes significantly decreased the progression to type 2 diabetes compared with placebo plus lifestyle changes (log-rank p=0.0032). Cumulative incidence rates after four years were 6.2 vs. 9.0%. The hazard ratio (0.627 [95% CI 0.455–0.863]) corresponds to a 37.3% decrease in the risk of developing diabetes with orlistat compared with placebo.**	
Secondary findings	**Mean weight loss was significantly greater with orlistat than placebo at one year (10.6 vs. 6.2 kg; p<0.001) and remained significantly greater at the end of the four year study (5.8 vs. 3.0 kg; p<0.001). The least-square mean difference between orlistat and placebo groups after four years of treatment was -2.7 kg (p<0.001) by LOCF analysis. A second analysis in which the baseline weights of subjects who dropped out of the study was carried forward (i.e., assuming these subjects lost no weight) also demonstrated greater weight loss in the orlistat group (3.6 vs. 1.4 kg; p<0.001). For those patients who completed four years of treatment (52% of the orlistat patients and 34% of the placebo patients initially randomised), weight loss was significantly greater with orlistat than placebo at year 1 (11.4 vs. 7.5 kg; p<0.001) and year 4 (6.9 vs. 4.1 kg; p<0.001). Significantly more orlistat patients (72.8%) than placebo patients (45.1%) achieved weight loss ≥5% after one year of treatment (p<0.001). A similar significant difference was apparent for patients achieving a weight loss ≥10% (41.0% with orlistat vs. 20.8% with placebo; p<0.001). For those patients who completed four full years of treatment, 52.8 and 37.3%, respectively, lost ≥5% of baseline body weight (p<0.001) and 26.2 and 15.6%, respectively, lost ≥10% of baseline body weight (p<0.001).**	
Follow up	**Four years**	
Intention to Treat analysis	**Yes**	
Adverse events	**Orlistat was well tolerated during the study. The overall incidence of adverse events was similar in the two treatment groups, with the exception of a higher incidence of gastrointestinal events. Most gastrointestinal events were mild to moderate in intensity and occurred during the early phase of treatment. During the first year of treatment, the proportion of patients experiencing at least one gastrointestinal event with orlistat or placebo was 91 vs. 65%, respectively. This compares with 36% vs. 23% for orlistat or placebo, respectively, during the 4th year. Over the four year period, a similar proportion of placebo-treated patients had at least one serious adverse event as compared with orlistat-treated patients (13 vs. 15%). Similar proportions of serious gastrointestinal events occurred in the placebo (n = 32; 2%) and orlistat (n = 32; 2%) groups. No deaths were attributed to study medication. Overall, 4% of placebo patients and 8% of orlistat patients withdrew from the study because of adverse events or laboratory abnormalities; the difference was primarily due to gastrointestinal events.**	
Other properties	**-**	
Cost Effectiveness	**-**	
Reviewer comments		
Authors conclusions	**The addition of orlistat to lifestyle changes significantly reduces the incidence of type 2 diabetes in obese subjects. With this study design, reduction was only apparent in the IGT subgroup. Adding orlistat also significantly increases weight loss in obese patients with either IGT or NGT and improves other cardiovascular risk factors. Orlistat treatment is safe and well tolerated over four years of treatment.**	

Quality Assessment	**Jadad 3 (Gillies)** **NICE ++**	

Appendix 9: Statistical methods used within meta-analysis

We present the basic details for the meta-analysis of the data described in this report.

Unadjusted model

The log hazard ratio from two-arm trials comparing treatments *k* and *b* are assumed to be normally distributed such that:

$$\bar{x}_{s,k,b} \sim N\left(ln\left(\frac{\boldsymbol{h}_{s,k}}{\boldsymbol{h}_{s,b}}\right), se^2_{s,k,b}\right)$$

where $\bar{x}_{s,k,b}$ is the log hazard ratio estimate for study *s* comparing treatments *k* to *b* and $se^2_{s,k,b}$ is the corresponding variance.

Furthermore, for a two-arm trial comparing treatment *k* with treatment *b* in study *s*, we use the random effects model:

$$\ln\left(\frac{h_{s,k}}{h_{s,b}}\right) = \beta_k - \beta_b + re_{s,k} - re_{s,b}$$

where $re_{s,k}$ is the random effect deviation for arm *k* of study *s* and is assumed to be normally distributed with zero mean and variance $\frac{\sigma^2}{2}$ and σ^2 is the random effect variance for a treatment contrast. β_k is the log hazard ratio for treatment *k* relative to the baseline treatment and β_b is the log hazard ratio for the baseline treatment in study *s*.

