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PREVENTING TYPE 2 DIABETES: SYSTEMATIC REVIEW OF STUDIES OF COST-EFFECTIVENESS OF LIFESTYLE PROGRAMMES AND METFORMIN, WITH AND WITHOUT SCREENING, FOR PREDIABETES

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ABSTRACT:
(300 words)

Objective: To explore the cost-effectiveness of lifestyle interventions and metformin in reducing subsequent incidence of type 2 diabetes, both alone and in combination with a screening programme to identify high-rick individuals.

Design: Systematic review of economic evaluations.

Data sources and eligibility criteria: Database searches (Embase, Medline, PreMedline, NHS EED) and citation tracking identified economic evaluations of lifestyle interventions or metformin alone or in combination with screening programmes in people at high risk of developing diabetes. We used ISPOR's Questionnaire to Assess Relevance and Credibility of Modelling Studies for Informing Healthcare Decision Making.

Results: 27 studies were included; all had evaluated lifestyle interventions and 12 had also evaluated metformin. Primary studies exhibited considerable heterogeneity in how pre-diabetes was defined and in the intensity and duration of the lifestyle programme. Lifestyle programmes and metformin appeared to be cost-effective in preventing diabetes in high-risk individuals (median ICERs of £7,490/QALY and £8,428/QALY respectively) but economic estimates varied widely between studies. Intervention-only programmes were in general more cost-effective than programmes that also included a screening component. The longer the period evaluated, the more cost-effective interventions appeared. In the few studies that evaluated other economic considerations, budget impact of prevention programmes was moderate (0.13-0.2% of total healthcare budget), financial payoffs were delayed (by 9-14 years), and impact on incident cases of diabetes was limited (0.1-1.6% reduction). There was insufficient evidence to answer the question of 1) whether lifestyle programmes are more cost effective than metformin or 2) whether pragmatic (low-intensity) lifestyle interventions are more cost-effective than the more intensive lifestyle programmes that were tested in trials.

Conclusions: The economics of preventing diabetes are complex. Whilst there is some evidence that diabetes prevention programmes may be cost-effective, the evidence base to date provides few clear answers because of differences in denominator populations, definitions, interventions and modelling assumptions.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

STRENGTHS

- Largest and most up to date summary of economic evaluations of diabetes prevention programmes published to date
- Includes novel comparison of lifestyle interventions with metformin and consideration of relevance and credibility for policy makers.
- Offers detailed analysis of assumptions underpinning modelling studies

LIMITATIONS

- Very few economic evaluations of primary studies reflect prevailing national policy in UK or elsewhere
- Most primary studies are from high-income countries so applicability to low and middle-income settings is questionable

What this study adds

What is already known on the subject

- Diabetes is a global health priority due to high prevalence and associated costs, with many countries developing or seeking to develop diabetes prevention programmes
- Studies of diabetes prevention programs identify participants with different types of pre-diabetes (based on a number of different measures of abnormal glucose metabolism) and provide interventions that differ in duration and intensity.
- Lifestyle programmes for diabetes prevention are cost-effective on average

What this study adds

- This is the first study to review metformin alongside lifestyle programs, finding that metformin is a cost-effective intervention for reducing incidence of diabetes in people at high risk, but there is insufficient evidence to suggest it is more or less cost-effective than lifestyle programmes.
- Intervention-only programmes were in general more cost-effective than screening and intervention programmes and the longer the period evaluated, the more cost-effective interventions appeared.
- National diabetes prevention policy in the UK and US advocates pragmatic lifestyle programmes (less than 3 years in duration), and in the UK the use of HbA1c or fasting plasma glucose is recommended for diagnosing pre-diabetes. However, the majority of cost-effectiveness studies relate to a different definition of pre-diabetes and a higher intensity of intervention, which limits the direct applicability of findings.

INTRODUCTION:

Diabetes is a global health priority, with 415 million known adult cases worldwide, of which 91% are type 2 diabetes (1). Ageing of the population is predicted to drive substantial increases in prevalence (estimated to 642 million by 2040) (2), with particularly rapid increases in low- and middle-income countries (3). The burden of complications in diabetes is high, including heart disease, stroke, neuropathy, nephropathy and retinopathy (4). Type 2 diabetes develops as a result of genetic, environmental and behavioural factors, including sedentary lifestyle and energy-rich, nutrient-poor diet, both of which predispose to obesity (5).

Diabetes takes a significant toll on health budgets around the world, accounting for 5-20% of total healthcare expenditure in many countries (6). Both absolute costs and proportion of overall health budget for type 2 diabetes are set to increase further in future decades as prevalence rises, in the context of a marked reduction in the proportion of the population who are economically active (e.g. in the UK, the relative economic burden per worker is expected to increase by 40-50% by 2060 (6)). Cost-effective treatment and prevention strategies, with acceptable budget impact, will therefore become increasingly important as resources become stretched.

Types of pre-diabetes: Type 2 diabetes is often preceded by a phase of abnormal glucose regulation (pre-diabetes). Pre-diabetes is a generic term that includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and HbA1c in the 'at risk' range (7). One individual may have one, two or all of these types of pre-diabetes. Table 1 describes these different pre-diabetic states, how they are diagnosed and current diagnostic guidelines. The distinction between types of pre-diabetes is important for a number of reasons. Firstly, different definitions of pre-diabetes are associated with distinct physiological changes. Impaired fasting glucose is associated with reduced hepatic insulin sensitivity, and first phase insulin response; impaired glucose tolerance is associated with reduced peripheral insulin sensitivity and second phase insulin response and HbA1c reflects aggregated blood glucose levels over time (8). Secondly, progression to diabetes ranges from 3.6% to 7.6% annually depending on the type of pre-diabetes (9). Thirdly, impaired glucose tolerance is associated with increased risk of microvascular disease whereas the relationship is less clear for other types of pre-diabetes (10). Finally, there is evidence that people with different types of pre-diabetes respond differently to the same intervention. For example, in a large US trial, the US Diabetes Prevention Program, lifestyle programs were less effective and metformin more effective in participants with IGT *and* HbA1c in the 'at risk range' compared to the entire cohort which were identified on the basis of IGT (68).

Types of screening and prevention programmes: Pre-diabetes is almost always asymptomatic. It tends to be diagnosed incidentally (when blood tests are performed for other reasons) or as part of a pro-active screening programme delivered either to an entire population or to selected individuals. Most commonly, screening blood tests are offered to people identified as at high risk of developing diabetes based on demographic variables (e.g. age, ethnicity), survey questions (e.g. family history of diabetes, personal history of

gestational diabetes) or biomarkers (e.g. body mass index, blood pressure), typically combined in a 'diabetes risk score' (14). People diagnosed with pre-diabetes may be offered a lifestyle programme (to encourage a healthy diet and increased physical activity) or metformin. These interventions have been shown to delay or prevent type 2 diabetes in a significant proportion of participants in large randomised trials in the US (15), Europe (16), China (17) and India (18). Lifestyle programmes in these trials were intensive and sustained: 3-10 years of individual and group sessions provided by specialist staff (dieticians or exercise physiologists with annual physician review). Subsequent translation of these findings into large-scale community-based programmes produced interventions that were both shorter (3-12 months) and less intense (e.g. they offered less sessions and were delivered to groups rather than individuals by non-specialist staff such as lay workers or prevention managers). These large-scale community-based programmes have been offered to populations of similar age and BMI to the large trials but with different types of pre-diabetes (e.g. selection based on elements of the metabolic syndrome rather than the criteria of impaired glucose tolerance seen in the large trials) (19). There is some evidence that these pragmatic interventions offered to a real-world population deliver more limited and less sustained benefits than were seen with more intensive interventions in trial populations (20).

Given the potential impact on populations and health budgets, the burden of type 2 diabetes is a key issue for policy makers. In response, a number of countries, including the US and UK, are developing (or seeking to develop) national diabetes prevention programmes (21, 22). The design of large-scale prevention programmes incorporates a number of important choices: i) whether to screen a portion of the population for pre-diabetes or focus on people who are already known to have pre-diabetes, ii) if no screening programme is in place, how to identify participants who may benefit from a diabetes prevention programme and iii) the role of different types of interventions (lifestyle programmes or metformin) and iv) the optimum intensity and duration of the programme.

This study was designed to help inform decision-making by local and national policy makers and health insurers in countries with a high and/or rising incidence of type 2 diabetes. Our research question were:

1. What is the evidence on cost-effectiveness of lifestyle programmes or metformin in diabetes prevention?
2. What is the impact of the following factors on the cost-effectiveness of these interventions?
    a. Type of pre-diabetes (IFG, IGT or 'at risk' HbA1c)
    b. Intensity of lifestyle intervention: Including three different measures of intensity, each of which was examined separately: i) frequency of contact in initial 'core' teaching/coaching sessions, ii) duration of core and maintenance intervention and iii) group or individual format of sessions)
    c. Inclusion of screening: Intervention-only studies on a predefined pre-diabetic *or* high-risk population or screening for pre-diabetes followed by intervention
    d. Years of follow-up to evaluate diabetes incidence: less than 10 years and more than 25 years.

3. What are the implications of these findings for policy makers and health insurers?

A number of systematic reviews of economic evaluations of diet and exercise in diabetes prevention have been undertaken in the last 10 years (23-27). This paper is the first review to consider the cost-effectiveness of metformin and the first review to examine intervention-only and screening-plus-intervention studies separately. In addition, this paper adds to previous reviews by updating the dataset with two new primary studies not included in previous systematic reviews (62,63) and evaluating studies' relevance for decision making by policy makers and health insurers.

METHODS:

Search strategy and inclusion criteria: A database search (covering Embase, PreMedline, Medline and NHS EED) for peer-reviewed articles on pre-diabetes and diabetes prevention between 2004 (the year before the publication of the first cost-effectiveness review of the Us Diabetes Prevention Program) and 2014 identified 3833 papers. Citation tracking and screening of references (in included studies and review articles) identified a further 23 papers up to April 2016. All abstracts were exported for review and a sample of 30% of abstracts were dually reviewed. We included studies that reported full economic evaluation (cost-effectiveness, cost-utility or cost benefit analysis) of i) lifestyle programmes, ii) metformin or iii) screening in combination with lifestyle programmes and/or metformin against a base case of usual care or no intervention.

To meet our inclusion criteria, economic evaluations needed to have:

1. Evaluated the treatment of pre-diabetes with either metformin and/or lifestyle programmes (that addressed diet *and* physical activity);
2. Included 12 months or more of intervention and follow up;
3. Quantified outcomes (such as change in quality adjusted life years, disability adjusted life years, life years gained or numbers needed to treat to prevent one case of type 2 diabetes);
4. Described the method used to classify people as high-risk of developing type 2 diabetes (hence eligible for interventions), including blood tests for pre-diabetes (any in Table 1); screening questionnaires, diabetes risk algorithms or presence of particular risk factors.