The log hazard ratios from a multi-arm trial are dealt with as follows to account for the fact that log hazard ratios from multi-arm trials are correlated. For the baseline treatment, *b*:

$$\bar{x}_{s,b} \sim N(0, se^2_{s,b}).$$

For other treatments:

$$\bar{x}_{s,k} \sim N(ln(\boldsymbol{h}_{s,k}), se^2_{s,k})$$

where $\bar{x}_{s,k}$ is the log hazard for treatment arm *k* from study *s* and $se^2_{s,k}$ is the associated variance.

Furthermore, for a multi-arm trial, we use the random effects model:

$$\ln(h_{s,k}) = \alpha_s + \beta_k - \beta_b + re_{s,k} - re_{s,b}$$

where α_s is a study-specific baseline term.

The variance terms are estimated as:

$$se_b^2 = \frac{se_{k_1,b}^2 + se_{k_2,b}^2 - se_{k_1,k_2}^2}{2}$$

and

$$se_k^2 = se_{k,b}^2 - se_b^2 .$$

The parameters were given the following prior distributions:

β_k ~N(0, 1000), α_s ~N(0, 1000) and σ ~Unif(0,2).

Adjusted model

The meta-regression model uses the basic model described above but now allows for two treatment-specific covariates for mean age and mean BMI such that:

$$\ln\left(\frac{h_{s,k}}{h_{s,b}}\right) = \beta_k - \beta_b + (\gamma.age_k - \gamma.age_b) \times (age_{s,k} - \mu_{age}) +$$
$$(\gamma.BMI_k - \gamma.BMI_b) \times (BMI_{s,k} - \mu_{BMI}) - re_{s,k} - re_{s,b}$$

The regression coefficients represent the change in the log hazard ratio per unit change in the covariates.

It is not possible to estimate separate intervention by covariate terms for all interventions because of the limited amount of data available. We assume that all intervention by covariate interactions are different for each intervention by are exchangeable. We assume that:

$$\gamma.age_k \sim N(\mu_{\gamma.age}, \sigma_{age}^2)$$

and

$$\gamma.BMI_k \sim N(\mu_{\gamma.BMI}, \sigma_{BMI}^2)$$

This model assumes that the coefficients are different but related and strength is borrowed across intervention in their estimation.

With relatively little sample data with which to estimate the extra parameters, we given the parameters weakly informative prior distributions such that:

β_k ~N(0, 100), α_s ~N(0, 100), σ ~Unif(0,2), $\mu_{\gamma.age} \sim N(0, 100)$, $\sigma_{age} \sim N(0,0.25)$, $\mu_{\gamma.BMI} \sim N(0.100)$ and $\sigma_{BMI} \sim N(0,0.25)$.

We present the basic details for the meta-analysis of the data described in this report.

Unadjusted model

The log hazard ratio from two-arm trials comparing treatments *k* and *b* are assumed to be normally distributed such that:

$$\bar{x}_{s,k,b} \sim N\left(ln\left(\frac{h_{s,k}}{h_{s,b}}\right), se^2_{s,k,b}\right)$$

where xs,k,b is the log hazard ratio estimate for study *s* comparing treatments *k* to *b* and ses,k,b2 is the corresponding variance.

Furthermore, for a two-arm trial comparing treatment *k* with treatment *b* in study *s*, we use the random effects model:

$$\ln\left(\frac{h_{s,k}}{h_{s,b}}\right) = \beta_k - \beta_b + re_{s,k} - re_{s,b}$$

where $re_{s,k}$ is the random effect deviation for arm *k* of study *s* and is assumed to be normally distributed with zero mean and variance $\frac{\sigma^2}{2}$ and σ^2 is the random effect variance for a treatment contrast. β_k is the log hazard ratio for treatment *k* relative to the baseline treatment and β_b is the log hazard ratio for the baseline treatment in study *s*.

The log hazard ratios from a multi-arm trial are dealt with as follows to account for the fact that log hazard ratios from multi-arm trials are correlated. For the baseline treatment, *b*:

xs,b~N0,ses,b2.

For other treatments:

xs,k~Nlnhs,k,ses,k2

where xs,k is the log hazard for treatment arm *k* from study *s* and ses,k2is the associated variance.

Furthermore, for a multi-arm trial, we use the random effects model:

$$\ln\left(h_{s,k}\right) = \alpha_s + \beta_k - \beta_b + re_{s,k} - re_{s,b}$$

where α_s is a study-specific baseline term.

The variance terms are estimated as:

$$se^2_b = \frac{se^2_{k_1,b} + se^2_{k_2,b} - se^2_{k_1,k_2}}{2}$$

and

$$se^2_k = se^2_{k,b} - se^2_b .$$

The parameters were given the following prior distributions:

β_k ~N(0, 1000), α_s ~N(0, 1000) and σ ~Unif(0,2).

Adjusted model

The meta-regression model uses the basic model described above but now allows for two treatment-specific covariates for mean age and mean BMI such that:

$$\ln\left(\frac{h_{s,k}}{h_{s,b}}\right) = \beta_k - \beta_b + (\gamma.age_k - \gamma.age_b) \times (age_{s,k} - \mu_{age}) + (\gamma.BMI_k - \gamma.BMI_b) \times (BMI_{s,k} - \mu_{BMI}) - re_{s,k} - re_{s,b}$$

The regression coefficients represent the change in the log hazard ratio per unit change in the covariates.

It is not possible to estimate separate intervention by covariate terms for all interventions because of the limited amount of data available. We assume that all intervention by covariate interactions are different for each intervention by are exchangeable. We assume that:

$$\gamma.age_k \sim N(\mu_{\gamma.age}, \sigma^2_{age})$$

and

$$\gamma.BMI_k \sim N(\mu_{\gamma.BMI}, \sigma^2_{BMI})$$

This model assumes that the coefficients are different but related and strength is borrowed across intervention in their estimation.

With relatively little sample data with which to estimate the extra parameters, we given the parameters weakly informative prior distributions such that:

β_k ~N(0, 100), α_s ~N(0, 100), σ ~Unif(0,2), $\mu_{\gamma.age} \sim N(0, 100)$, $\sigma_{age} \sim N(0,0.25)$, $\mu_{\gamma.BMI} \sim N(0.100)$ and $\sigma_{BMI} \sim N(0,0.25)$.