Review articles were excluded as were articles focusing only on women with a history of gestational diabetes.

Full papers meeting the above criteria were reviewed; data were extracted from included papers (by SR) and data extraction for a third of papers was checked by a second reviewer (EB).

Quality assessment: A checklist developed by the International Society for Pharmaco-economics and Outcomes Research (the ISPOR-AMCP-NCP questionnaire (28)) was used to evaluate the relevance and credibility of modelling studies for decision-making by policy makers.

Assumptions and calculations: All the economic evaluations included in this review were cost-effectiveness analyses (including cost-utility analyses), which measure both the cost of the intervention and the impact of the intervention on participants' quality and/or length of life (29). No full cost-benefit analyses were identified. Cost effectiveness analyses report their results as ratios of incremental costs (costs of new intervention in addition to normal care minus costs of normal care) divided by incremental benefits (quality and or length of life with the intervention minus without the intervention); in an incremental cost effectiveness ratio (ICER). Resources to spend on healthcare are finite, so policy makers set an amount they are willing to pay for a year in perfect health against which a treatment's incremental cost-effectiveness ratio is compared. This measure is called the 'willingness to pay threshold' and differs from country to country. Historically, the National Institute for Health and Clinical Excellence in the UK has approved new technologies below the willingness to pay threshold of £20,000 – £30,000/QALY (30), the US has used a threshold of $50,000/QALY (31) and the WHO has recommended cost less than the per capita gross domestic product of the relevant country per disability adjusted life year as the threshold (32). For this review we used a willingness to pay threshold of £20,000/QALY. This means that if an intervention is below the willingness to pay threshold (costs less than £20,000 per quality adjusted life year), the intervention is considered *cost-effective.* If the intervention costs more than the willingness to pay threshold, it is considered not cost-effective. An intervention is only *cost-saving* if it is more effective *and* costs less than current treatment.

Costs are reported in British pounds 2015 using purchasing power parity and currency exchange rates from the CCEMG - EPPI-Centre Cost Converter (33). Costs of lifestyle interventions were calculated in 2015 British pounds where sufficient data was available on constituent activities and staff involved, drawing on the PSSRU (34) for UK staff cost estimates.

Incremental Cost Effectiveness Ratios (ICERs) are reported separately for each outcome measure: as either cost saving or £/Quality adjusted life year gained (£/QALY), £/disability adjusted life year averted (£/DALY) or £/life year gained (£/LYG).

Definitions of measures of effectiveness used in included studies (35, 36):

Quality adjusted life year (QALY): A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.

Disability adjusted life year (DALY): A measure of the impact of a disease or injury in terms of healthy years lost.

Life years gained (LYG): A measure of the impact of a disease or treatment on the length of life. Years of life are not adjusted to reflect health or disability.

Incremental cost-effectiveness ratios (ICERs) are reported from two different perspectives: health system and societal perspective. The health system perspective includes only direct medical costs such as: i) staff, facilities, medication and consumables costs required for provision of the intervention, and ii) general healthcare of participants. In addition, studies of cost effectiveness from a societal perspective include some or all elements of i) indirect costs of the intervention (e.g. exercise equipment, food preparation equipment), ii) participant time (travelling to and participating in intervention's activities), iii) lost productivity due to absence from work and iv) disability benefits payments.

Studies were grouped on a number of dimensions to identify key drivers of differences through subgroup analysis. Subgroups examined included: type of pre-diabetes, intensity of lifestyle intervention (defined by number of sessions in 'core' intervention, duration of core and maintenance program, group vs. individual format), inclusion of screening, years of follow-up to evaluate diabetes incidence. Sub-group medians could not be derived for the type of pre-diabetes, as the majority of studies used impaired glucose tolerance to identify eligible participants (with or without impaired fasting glucose), and there were 2 or less studies that reported £/QALY using each of the remaining methods of identification. Therefore, in order to understand the potential significance of the type of pre-diabetes we undertook a meta-analysis of randomised controlled trials of lifestyle programmes for diabetes prevention. Data was extracted from the 22 primary studies that reported diabetes incidence as an end-point that were included in three recent systematic reviews of lifestyle programmes in diabetes prevention (71, 72, 73). Data was analysed in RevMan (Review Manager version 5.3) using a random-effects model due to the heterogeneity of the primary studies. Studies were grouped according to the trials' inclusion criteria (IFG, IGT, HbA1c or risk score) and duration of the intervention. Forest plots were generated to illustrate the relative risk of diabetes following a lifestyle programme for each of these groups compared to no intervention.

Patient and public involvement: This review was conceptualized by a multi-disciplinary group, including lay members, in Newham, East London. The authors attended regular project meetings of this group, reporting back the results of the review to the rest of the team. Findings of this review are being used to inform the evaluation of a large voluntary-sector led prevention initiative in this borough.

RESULTS

42 full papers were reviewed and 15 were excluded for reasons outlined in Figure 1.

In total, 27 studies of diabetes prevention programmes with economic evaluations have been published from 15 countries between 2004 and 2016 (38-65). 6 of the economic evaluations were within-trial cost-utility analyses and 21 were modelling studies (16 Markov models, two simulation models, two decision trees and one combination Markov model and decision tree). Within the modelling studies there were a wide range of model structures, parameters and parameter values (some of which are summarised in Appendix 5) which in part drive the variability observed in study results (66).

Type of intervention: All 27 studies evaluated lifestyle interventions and 12 also evaluated metformin (Appendix 1). 13 reported interventions in a population previously identified as pre-diabetic (people with IFG, IGT or high HbA1c) and 14 reported screening of a broader population and subsequent intervention on those identified at high risk of developing type 2 diabetes. The majority of studies evaluated intensive trial-based interventions, although there was a great deal of heterogeneity in the type of lifestyle interventions evaluated. Table 2 describes some of the dimensions on which lifestyle programmes differed: frequency of contact, duration, staff providing intervention, individual vs group interventions and frequency of contact.

3 studies (52, 57, 42) did not specify the details of their lifestyle interventions.

Intensive trial-based lifestyle programmes: 18 of the 24 studies that did describe in detail the lifestyle intervention being evaluated were based on intensive trial-based lifestyle interventions (8 based on the US Diabetes Prevention Program, 4 on the US Diabetes Prevention Program together with the US Diabetes Prevention Program Outcome Study, 3 on the Finnish Diabetes Prevention Study, one on the Da Qing study, one on the Indian Diabetes Prevention Programme and one on DE-PLAN-CAT) and 3 were based on community translation of these intensive interventions lasting 3-5 years. The primary studies were generously resourced, large (300-3000 participants) and provided lengthy interventions (3-10 years duration) including 7-16 initial contacts in the 'core program' delivered by specialist staff (dieticians, exercise physiologists and annual medical review). Two within-trial studies (37,64) reported intensive trial-based lifestyle programme costs in sufficient detail for costs to be reconstituted on an activity based costing basis (Appendix 2). The costs in 2015 British pounds of these interventions were as follows: £2,915 per participant over 3 years for the USDPP lifestyle program, £4,001 per participant over 3 years for the Indian DPP lifestyle programme (excluding staff travel costs).

Translational community-based programmes: 3 of the 24 studies were based on community translation of these intensive interventions lasting 3-5 years and 3 studies were based on other published studies covering much smaller populations (<150 participants) and providing less intensive interventions (ranging from 12 weeks to 1 year in duration), delivered by non-specialist staff (diabetes prevention facilitators and lay workers).

Target population – demographics and type of pre-diabetes: The target population for 16 of the 27 studies were overweight individuals with impaired glucose tolerance (IGT), with or without impaired fasting glucose (IFG). 4 used IFG alone (39, 50, 54, 61), 2 used IGT *or* IFG (41, 49), 1 used IFG or HbA1c (51), 1 used HbA1c alone (63) and 3 used other methods of screening (such as diabetes risk algorithms, BMI or other elements of metabolic syndrome) (38,40,42). 17 out of 27 studies included participants based on a BMI greater than or equal to 24kg/m^2, 3 included participants based on a BMI greater than or equal to 30mg/kg2 and the remainder did not state a BMI cut-off for participation. A wide range of ages (from 18 years and older) were included.

Benefits of interventions: The primary benefit of diabetes prevention programmes is reduction in incidence of type 2 diabetes and its associated complications, measured in the number needed to treat to delay or prevent a case of diabetes or improvements in quality adjusted life years (QALYs), disability adjusted life years (DALYs) and life years gained (LYG) as summarised in Appendix 3.

Lifestyle interventions: 21 studies reported change in quality adjusted life years associated with lifestyle interventions with a median 0.159 (range: 0.003-2.91) increase in QALYs and 13 reported life years gained with a median increase of 0.30 (range: 0.04-0.84) increase relative to usual care. This is equivalent to a median increase in 110 days of life or 58 days of life in optimal health for lifestyle programmes. Four studies reported numbers needed to treat with lifestyle programmes to prevent 1 case of type 2 diabetes with results ranging from 4.2-30.

Metformin: 8 studies measured change in quality adjusted life years associated with metformin therapy with a median of 0.105 (range: 0.01-2.83) increase in QALYs and 5 studies reported increase in life years gained with a median gain of 0.14 (range: 0.05 to 0.3). This is equivalent to a median increase of 51 days of life and 38 days of life in optimal health for metformin. Two studies reported number needed to treat with metformin to prevent 1 case of type 2 diabetes as 6.9 and 27.9.

Side effects of screening or intervention: The impact of screening and intervention on length of quality of life was included as a change in incremental QALYs in a number of studies (46,47,48), and three studies modelled the impact of adverse effects explicitly (37,44,55).

'Value for money': Policy makers may consider a range of economic factors when considering a new programme or therapy: cost-effectiveness, budget impact, effect on incident cases of the disease and equity of healthcare provision (66). All studies included in this review considered cost effectiveness, reporting incremental cost-effectiveness ratios, 5 described budget impact, 2 modelled impact on incident cases of diabetes and none considered impact on equity of healthcare provision.

Cost-effectiveness: Overall, lifestyle interventions and metformin appeared to be cost effective in preventing diabetes in high-risk individuals, as summarised in Table 3, though there was wide variation in economic estimates between studies. Substantial differences in participant selection and intervention design, which reflect the different types of pre-diabetes and different types of interventions, as well as differences in model structure, parameters and parameter values make comparison between studies difficult.

There is insufficient evidence to suggest that lifestyle interventions or metformin will be cost saving. Out of 27 studies, lifestyle interventions were found to be cost saving in 2 studies from a health system perspective (51,55), cost saving from a health system perspective in some countries but not others in 1 study (44) and cost saving from a societal perspective in 3 studies (50,54,60). Of the 12 studies evaluating metformin, 2 studies concluded metformin was cost saving from a health system perspective (38,44), 1 study concluded metformin was cost saving from a health system perspective in some countries

but not others (44) and 2 concluded metformin was cost saving from a societal perspective (37,59).

Lifestyle programmes appear to be cost effective. Of the 16 studies measuring effectiveness as £ per quality adjusted life years (£/QALY), the median incremental cost effectiveness ratio (ICER) from a health system perspective was £7,490/QALY (range: cost saving to £134,420/QALY) (Figure 2). Only 2 studies reported lifestyle interventions that were not cost effective (costing more than £20,000 per quality adjusted life year gained); of these, one used a model substantially different in structure to other modelling studies included (the Archimedes model, which analyses changes in biological variables, such as insulin resistance, rather than transitions between disease states, such as prediabetes, which are used by other models) (45) and the other included analysis lasting only 1 year therefore the benefits of reduced incidence of diabetes were not included (39).

Metformin also appears to be cost effective from a health system perspective. Of the 7 studies measuring effectiveness as £ per quality adjusted life years (£/QALY), the median incremental cost effectiveness ratio (ICER) from a health system perspective was £8,428/QALY (range: cost saving to £32,430/QALY). 2 studies reported metformin to not be cost effective (costing more than £20,000 per quality adjusted life year gained): of these, one used a model substantially different in structure to other modelling studies included (the Archimedes model) (45) and the other was the first economic model of the US Diabetes Prevention Programme (46). The subsequent models based on the US Diabetes Prevention Programme and its follow up study have found metformin to be cost saving or cost effective (37).

Twelve studies compared lifestyle programmes and metformin directly. From a health system perspective, neither intervention appears more cost-effective than the other with 6 studies reporting lifestyle programmes more cost effective than metformin (43, 46, 55, 52, 56, 58), 5 studies (45, 37, 63, 44, 53) reporting metformin more cost effective than lifestyle programmes and one (59) showing less than 1% difference in cost effectiveness between the two. However, from a societal perspective, metformin appears more cost-effective than lifestyle programmes, with four (59,37, 45, 56) out of the five (58) studies undertaking this analysis finding metformin more cost effective. This is because the cost of participants' time travelling to and attending lifestyle programme sessions is included in the calculations of cost from a societal perspective, but not from a health system perspective.

Given the range of screening and lifestyle interventions provided, and the range of cost effectiveness ratios, studies which reported ICERS as £/QALY from a health system perspective were grouped on a number of dimensions to identify key drivers of differences. The analyses revealed that:

1) Screening plus intervention studies tended to be less cost-effective than intervention-only studies on average, but both approaches were associated with a wide range of ICERs highlighting current uncertainties. Of the 10 studies that reported £/QALY from a health system perspective for intervention-only studies the median ICER was £4,606/QALY (range: cost saving to £134,420/QALY). And the

median ICER for the 8 screening-plus-intervention studies was £7,814/QALY (range: £573 - £76,566/QALY).

2) In general, the longer the period evaluated the more cost-effective the interventions appeared. Studies that measured cost-effectiveness over a period of 25 years or more appeared more cost effective (median ICER: £2,976/QALY) than studies that measured cost effectiveness over 10 years or less (median ICER: £10,416).
3) There was insufficient evidence to conclude whether lifestyle programmes with a duration of less than 2 years, 2-6 years or more than 6 years were more or less cost-effective: Of the 9 studies that included lifestyle programs with a duration of more than 2 years and less than 6 years the median ICER was £3,275/QALY (range: cost saving to £134,420/QALY). Three studies included interventions less than 2 years' duration with a wide variety of results (ICERs of £3,215 [38], £10,471 [40] and £76,566 [39]). And three reported interventions of more than six years' duration with a median ICER of £7,628/QALY (range: cost-saving to £15,191/QALY).
4) There was insufficient evidence to conclude whether higher frequency of contact during 'core sessions' was more or less cost-effective: Of the 11 studies that included lifestyle programs with 16 or more core sessions the median ICER was £7,628/QALY (range: cost saving to £134,420/QALY). Three studies reported £/QALYs for lifestyle programs with <16 core sessions with widely varying results (ICERs of £3,215 [38], £3,275 [41] and £76,566 [39]).
5) There was insufficient evidence to conclude whether group or individual core sessions were more or less cost-effective: Of the 11 studies that included the core component of the lifestyle programme delivered on an individual basis the median ICER was £7,628/QALY (range: cost saving to £134,420/QALY). Three studies included lifestyle programs where the core component was delivered in groups with a wide range of results (ICERs of -£6,214 [51], £3,215 [38], £3,275 [41] and £76,566 [39]).

There were insufficient studies in each group to conduct cost-effectiveness sub-group analysis by type of pre-diabetes. However, our meta-analysis of intervention trials suggests that this may be an important factor. Meta-analysis (Figure 2) showed that lifestyle interventions greater than or equal to 3 years duration for participants with IGT reduced the relative risk of developing diabetes by 45% (95% CI 28-57%). This translates to 241 out of 1000 people in the lifestyle intervention group developing diabetes compared to 301 out of 1000 in the usual care group. Lifestyle interventions lasting less than 3 years in participants with IGT showed a 26% (95% CIs 0 to 45%) relative risk reduction, equating to 171 (95% CI 129 to 172) out of 1000 people in the lifestyle intervention group developing diabetes compared to 255 of 1000 in the usual care group. There were insufficient studies to divide participants identified by other diagnostic criteria by duration of intervention. But for all studied that identified participants by IFG alone, IFG or IGT and presence of risk factors the relative risk of diabetes was reduced by 37% (95% CI 12%-55%), 23% (95% CI 5%-38%) and 11% (95% CI -0.2-22%) respectively. No studies used HbA1c alone as the diagnostic criteria for selecting participants.

Other measures impacting the 'value for money' judgement: Cost-effectiveness analysis only measures cost and benefit of an intervention for an individual participant. Policy makers, who are responsible for overall health budgets and the health of the population as a whole,

may consider other measures (such as budget impact, impact on equity and impact on incident cases of the disease) when evaluating the impact of an intervention. In terms of budget impact, three studies (42, 57, 58) estimated the cost of implementing a national diabetes prevention programme to be between 0.13 and 0.2% of annual national health expenditure in the Netherlands, Germany and Australia. Two studies (57, 51) modelled annual expenditures of lifestyle programmes, showing that net savings only exceeded net expenditures 9-14 years after initiating the prevention programme.

Failure to attend screening, enrol in an intervention or comply with an intervention means that the number of cases of diabetes prevented is lower than might be anticipated when extrapolating from trials. As a result of these factors, as well as the partial and finite impact of interventions, Icks (58) and Jacobs van der Bruggen (42) estimate that only 0.1-1.6% of cases of diabetes would be prevented by a population-wide programme in a region of Germany and the Netherlands respectively. As an example of how this population-wide impact is calculated, Icks calculated that 29% of incident cases of diabetes in 3 years would be due to people with pre-diabetes (defined as impaired glucose tolerance in this study). Of this pre-diabetic population, 30% of people would attend the screening test (OGTT), 40% and 59% would participate in the lifestyle intervention and metformin respectively, with 3.6% and 23.1% reduction in cumulative diabetes incidence at 3 years. 32% of these would develop diabetes in 3 years with no intervention and 9.3% and 28.8% would develop diabetes with lifestyle and metformin respectively which resulted in 0.2% of incident cases of diabetes being prevented by metformin and 0.8% by lifestyle programmes. These rates of attendance and enrolment are based on best estimates, a recent systematic review found significant variation in participation rates seen in studies of lifestyle programmes (74).

Quality, relevance/applicability and credibility of existing economic evaluations for current healthcare decision making: Evaluation of studies against ISPOR's Questionnaire to Assess Relevance and Credibility of Modelling studies for Healthcare Decision Making (28) (Appendix 4) raised a number of issues. The most important of these for policy makers are outlined below. No studies were excluded on the basis of this evaluation.

Relevance/applicability of included studies (Table 4): Given the variety of lifestyle programmes and range of different types of pre-diabetes, we examined the extent to which the included studies reflect national guidance in the UK and the US, and the areas in which they differ.

Health system context: 24 out of 27 studies were undertaken in high-income, predominantly Caucasian nations. Only two studies (60,64) were undertaken in developing countries, China and India.

Target population: Only 6 (39, 50, 51, 54, 61, 63) out of 27 studies used diagnostic tests for pre-diabetes that are in line with current UK guidance, that is HbA1c and fasting plasma glucose. The majority of studies, 16 out of 27 included participants with a positive oral glucose tolerance test (with or without fasting blood glucose). Prevalence differs between different types of pre-diabetes, with the potential to have a large impact on budgets. For example, one study in this review (48) compared the cost-effectiveness of different diagnostic tests and found that expanding the definition of pre-diabetes from IGT *and* IFG to IFG *or* IGT increased the number of eligible participants three-fold, with the savings from

reduced diabetes incidence insufficient to offset the increase in cost, with a resulting small reduction in cost-effectiveness.

Type of intervention: 21 of the 27 studies evaluated intensive trial-based interventions or intensive translations of trial interventions, which reflect current ADA guidance (lifestyle interventions modelled on the USDPP, targeting 7% weight loss). However, a review of community translations of the US DPP trial showed that whilst these translational programs cost less to implement they were also less effective (19,20). The modelling studies based on the USDPP trial data may therefore not be relevant comparators for a USDPP-based community programme. In contrast, the National Institute of Clinical Excellence in the UK and the Community Preventative Services Task Force in the US advocate a more pragmatic approach to lifestyle programmes. Only 3 studies (40, 38, 39) in this review are relevant comparators in terms of duration and intensity of lifestyle intervention and they report a wide range of cost effectiveness (from £3,215/QALY to £76,566). One study (39) (ICER £76,566) was an in-trial cost utility analysis over 1 year, therefore was unable to quantify the impact of the prevention programme on diabetes incidence. And one (38) assumed treatment effects equivalent to those seen in a trial of an intensive lifestyle programme.

Credibility of included studies: Two key issues emerged with the assessment of the credibility of the modelling studies included in this review: i) areas where updated evidence is available that may impact the evaluation and ii) areas where uncertainty persists and a range of assumptions are observed.

Availability of updated meta-analyses: 12 of the 21 modelling studies assumed reductions in diabetes incidence equivalent to that achieved in the US Diabetes Prevention Programme or Finnish Diabetes Prevention Study trials (relative risks of 0.50 at 3 years [15] and 0.40 at 6 years [16] respectively). However, two recent meta-analyses (71,72) (including both trial-based and translational pragmatic lifestyle interventions), have shown a relative risk of diabetes of 0.59 and 0.64. And a meta-analysis of pragmatic lifestyle interventions excluding large trials showed a relative risk of 0.74 (73). The higher the relative risk, the less the effect of the intervention, therefore these recent meta-analyses suggest that models based on DPP or DPS trial data will over-state the impact of interventions.