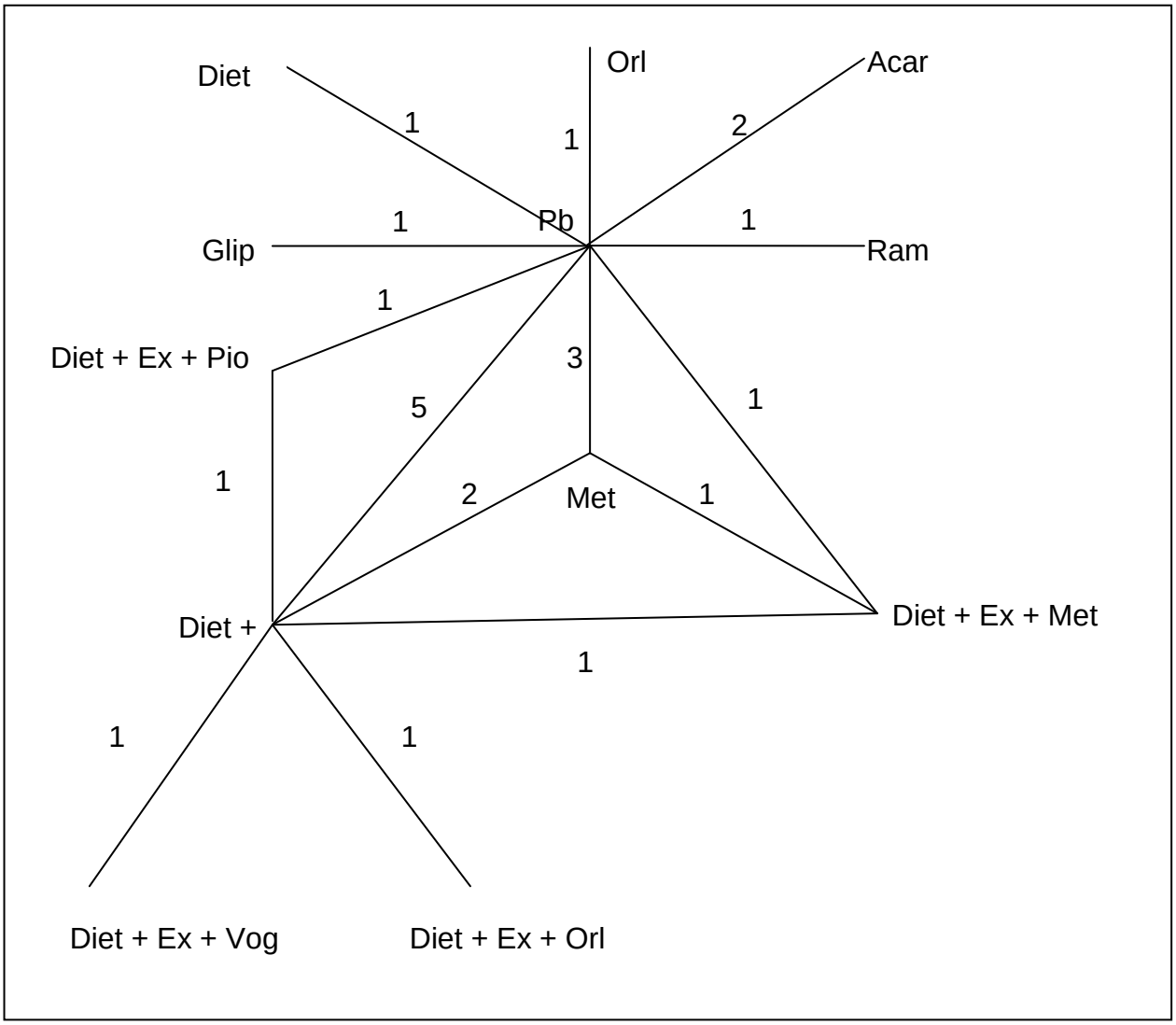

Figure A: Short term trials – network of evidence
Nodes correspond to interventions
The numbers represent the number of times that pairs of interventions have been compared

KEY:
Pbo: Placebo
Diet: Diet
Diet + Ex: Diet + Exercise
Acar: 75-150mg, 150mg & 300mg Acarbose (Daily)
Glip: 2.5mg Glipizide (Daily)
Met: 750mg, 500-1000mg & 1000mg Metformin (Daily)
Orl: 360mg Orlistat (Daily)
Ram: 15mg Ramipril (Daily during year one)
Diet + Ex +met: Diet + Exercise +750mg, 500-1000mg Metformin (Daily)
Diet + Ex + Orl: Diet + Exercise + 360mg Orlistat (Daily)
Diet + Ex + Pio: Diet + Exercise + 30-40mg Pioglitazone (Daily)
Diet + Ex + Vog: Diet + Exercise + 0.6mg Voglibose (Daily)