Key uncertainties regarding modelling assumptions: Firstly, uncertainty remains over the extent to which the reduction in diabetes incidence persists once the intervention has ended. Studies included in this review made a wide range of assumptions on this point, ranging from no effect after the intervention ended to effects persisting until the participant developed type 2 diabetes or died. One recent meta-analysis (72), showed relative risks of 0.80 at up to 20 years follow up. However, this analysis includes predominantly the large trials (US DPP, FDPS and Da Qing) as long term follow up data is not available on community-based translational studies. Therefore, this relative risk likely overstates the long term benefits of interventions outside the trial context. Secondly, uncertainty persists over the percentage of people that fail to enrol in lifestyle interventions following screening. Reflecting this uncertainty, 5 studies included in this review assumed 100% enrolment, 2 assumed between 50 and 99% and 5 assumed less than 50% enrolment. A recent systematic review (74) found that enrolment in interventions varies widely (from 0.28% to 100%) depending on method of communication, setting, and type of intervention. Finally, based on

included studies, the relationship between the type of pre-diabetes and cost-effectiveness of the study is unclear. A factor which may be important given the differences in relative risk reductions illustrated by our meta-analysis.

DISCUSSION:

Principal findings: This systematic review of economic evaluations of diabetes prevention programmes has produced seven major findings. First, that numerous economic evaluations have been undertaken in fifteen different countries and produced diverse results, due to differences in model structure and parameter values and to differences in health systems, types of prediabetes and types of lifestyle interventions included. Second, that the majority of evaluations relate to intensive trial-based interventions in populations in high-income countries identified with the oral glucose tolerance tests. Third, that with these caveats in mind, both metformin and lifestyle interventions in people with pre-diabetes appear to be cost-effective but not cost saving despite their impact on reducing diabetes incidence, with median ICERs of £8,428/QALY and £7,490/QALY respectively. To place this figure in context, smoking cessation services are estimated by NICE to have ICERs ranging from cost-saving to £984/QALY (98) and breast cancer screening is estimated to have an ICER of £20,800/QALY by the UK Panel on Breast Cancer Screening (99). The fact that diabetes prevention programmes are not cost saving is not due solely to the issue of discounting, as three studies (37, 52, 59) report undiscounted cost-effectiveness ratios with only one of those appearing cost saving. Fourth, that metformin and lifestyle programmes appear equally cost-effective when only the costs of the health system are taken into account, but metformin is more cost-effective when costs of participants' time (participating in and travelling to programme activities) is taken into account. Fifth, screening plus intervention programmes were less cost effective on average than intervention-only programmes. But both approaches were associated with a wide range of cost effectiveness ratios and the population benefit of screening in identifying people with previously undiagnosed prediabetes is not taken into account in a cost-effectiveness calculation. Sixth, there is insufficient evidence to deduce what intensity, duration or format or lifestyle programmes are more cost-effective than others. Finally, programmes that evaluated costs and benefits over 25 years or more were more cost effective than those that looked at 10 years or less.

Implications for policy makers: Meta-analyses show that the both the type of pre-diabetes and the type of lifestyle program have a substantial impact on the number of cases of diabetes that are delayed or prevented. Guidance in the UK and the US advocate lower intensity pragmatic lifestyle programmes. The small amount of evidence that these are cost-effective should be treated cautiously. In light of recent meta-analyses, historical studies are likely over-stating treatment effects and uncertainty over duration of impact limits accurate long-term modelling. Guidance in the UK advocates the use of fasting plasma glucose or HbA1c in identifying people with pre-diabetes. There is currently insufficient data to conclude that interventions in people identified solely with HbA1c are cost-effective, and no randomised controlled trials with HbA1c as the inclusion criteria to enable estimation of treatment effects. Given the emerging evidence that people with different types of pre-diabetes respond differently to the same intervention (68), studies on people identified with IGT should be interpreted cautiously when applying findings to a population defined with a

different test of pre-diabetes (such as HbA1c or fasting plasma glucose). In addition to these considerations of cost effectiveness, policy makers may need to balance impact on health budgets, incident cases of diabetes and equity of healthcare provision. In the few studies where these were modelled, budget impact was moderate (prevention programmes required 0.13-0.2% of respective countries total healthcare budget), financial payoffs were delayed (net expenditure on treatment and prevention of diabetes only declined after 9-14 years) and impact on incident cases of diabetes was limited (0.1-1.6% reduction in incident cases). Whilst none of these factors should be absolute barriers to implementation, they suggest policy makers should consider rigorous economic evaluation of national programmes including pragmatic lifestyle interventions aimed at people identified with HbA1c or IFG. And explore other avenues to reducing incident cases of diabetes if substantial inroads are to be made in controlling the diabetes 'epidemic'. These may include population-wide measures to address obesity, a primary determinant of progression to type 2 diabetes in a person with pre-diabetes (77).

Comparison with previous systematic reviews: Our findings confirm those of previous systematic reviews which have shown that lifestyle interventions are generally cost effective but with a wide range of cost effectiveness ratios, reflecting heterogeneity of interventions, target populations and modelling approaches. They have shown that lifestyle interventions appear more cost effective if group, rather than individual sessions, are provided and a long time horizon is adopted for analysis. They have raised the issue of the limited number of studies in developing countries, the concern that real-life implementation of programmes will be less effective than trial-based interventions, and the uncertainty that persists regarding long-term efficacy of these interventions. This review has added to previous work in three key areas: evaluation of metformin, comparison of screening plus intervention against intervention-only studies and consideration of the relevance and credibility of interventions for decision making.

SUGGESTIONS FOR FURTHER RESEARCH

This study has identified three areas where further research would be beneficial. Firstly, developing an understanding of how people with different types of pre-diabetes respond to interventions and the subsequent cost-effectiveness profiles for different diagnostic-treatment combinations. This could be undertaken in both modelling studies, using recent evidence from meta-analyses, or retrospective analysis of existing trial data where different types of pre-diabetes may co-exist (e.g. IGT and HbA1c, IGT and IFG or IGT only participants). Secondly, long-term follow up studies of pragmatic lifestyle intervention programmes are important to understand the duration of impact on diabetes incidence following cessation of studies, uncertainty in this area limits the accuracy of long-term modelling studies. Finally, consideration of the role of broader social and environmental programmes (e.g. sugar tax, increasing walkability of neighbourhoods) on diabetes incidence will be important as, based on studies in this review, individual lifestyle programs and metformin are unlikely to be sufficient to address the vast majority of incident cases of diabetes.

CONCLUSIONS:

National diabetes prevention policy in the UK and US advocates pragmatic lifestyle programmes (less than 3 years in duration), and in the UK the use of HbA1c or fasting

plasma glucose is recommended for diagnosing pre-diabetes. However, the majority of cost-effectiveness studies relate to a different definition of pre-diabetes and a higher intensity of intervention, which limits the direct applicability of findings. In the few studies that evaluated other economic considerations, budget impact of prevention programs was moderate (0.13-0.2% of respective countries total healthcare budget), financial payoffs were delayed (net expenditure on treatment and prevention of diabetes declined after 9-14 years) and impact on incident cases of diabetes was limited (0.1-1.6% reduction). There remains a need for long-term economic evaluation of programmes that reflect current policy and consideration of the role of broader social and environmental programmes on diabetes incidence.

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All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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REFERENCES

1. IDF, *International Diabetes Federation Diabetes Atlas*, International Diabetes Federation (IDF), 7th edition, 2015
2. Wild S et al. Global Prevalence of Diabetes: estimates for the year 2000 and Projections for 2030. *Diabetes Care* 27. 5 (2004): 1047-1053
3. WHO Diabetes Fact Sheet. Accessed at http://www.who.int/mediacentre/factsheets/fs312/en/ on 1st June 2016
4. Alberti KGMM, Zimmett P, Shaw International Diabetes Federation. A Consensus on Type 2 Diabetes Prevention. Diabet Med. 2007; 24: 451-63
5. P Zimmet, KG Alberti, J Shaw Global and societal implications of the diabetes epidemic. Nature. 2001; 414 (6865):782-787
6. Bagust A, Hopkinson PK, Maslove L, Currie CJ. The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060.Diabet Med. 2002 Jul;19 Suppl 4:1-5.
7. Yudkin J, Montori VM. The epidemic of pre-diabetes: the medicine and the politics. BMJ. 2014; 349: g4485
8. Faerch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired glucose tolerance: does it matter for treatment and prevention of type 2 diabetes. Diabetologica. 2009; 52: 1714-1723
9. Morris DH, Khunti K, Achana F, Srinivasan B, Gray LJ, Davies MJ, Webb D, Progression rates from HbA1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologica. 2013;56: 1489-1493
10. Yudkin JS, Montori VM. The epidemic of pre-diabetes: the medicine and the politics. Bmj. 2014;349:g4485
11. World Health Organization (2011) Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. World Health Organization, Geneva
12. American Diabetes Association. Standards of Medical Care in Diabetes 2016. Diabetes Care. 2016; 39: Suppl
13. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327– 1334
14. Noble D, Mathur R, Dent T, Meeds C, Greenhalgh T. Risk models and scores for Type 2 Diabetes: A systematic review. BMJ 2011;343:d7163
15. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393-403.
16. Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, et al, Finnish Diabetes Prevention Study Group. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care. 2003; 26:3230-6.
17. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997; 20:537-44.
18. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian

Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006; 49:289-97.

19. Ali MK, Echouffo-Tcheugui J, Williamson DF. How Effective Were Lifestyle Interventions In Real-World Settings That Were Modeled On The Diabetes Prevention Program? Health Affairs. 2012: 1 (31): 67–75
20. Kahn R, Davidson MB. The reality of Type 2 Diabetes Prevention. Diabetes Care. 2014;37(4):943-949
21. The Community Guide. Diabetes Prevention and Control: Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among People at Increased Risk. Atlanta, GA: Community Preventive Services Task Force; 2014. Accessed at www.thecommunityguide.org/diabetes/supportingmaterials/SScombineddietandpa-econ.html on 19 April 2015.
22. The NHS Diabetes Prevention Program accessed at https://www.england.nhs.uk/ourwork/qual-clin-lead/diabetes-prevention/
23. Alouki K, Delisle H, Bermudez-Tamayo C, Johri M, Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies Journal of Diabetes Research, 2016
24. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. Int J Environ Res Health. 2010 Aug;7(8):3150-95.
25. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010 Aug;33(8):1872-94.
26. Li R, Qu S, Zhang P, Chattopadhyay S, Gregg EW, Albright A, Hopkins D, Pronk NP. Economic Evaluation of Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Ann Intern Med. 2015 Sep 15;163(6):452-60.
27. Radl KI, Ianuale C, Boccia S. A systematic review of the cost-effectiveness of lifestyle modification as primary prevention intervention for diabetes mellitus type 2. Epidemiology Biostatistics and Public Health 2013 (10);2
28. Caro J, Eddy DM, Kan H et al. Questionnaire to Assess Relevance and Credibility of Modeling Studies for Informing Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. Value in Health. 2014;17: 174-182
29. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. 2006 Oxford University Press
30. Devlin N, Parkin P. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? Department of Economics Discussion Paper Series, City University. Accessed on 14.10.2016 on https://www.city.ac.uk/__data/assets/pdf_file/0015/90501/0301_devlin-parkin.pdf
31. Groose SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert Rev Pharmacoecon Outcomes Res. 2008;8:165-178
32. World Health Organisation. Macroeconomics and Health: Investing in Health for Economic Development. Geneva.: World Health Organisation; 2001
33. http://eppi.ioe.ac.uk/costconversion/default.aspx. Accessed on the 20th September 2016

34. Curtis B, Burns A. Unit Costs of Health and Social Care 2015. Personal Social Services Research Unit Accessed 14.10.2016 on http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php
35. National Institute of Clinical Excellence. Glossary. Accessed 14.10.2016 on https://www.nice.org.uk/Glossary
36. Robberstad B. QALYs vs DALYs vs LYs gained: What are the differences, and what difference do they make for health care priority setting? Norsk Epidemiologi 2005; 15 (2): 183-191
37. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care. 2012; 35:723-30
38. Smith KJ, Hsu HE, Roberts MS, Kramer MK, Orchard TJ, Piatt GA, et al. Cost-effectiveness analysis of efforts to reduce risk of type 2 diabetes and cardiovascular disease in southwestern Pennsylvania, 2005–2007. Prev Chronic Dis. 2010; 7:A109.
39. Irvine L, Barton GR, Gasper AV, Murray N, Clark A, Scarpello T, et al. Cost-effectiveness of a lifestyle intervention in preventing type 2 diabetes. Int J Technol Assess Health Care. 2011; 27:275-82
40. Feldman I, Hellström L, Johansson P. Heterogeneity in cost-effectiveness of lifestyle counseling for metabolic syndrome risk groups—primary care patients in Sweden. Cost Eff Resour Alloc. 2013; 11:19
41. Sagarra R, Costa B, Cabré JJ, Solà-Morales O, Barrio F, el Grupo de Investigación DE-PLAN-CAT/PREDICE. Lifestyle interventions for diabetes mellitus type 2 prevention. Rev Clin Esp (Barc). 2014; 214:59-68
42. Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, Hoogenveen RT, Vijgen SM, Baan CA. Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. Diabetes Care. 2007; 30:128-34
43. Caro JJ, Getsios D, Caro I, Klittich WS, O'Brien JA. Economic evaluation of therapeutic interventions to prevent type 2 diabetes in Canada. Diabet Med. 2004; 21:1229-36
44. Palmer AJ, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland, and the United Kingdom. Clin Ther. 2004; 26:304-21
45. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med. 2005; 143:251-64
46. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al, Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005; 142:323-32
47. Ackermann RT, Marrero DG, Hicks KA, Hoerger TJ, Sorensen S, Zhang P, et al. An evaluation of cost sharing to finance a diet and physical activity intervention to prevent diabetes. Diabetes Care. 2006; 29:1237-41
48. Hoerger TJ, Hicks KA, Sorensen SW, Herman WH, Ratner RE, Ackermann RT, et al. Cost-effectiveness of screening for pre-diabetes among overweight and obese U.S. adults. Diabetes Care. 2007; 30:2874-9

49. Hoerger TJ, Hicks KA, Sorensen SW, Herman WH, Ratner RE, Ackermann RT, et al. Cost-effectiveness of screening for pre-diabetes among overweight and obese U.S. adults. Diabetes Care. 2007; 30:2874-9
50. Lindgren P, Lindström J, Tuomilehto J, Uusitupa M, Peltonen M, Jönsson B, et al, DPS Study Group. Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective. Int J Technol Assess Health Care. 2007; 23:177-83
51. Zhuo X, Zhang P, Gregg EW, Barker L, Hoerger TJ, Tony Pearson-Clarke, et al. A nationwide community-based lifestyle program could delay or prevent type 2 diabetes cases and save $5.7 billion in 25 years. Health Aff (Millwood). 2012; 31:50-60
52. Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT, et al. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. BMJ. 2008; 336:1180-5
53. Bertram MY, Lim SS, Barendregt JJ, Vos T. Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care. Diabetologia. 2010; 53:875-81
54. Neumann A, Schwarz P, Lindholm L. Estimating the cost-effectiveness of lifestyle intervention programs to prevent diabetes based on an example from Germany: Markov modelling. Cost Eff Resour Alloc. 2011; 9:17
55. Palmer AJ, Tucker DM. Cost and clinical implications of diabetes prevention in an Australian setting: a long-term modeling analysis. Prim Care Diabetes. 2012; 6:109-21
56. Png ME, Yoong JS. Evaluating the cost-effectiveness of lifestyle modification versus metformin therapy for the prevention of diabetes in Singapore. PLoS One. 2014; 9:e107225
57. Colagiuri S, Walker AE. Using an economic model of diabetes to evaluate prevention and care strategies in Australia. Health Aff (Millwood). 2008; 27:256-68
58. Icks A, Rathmann W, Haastert B et a', Clinical and cost-effectiveness of primary prevention of Type 2 diabetes in a real world routine healthcare setting: model based on the KORA survey 2000. Diabetic Med 2007; 24(5):473-80
59. Herman WH, Edelstein SL, Ratner RE et al, Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. Am J Manag Care 2013; 19(3):194-202
60. Liu X, Li C, Gong H et al, An economic evaluation for prevention of diabetes in a developing country: a modelling study. BMC Public Health 2013; 13(279)
61. Mortaz S, Wessman C, Duncan R, Gray R, Badawi A. Impact of screening and early detection of impaired fasting glucose tolerance and type 2 diabetes in Canada: A Markov model simulation. Clinicoecon and Outcomes Research. 2012;4:91-97
62. Schaufler TM, Wolff M Cost effectiveness of preventive screening programs for type 2 diabetes mellitus in Germany. Appl Health Econ Health Policy. 2010;8(3):191-202
63. Dall TM, Storm MV, Semilla AP, Wintfield N, O'Grady M, Narayan KM, Value of lifestyle intervention to prevent diabetes and sequelae. Am J Prev Med. 2015 Mar;48(3):271-80
64. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial

results of the Indian Diabetes Prevention Programme (IDPP). Diabetes Care. 2007 Oct;30(10):2548-52.
65. Sculpher MJ, Pang FS et al. Generalisability in Economic Evaluations studies in healthcare: a review and case studies. Health Technol Assess. 2004;8: 1-192
66. Daniels N, Porteny T, Urritia J. Expanded HTA: Enhancing Fairness and Legitimacy. Int J Health Policy Manag. 2016; 5(1): 1–3
67. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programmes: learnings from the last 15 years Implementation Science 2015 10:172
68. Diabetes Prevention Program Research Group. HbA1c as a Predictor of Diabetes and as an Outcome in the Diabetes Prevention Program: A Randomized Clinical Trial. Diabetes Care. 2014. Suppl. DOI: 10.2337/dc14-0886
69. National Institute for Health and Care Excellence. Type 2 diabetes: prevention in people at high risk. NICE Guideline PH 38. Accessed at https://www.nice.org.uk/guidance/ph38 on 20.3.16.2012
70. National Institute of Clinical Excellence. Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. Costing template. July 2012. Accessed on 07.09.2016 at https://www.nice.org.uk/guidance/ph38/resources/costing-report-68964013
71. Balk EM et al. Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Annals of Internal Medicine. 2015;163 doi:10.7326/M15-0452
72. Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh TCan type 2 diabetes be prevented using screen-and-treat policies? Systematic review and meta-analysis of screening tests and interventions for pre-diabetes. Submitted for publication
73. Ashra NB, Spong R, Carter P, et al. *A systematic review and meta- analysis assessing the effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes mellitus in routine practice*. London: Public Health England, 2015. Accessed 01.10.15 on https://www.gov.uk/government/publications/diabetes-prevention-programmes-evidence-review
74. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programs: learnings from the last 15 years Implementation Science 2015 10:172
75. Balk EM et al. Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Annals of Internal Medicine. 2015;163 doi:10.7326/M15-0452
76. Ashra NB, Spong R, Carter P, et al. *A systematic review and meta- analysis assessing the effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes mellitus in routine practice*. London: Public Health England, 2015. Accessed 01.10.15 on https://www.gov.uk/government/publications/diabetes-prevention-programmes-evidence-review
77. Cobiac LJ, Veerman L, Vos T. The Role of Cost-Effectiveness Analysis in Developing Nutrition Policy. Annu Rev Netr 2013;33: 373-93

78. Yates T, Davies M, Gorely T, Bull F, Khunti K. 2009. Effectiveness of a pragmatic education program designed to promote walking activity in individuals with impaired glucose tolerance. Diabetes Care, 32, 1404-1410
79. Parikh P, Simon EP, Fei K, Looker H, Goytia C, Horowitz CR. 2010. Results of a pilot diabetes prevention intervention in East Harlem, New York City: project HEED. Am J Public Health, 100, s232-s239.
80. Iqbal Hydrie MZ,Basit A,Shera AS,Hussain A. Effect of intervention in subjects with high risk of diabetes mellitus in Pakistan. J Nutr Metab. 2012;2012:867604. [PMID: 22888411] doi:10.1155/2012 /867604
81. Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, et al. Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. The Lancet Diabetes & Endocrinology. 2013;1(3):191-8
82. Oldroyd JC, Unwin NC, White M, Mathers JC, Alberti K. Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance. Diabetes research and clinical practice. 2006;72(2):117-27
83. Penn L, White M, Oldroyd J, Walker M, Alberti KGM, Mathers JC. 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(1):1
84. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar A, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289-97
85. Roumen C, Corpeleijn E, Feskens EJM, Mensink M, Saris WHM, Blaak EE. Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine. 2008;25(5):597-605
86. Sakane N, Sato J, Tsushita K, Tsujii S, Kotani K, Tsuzaki K, et al. Prevention of type 2 diabetes in a primary healthcare setting: three-year results of lifestyle intervention in Japanese subjects with impaired glucose tolerance. BMC Public Health. 2011;11(1):40
87. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract. 2005 Feb;67(2):152-62
88. Eriksson KF, Lindgarde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. Diabetologia. 1991 Dec;34(12):891-8
89. Katula JA, Vitolins MZ, Morgan TM, Lawlor MS, Blackwell CS, Isom SP, et al. The Healthy Living Partnerships to Prevent Diabetes study: 2-year outcomes of a randomized controlled trial. Am J Prev Med. 2013 Apr;44(4 Suppl 4):S324-32
90. Ma J, Yank V, Xiao L, Lavori PW, Wilson SR, Rosas LG, et al. Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Intern Med. 2013;173:113-21
91. Saito T, Watanabe M, Nishida J, et al. Lifestyle modification and prevention of type 2 diabetes in overweight japanese with impaired fasting glucose levels: A randomized controlled trial. Archives of Internal Medicine. 2011;171(15):1352-60
92. Xu DF, Sun JQ, Chen M, Chen YQ, Xie H, Sun WJ, et al. Effects of lifestyle intervention and meal replacement on glycaemic and body-weight control in Chinese subjects

with impaired glucose regulation: a 1-year randomised controlled trial. The British journal of nutrition. 2013 Feb 14;109(3):487-92