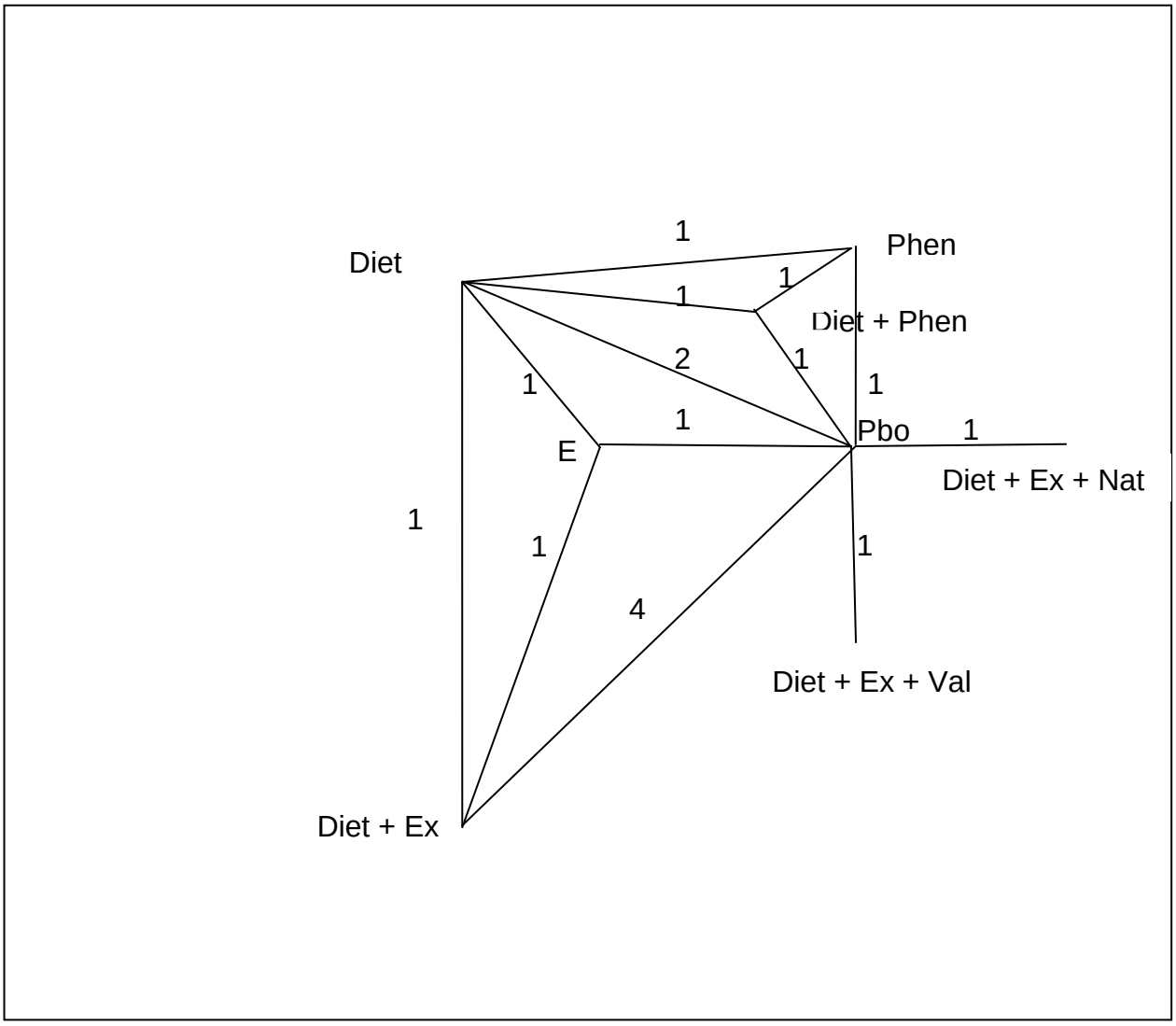

Figure B: Medium-term trials – network of evidence
Nodes correspond to intervention
The numbers represent the number of times that pairs of interventions have been compared

KEY:

Pbo:	Placebo
Diet:	Diet
Ex:	Exercise
Diet + Ex:	Diet + Exercise
Phen:	50mg Phenformin
Diet + Phen:	Diet + 50mg Phenformin
Diet + Ex + Nat:	Diet + Exercise + up to 60mg Nateglinide (3 times daily)
Diet + Ex + Val:	Diet + Exercise + up to 160mg Valsartan (Daily)

Appendix 10: Tables of Secondary Outcome Measures

Study	BMI		Weight		Fasting Glucose		HbA1c		SBP		DBP		Sample size
	Baseline data available?	Followup data available?	Baseline data available?	Followup data available?	Baseline data available?	Followup data available?	Baseline data available?	Followup data available?	Baseline data available?	Followup data available?	Baseline data available?	Followup data available?	Baseline and followup sample sizes available?
DPPOS (2009)	✓		✓		✓		✓		✓		✓		
Ramachandran et al. (2009)	✓	✓	✓	✓	✓	✓	✓	✓					
Roumen et al. (2008)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Lindahl et al. (2009)	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	
Li et al. (2008)	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓
Penn et al. (2009)	✓		✓	✓	✓								
DREAM Trial Investigators (2006a)	✓		✓		✓	✓			✓		✓		
Kawamori et al. (2009)					✓	✓							
Lindstrom et al. (2003)	✓	✓	✓	✓	✓	✓	✓	✓					✓
Lindstrom et al. (2006)			✓	✓									
Eriksson et al (2006)	✓	✓			✓	✓			✓	✓			
Heymsfield et al (2000)	✓		✓		✓	✓							
Ramachandran et al. (2006)	✓				✓		✓		✓		✓		
Jarrett et al. (1979)													
Kosaka et al (2005)	✓				✓				✓		✓		
Li et al. (1999)	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓
Liao et al. (2002)	✓	✓	✓	✓									
Pan et al. (2003)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Pan et al. (1997)	✓	✓	✓	✓	✓	✓							✓
STOP-NIDDM (2002)	✓		✓		✓				✓		✓		
Wein et al. (1999)	✓	✓	✓		✓	✓							
XENDOS (2004)	✓		✓	✓	✓	✓			✓	✓	✓	✓	✓
DPP (2002)	✓		✓		✓								
NAVIGATOR (2010a)	✓		✓		✓				✓		✓		
NAVIGATOR (2010b)	✓		✓		✓				✓		✓		
DeFronzo et al. (2011)	✓				✓		✓		✓		✓		

As seen in the above table, only 5 of 26 RCTs provide both baseline and follow-up measures, and sample sizes for at least one of the six secondary outcomes. Given this result, a meta-regression should not be considered, since the general belief is that a minimum of ten studies should be included when completing a meta-regression analysis.