93. Bhopal RS, Douglas A, Wallia S, Forbes JF, Lean ME, Gill JM, et al. Effect of a lifestyle intervention on weight change in south Asian individuals in the UK at high risk of type 2 diabetes: a family-cluster randomised controlled trial. The Lancet Diabetes & Endocrinology. 2014;2(3):218-27
94. Davies MJ, Gray LJ, Troughton J, Gray A, Tuomilehto J, Farooqi A, et al. A community based primary prevention programme for type 2 diabetes integrating identification and lifestyle intervention for prevention: The Let's Prevent Diabetes cluster randomised controlled trial. Preventive medicine. 2016 Mar;84:48-56
95. Costa B, Barrio F, Cabre´ JJ, Pin˜ol JL, Cos X, Sole´ C, et al; DEPLAN-CAT Research Group. Delaying progression to type 2 diabetes among high-risk Spanish individuals is feasible in real-life primary healthcare settings using intensive lifestyle intervention. Diabetologia. 2012;55:1319-28
96. Ockene IS, Tellez TL, Rosal MC, Reed GW, Mordes J, Merriam PA, Olendzki BC, Handelman G, Nicolosi R, Ma Y. 2012. Outcomes of a Latino community-based intervention for the prevention of diabetes: the lawrences latino diabetes prevention project. Am J Public Health, 102, 336-342
97. Vermunt PW, Milder IE, Wielaard F, de Vries JH, van Oers HA, Westert GP. Lifestyle counseling for type 2 diabetes risk reduction in Dutch primary care: results of the APHRODITE study after 0.5 and 1.5 years. Diabetes Care. 2011;34:1919-25
98. National Institute of Clinical Excellence. Cost effectiveness of Interventions for Smoking Cessation: Final Report. 2007
99. Pharoah P, Sewell B, Fitzsimmons D, Bennett HS, Pashayan N. Cost effectiveness of the NHS breast screening programme: life table model. BMJ 2013;346:f2618

Figure 1- PRISMA Flow diagram

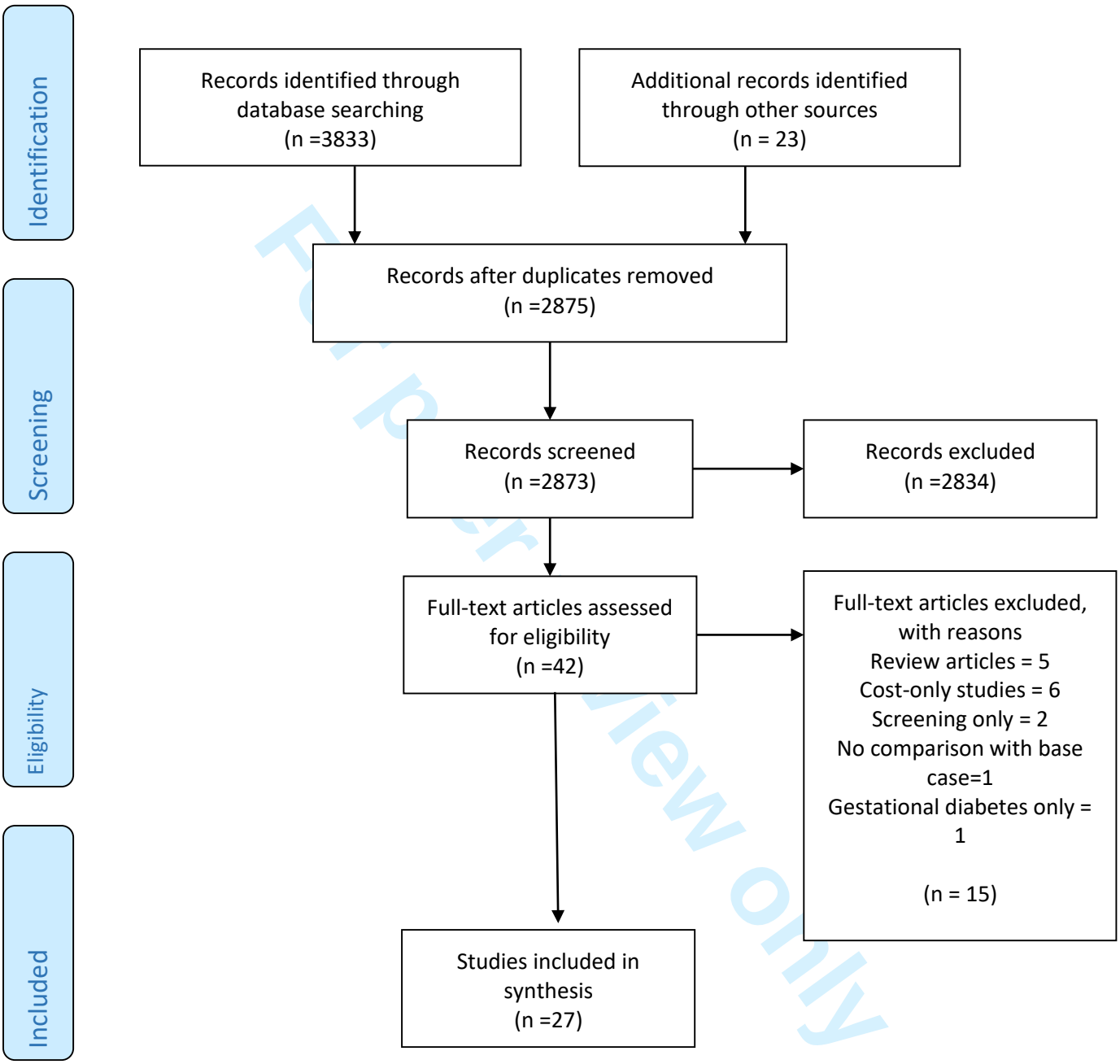


Table 1: Diagnosis of Pre-diabetes

Type of pre-diabetes	*Description*	*Diagnostic test used*	*Criteria for diagnosis*			*Incidence of T2DM (per person-year)* (9)
			WHO (11)	*ADA* (12)	*IEC* (13)	
Impaired glucose tolerance	High blood glucose 2-hours after a drink containing 75g of sugar (e.g. Lucozade)	Oral glucose tolerance test	2-hour post-load glucose of 7-11.1 mmol/L	2-hour post-load glucose of 7-11.1 mmol/L	N/A	0.045
Impaired fasting glucose	High blood glucose following a period of fasting	Fasting plasma glucose	6.0-6.9 mmol/L	5.6-6.9 mmol/L	N/A	WHO criteria: 0.047 ADA criteria: 0.036
HbA1c 'at risk' range	Glycated haemoglobin which estimates blood glucose levels over the previous 2-3 months	HbA1c	6.0-6.4%	5.7-6.4%	6.0-6.4%	WHO criteria: 0.036
Impaired glucose tolerance AND impaired fasting glucose	As above	Fasting plasma glucose AND oral glucose tolerance test	2-hour post-load glucose: 7-11.1 mmol/L and Fasting plasma glucose: 6.0-6.9 mmol/L	2-hour post-load glucose: 7-11.1 mmol/L and Fasting plasma glucose: 5.6-6.9 mmol/L	N/A	0.70

WHO: World Health Organisation, IEC: International Expert Committee, ADA: American Diabetes Association.

Table 2: Lifestyle programmes evaluated in studies in this review

A. INTENSIVE TRIAL-BASED LIFESTYLE PROGRAMMES					
Clinical trial on which intervention is based	**Included studies in this review**	**Number of sessions**	**Length of intervention**	**Staff delivering programme**	**Group or individual**
US Diabetes Prevention Program (US DPP)	Palmer, 2004 Eddy, 2005 Herman, 2005 Ackermann, 2006 Hoerger, 2007 Schaufler, 2010 Mortaz, 2012 Png, 2014	16 core sessions Monthly follow-up	2.8 years	Exercise physiologists, dieticians, case managers	Predominantly individual
US Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study (US DPP and DPPOS)	DPPRG, 2012 Palmer, 2012 Dall, 2015 Herman, 2013	Years 1-3: 16 core sessions, monthly follow up Year 4: 16 session group programme Years 5-10: Quarterly 1-hour group sessions, 2 additional 'BOOST' sessions per year for participants originally randomised to lifestyle group	10 years	Exercise physiologists, dieticians, case managers	Individual and group
Finnish DPS lifestyle program (FDPS)	Caro, 2004	Year 1: 7 visits Year 2 onwards: 4 visits p.a. YMCA gym membership to enable 2 supervised exercise sessions per week	5 years	Dietician	Individual dietician visits, group exercise sessions
	Lindgren, 2007	Year 1: 7 visits Year 2 onwards: 4 visits p.a. Supervised circuit type training	6 years	Nutritionist	Individual visits, group exercise sessions

	Bertram, 2010	Weekly visits for 1 month, monthly for a further 3 months, quarterly thereafter	As long as participant has IGT	Dietician, exercise physiologist	Individual
Indian Diabetes Prevention Programme (IDPP)	Ramachandran, 2007	Individual sessions twice a year Monthly phone calls	3 years	Dieticians, CHW workers and helpers	Individual
Da Qing Lifestyle Program	Liu, 2002	Individual counselling by physicians or group counselling in 9 sessions/year	6 years	Physicians	Individual and group
DE-PLAN-CAT/PREDICE	Sagarra, 2013	4x90 minute teaching sessions Reinforced with telephone calls, text messages, letters and interviews every 6-8 weeks.	4.2 years	Doctors and nurses	Individual or group
TRANSLATIONAL COMMUNITY-BASED LIFESTYLE PROGRAMMES					
Community-based translations of USDPP	Icks, 2007	16 core sessions in community setting Monthly follow-up	3 years	Diabetologists and dieticians	NR
	Zhuo, 2012	Nation-wide program Year 1: 16 core sessions, post-core sessions every 6 months Year 2: 8 maintenance sessions Year 3: 1-2 sessions	3 years	Lifestyle coaches in year 1 and 2, any health care provider thereafter	Group
	Smith, 2010	12 sessions	12-14 week intervention, 1 year follow up	Health professionals, lay workers	Group
Hypothetical lifestyle program	Neumann, 2011	8 core sessions Follow up: quarterly sessions, monthly calls or emails, newsletter, quarterly journal	5 years	Prevention managers	Group

UEA-IFG	Irvine, 2011	4 core education sessions and group exercise sessions Peer support groups Telephone peer support from volunteers	7 months	Physiotherapists, diabetes prevention facilitators, volunteers, people with T”DM for more than 2 years)	
Kalmar Metabolic Syndrome Program	Feldman, 2013	NR	1 year	NR	NR

Table 3: Incremental cost-effectiveness ratios

ICERS - LIFESTYLE INTERVENTION								
Author, year of publication	**Duration of analysis**	**ICER in 2015 GBP Health system perspective**			**Cost elements included in ICER from societal perspective**	**ICER in 2015 GBP Societal perspective**		
		Range (in base case)	**Mean ICER**	**Unit**		**Range** (in base case)	**Mean ICER**	**Unit**
Herman, 2005 – DPP	Lifetime	1,057	1,057	£/QALY				
Eddy, 2005	30 years	134,420	134,420	£/QALY	Not specified		58,844	£/QALY
Diabetes Prevention Programme Research Group, 2012	10 years	7,628	7,628	£/QALY	Participant time, food, food preparation and exercise equipment and classes.	£ 10,917	£ 10,917	£/QALY
Ackermann, 2006	Lifetime	1,210-1,480	1,345	£/QALY				
Palmer, 2012	Lifetime	Cost saving	Cost saving	£/QALY				
Png, 2014	3 years	12,544	12,544	£/QALY	Participant time, transport costs, fitness equipment, food costs and food preparation costs, days of work lost due to T2DM	26,764	26,764	£/QALY
Lindgren, 2007	Lifetime				Participant time, travel and work absence	-£ 8,709	-£ 8,709	£/QALY
Hoerger, 2007	Lifetime	7,526-8,750	8,138	£/QALY	Not specified	15,03[illegible]-17,275	16,156	£/QALY

Liu, 2013	Lifetime simulation				Transport, lost income, cost of home care	Cost saving (-1,194 to -93)	Cost saving (-2,062)	£/QALY
Gilles, 2008	50 years	7,490	7,490	£/QALY				
Neumann, 2011	Lifetime				Participant transport	Cost saving (-1,359 to -321)	Cost saving (-23,490)	£/QALY
Smith, 2010	3 years	3,215	3,215	£/QALY				
Feldman, 2013	Simulation until 85 years of age	3,140 - 17,802	10,471	£/QALY	Participant and transport and non-healthcare organisations costs	Cost saving to 281	8,641	£/QALY
Jacobs Van der Bruggen, 2007	70 years	3,822-5,390	4,606	£/QALY				
Irvine, 2011	1 year	76,566	76,566	£/QALY				
Sagarra, 2013	4 years	3,275	3,275	£/QALY				
Schaufler, 2010	Lifetime	573	573	£/QALY				
Mortaz, 2012	10 years	10,416	10,416	£/QALY				
Zhuo, 2012	25 years	Cost saving (-6,149)	Cost saving (-6,149)	£/QALY				
Herman, 2013	10 years	15,191	15,191	£/QALY	Food, food preparation equipment, exercise classes, gym memberships, personal trainers and exercise equipment, transport, participant time	2,459	2,459	£/QALY

Dall, 2015	10 years intervention and analysis				Years of employment, household and personal income, missed work days and disability benefit payments	£R	NR	£/QALY
Palmer, 2004	Lifetime	Cost saving to 8,614	1,783	£/LYG				
Caro, 2004	10 years	577	577	£/LYG				
Bertram, 2010	Age 100 or death	15,460	15,460	£/DALY				
Colagiuri, 2008	10 years				Not specified		37,285	£/DALY
Icks, 2007	3 years	4,003	4,003	£/case of T2DM avoided	Participant and healthcare professionals' time	23,183	23,183	Cost per case of T2DM avoided

ICERS – METFORMIN							
		METFORMIN - ICER in 2015 GBP Health system perspective			**METFORMIN - ICER in 2015 GBP Societal perspective**		
Author, year of publication	**Duration of analysis**	**Range** (base case)	**Mean**	**Unit**	**Range** (base case)	**Mean**	**Unit**
Herman, 2005	Lifetime	29,409	29,409	£/QALY			
Eddy, 2005	30 years	32,430	32,430	£/QALY	33,392	33,392	£/QALY
Diabetes Prevention Programme Research Group, 2012	10 years	Cost saving	Cost saving	£/QALY	Cost saving	Cost saving	£/QALY
Palmer, 2012	Lifetime	5,477	5,477	£/QALY			

Png, 2014	3 years	15,371	15,371	£/QALY	4,648	4,648	£/QALY
Gilles, 2008	50 years	8,428	8,428	£/QALY			
Schaufler, 2010	Lifetime	332	332	£/QALY			
Herman, 2013	10 years	15,339	15,339	£/QALY	Cost saving (-10,735)	Cost saving (-10,735)	£/QALY
Palmer, 2004	Lifetime simulation	7,290	7,290	£/LYG			
Caro, 2004	10 years	Cost saving (-5,495)	Cost saving (-5,495)	£/LYG			
Bertram, 2010	Age 100 or death	14,960	14,960	£/DALY			
Icks, 2007	3 years	16,296	16,296	Cost per case of T2DM avoided	27,281	27,281	Cost per case of T2DM avoided

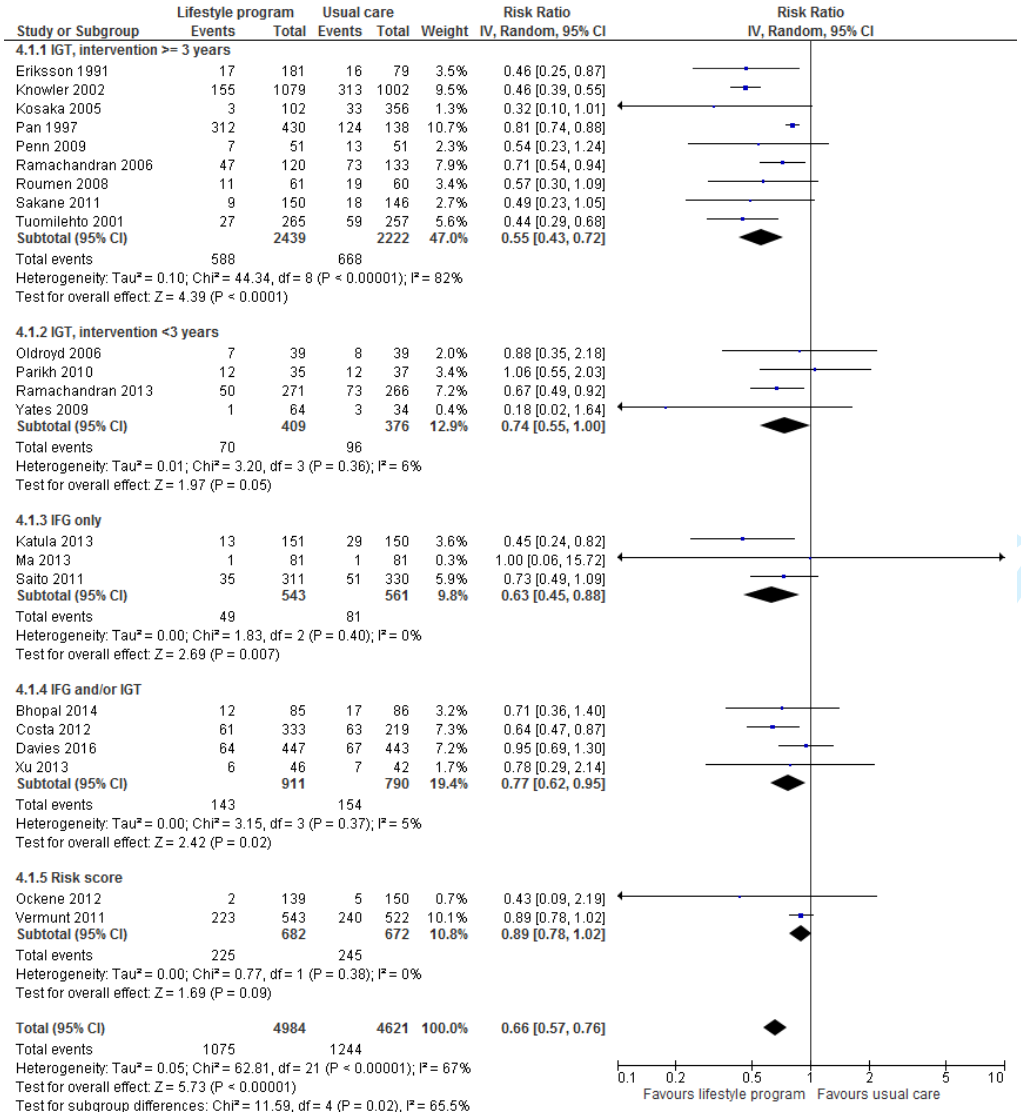
Table 4: Relevance of included studies

(Numbers refer to the number of studies in this review in each category. Some studies may be included in more than one category, for example if the study took place across multiple countries or used multiple diagnostic tests).

HEALTH SYSTEM CONTEXT								
	US	UK	Europe	Australia	Canada	Singapore	India	China
Which health system?	9	3	8	3	2	1	1	1
TARGET POPULATION								
	IGT (+/- IFG)	IFG		IFG or IGT	HbA1c	Other (e.g. risk score)	*Current guidance*	
Which diagnostic test for pre-diabetes?	16	5		2	2	3	**UK**: IFG or HbA1c for diagnosis **ADA:** IFG, IGT, or HbA1c for diagnosis	
TYPE OF INTERVENTION/S EVALUATED								
	Trial-based lifestyle programme	Pragmatic lifestyle programme	Not stated	*Current guidance*				
Trial-based lifestyle or pragmatic lifestyle?	18 trial based 3 translations of trials	3	3	**UK: Pragmatic lifestyle programmes**: Group lifestyle programme with 16 hours of contact time over 9-18 months and regular follow up for up to 2 years **US**: **Pragmatic lifestyle programmes**: Counselling, coaching and extended support relating to diet and physical activity for at least 3 months provided by trained staff in clinical or community settings **ADA:** Intensive diet and physical activity behavioural counselling programme adhering to the tenets of the Diabetes Prevention Programme (DPP) targeting a loss of 7% of body weight and an increasing moderate-intensity physical activity (such as brisk walking) to at least 150 min/week				

Sources: ADA: Standards of Medical Care in Diabetes (12), UK: NICE guidance (69), US: Community Preventative Services Task Force recommendations (21)

Figure 2: Lifestyle programme's effect on diabetes incidence (15-18, 77-97)



APPENDIX 1: SUMMARY OF INCLUDED STUDIES

OGTT = oral glucose tolerance test, FPG= fasting plamsa glucose, DPP = diabetes prevention programme, DPS=diabetes prevention study, IFG=impaired fasting gluose, IGT=impaired glucose tolerance											
First author	**Year of publication**	**Country**	**Type of study**	**Population size**	**Target Group**	**Lifestyle/ Metformin**	**Duration of intervention**	**Duration of intervention + follow up analysis**	**ICER (health system)**	**ICER (society)**	**Measure of effectiveness: QALY/DALY/LYG**
STUDIES BASED ON US DPP, DPPOS OR MODIFIED DPP											
Herman	**2005**	US	Clinical trial (Diabetes Prevention Program) + Lifetime simulation (Markov model)	3234 in clinical trial	IGT +IFG >25 years BMI>24kg/m2	a. Lifestyle	2.8 years	Lifetime simulation	$1,124 per QALY	NA	QALY
						b. Metformin	2.8 years	Lifetime simulation	$31,286 per QALY	NA	QALY
Eddy	**2005**	US	Simulation model (Archimedes)	10,000 people in Kaiser Permenente	IGT + IFG BMI>24kg/m2	a. DPP lifestyle program	2.8 years	30 years	$143,000/QALY	$62,600	QALY
						b. DPP metformin	2.8 years	30 years	$35,400/QALY	$35,523	QALY

DPPRG	**2012**	US	10-year, within-trial, intention-to-treat analysis	DPP: 3,234 DPPOS: 2,766	IGT + IFG >25 years BMI>24kg/ m2	a. Lifestyle	DPP: 3.2 years DPP/DPP OS bridge: 1 year DPPOS maintenance: 6 years	10 years	$10,037/QALY ($6,651 undiscounted)	$14,365/QALY (£11,274 undiscounted)	QALY
						b. Metformin			Cost saving	Cost saving	QALY
Ackermann	**2006**	US	Markov model	3,234	IGT, 50 years old	a. DPP lifestyle intervention: participants aged 50 years	Until participant gets DM or dies	Lifetime simulation	$1288/QALY		QALY
						b. DPP lifestyle intervention: participants aged 65 years		Lifetime simulation	$1575/QALY		QALY
Palmer	**2004**	Australia, France, Germany, Switzerland and the United Kingdon	Markov model simulation	Cohort based on US DPP (average age 50.6 yrs, mean BMI 34.0 kg/m2, 32.2% men)	IGT Mean age: 50.6 years 32.2% men Mean BMI: 34kg/m2	a. DPP lifestyle intervention	3 years	Lifetime simulation	Euro 6381/LYG in the UK Cost saving in Australia, Switzerland, France and Germany		LYG
						b. Metformin	3 years	Lifetime simulation	Euro 5400/LYG in the UK Cost saving in Australia, Switzerland, France and Germany		LYG

Palmer	**2012**	Australia	Markov model (TreeAge Pro)	Cohort based on US DPP (average age 50.6 yrs, mean BMI 34.0 kg/m2, 32.2% men)	IGT +/- IFG	a. US DPP lifestyle intervention, then DPP/DPPOS bridge and DPPOS	DPP: 3.2 years DPP/DPP OS bridge: 1 year DPPOS maintenance: 6 years	Lifetime simulation	Cost saving		QALY
						b. Metformin, then DPP/DPPOS bridge and DPPOS		Lifetime simulation	CAU $10,142		QALY
Png	**2014**	Singapore	Decision tree in Excel	Cohort based on US DPP	IGT +/- IFG	a. US DPP lifestyle intervention	3 years	3 years	$17,184/QALY	$36,663/QALY	QALY
						b. Metformin	3 years	3 years	$21,065/QALY	$6,367/QALY	QALY
STUDIES BASED ON FINNISH DPS OR MODIFIED DPS											
Lindgren	**2007**	Sweden	Markov model (evaluated using Monte Carlo simulation) based on Finnish Diabetes Prevention Study	397	60-year olds in the County of Stockholm with BMI>26mg/m2 and IFG	Lifestyle Program used in the Finnish Diabetes Prevention Study	6 years	Lifetime simulation		Cost saving (Euro -9265 per QALY Euro -14,692 per QALY undiscounted)	QALY

Caro	**2004**	Canada	Markov model	NA	IGT	a. Intensive lifestyle intervention (based on Finnish DPS)	5 years	10 years	$749/LYG		QALY
						b. Metformin	5 years	10 years	Cost saving (-$7136/LYG)		QALY
						c. Acarbose	5 years	10 years	Cost saving (-$4485/LYG)		QALY
STUDIES BASED ON INDIAN DPP											
Ramachandran	**2007**	India	Within-trial analysis	531	IGT (2 positive OGTTs in 35-55 year olds)	a. Lifestyle modification	3 years	3 years			Number needed to treat to prevent 1 case of T2DM
						b. Metformin	3 years	3 years			
						c. Lifestyle modification and metformin	3 years	3 years			
STUDIES INCLUDING SCREENING + INTERVENTION BASED ON US DPP OR DPPOS											
Hoerger	**2007**	US	Markov simulation model	Population cohort based on 1999-2000 NHANES	IFG and/or IGT US adults aged 45-74 with BMI>=25kg/m2.	1. Screening and DPP lifestyle for IFG and FPG	Intervention until T2DM develops	Lifetime simulation	$8,181/QALY	$16,345/QALY	QALY
						2. Screening and DPP for IFG or IGT or IFG and IGT	Intervention until T2DM develops	Lifetime simulation	$9,511/QALY	$18,777/QALY	QALY
Icks	**2007**	Germany	Decision analytic model	72,435	IGT +/- IFG Aged 60-74 years	1. Lifestyle program as in USDPP	3 years	3 years	£3,127/case of T2DM avoided	£18,112/case of T2DM avoided	Number of cases of

					BMI >=24kg/m2	2. Metformin	3 years	3 years	£12,731/case of T2DM avoided	£21,313/case of T2DM avoided	diabetes avoided
Schaufler	**2010**	Germany	Markov model (TreeAge Pro)	1 million individuals modelled	IGT	1. Lifestyle program as in USDPP	Not specified	Lifetime simulation	Euro 562/QALY		QALY
						2. Metformin	Not specified	Lifetime simulation	Euro 325/QALY		QALY
Zhou	**2012**	US	Markov model	Eligible population in the US	18-64 yrs, CDC diabetes risk test if BMI>=25kg/m2, if positive FPG or HbA1c	Community based lifestyle intervention (PLAN4WARD)	3 years	25 years	Cost saving		QALY
Mortaz	**2012**	Canada	Markov model (in TreeAge)	NA	IFG	Screening with FPG every 3 years followed by US DPP based lifestyle intervention or metformin	Not specfified	10 years analysis	CA$16,800/QALY		QALY
Herman	**2013**	US	10-year, within-trial, inention-to-treat analysis: DPP and DPPOS	3,234 participants in DPP	IGT +/- IFG BMI>24mg/kg Screen 45-74 year olds RCBG,	a. USDPP lifestyle intervention (individual sessions) and USDPPOS	DPP: 3.2 years DPP/DPP OS bridge: 1 year DPPOS	10 years	$19,988/QALY (cost-saving if undiscounted)	$3,235/QALY (undisounted)	QALY

					follow up OGTT	b. USDPP lifestyle intervention (in groups) and USDPPOS	maintenance: 6 years		9,688/QALY (cost saving if undiscounted)	Cost saving (undiscounted)	QALY
						b. USDPPOS Metformin			20,183 (cost saving if undiscounted)	Cost saving (undiscounted)	QALY
Dall	**2015**	US	Markov microsimulation model	Adults in the US	Elevated HbA1c (5.7-6.4%)	USDPPOS	10 years	10 years		Cost saving	QALY
STUDIES INCLUDING SCREENING + DA QING INTERVENTION											
Liu	**2013**	China	Markov model	NA	IFG and IGT	a. Screening with diet intervention	6 years	40 years		Initiation age: 25yrs: -- $2,044/QALY 40 yrs: -$1,527/QALY 60 yrs: -3,602/QALY	QALY
						b. Screening with exercise intervention	6 years	40 years		Initiaton age: 25: -$2,063/QALY 40: -$1,540/QALY 60: -$3,713/QALY	QALY

						c. Screening with duo intervention	6 years	40 years		Initiation age 25 yrs: -$2,061/QALY 40 yrs: -$1,507/QALY 60 yrs: -$3,713/QALY	QALY
						d. Screening alone	6 years	40 years		Initiation age 25 yrs: -$471/QALY 40 yrs: -$331/QALY 60yrs: -$1,195/QALY	QALY
STUDIES INCLUDING SCREENING + FINNISH DPS											
Bertram	**2010**	Australia	Discrete-time microsimulation model	8,000 individual life histories simulated	IGT and IFG (Opportunistic screening of Australians over the age of 45 years with risk factors for T2DM during GP visit for another reason using FPG followed by confirm-atory OGTT)	a Diet plus exercise	As long as a partici-pant remains pre-diabetic	Until age 100 or death	AU$23,000/DALY		DALY
						b. Exercise		Until age 100 or death	AU$30,000/DALY		DALY
						c. Diet		Until age 100 or death	AU$38,000/DALY		DALY
						d. Acarbose		Until age 100 or death	AU$37,000/DALY		DALY
						e. Metformin		Until age 100 or death	AU$22,000/DALY		DALY
						f. Orlistat		Until age 100 or death	AU$100,000/DALY		DALY

						g. Metformin plus diet and exercise		Until age 100 or death	AU$81,000/DALY		DALY
STUDIES INCLUDING SCREENING + OTHER INTERVENTION >2 YEARS DURATION											
Neumann	**2011**	Germany	Trial based cost utility analysis	NA	IFG and T2DM (FPG screening: 45-70 year-olds with elements of metabolic syndrome or GDM)	Group lifestyle program	5 years	Lifetime simulation		Age 30: Men (-Eur25,164), Women (Eur -31,407) Age 50: Men (Eur -15,108), Women (Eur -21,215) Age 70: Men (Eur 27,546), Women (Eur 19,433)	QALY
Sagarra	**2013**	Spain	Trial-based cost utility analysis	552 participants in trial 230 in group-based intervention 103 in individual intervention	IGT and/or IFG in people aged 45-75 identified with FINDRISC >14 or requesting OGTT regardless of FINDRISC score Av age: 62 yrs, Av BMI: 31kg/m2	1. Group intensive lifestyle program 2. Individual intensive lifestyle programme	5 years: 1 year: Screening 4 years: Intervention	Median: 4.2 years No analysis post-intervention	Euro 3243/QALY		QALY
STUDIES INCLUDING SCREENING + INTERVENTION OF UNSPECIFIED DURATION											

Gilles	**2008**	UK	Decision tree and Markov model	NA	IGT (One-off screening with FPG and OGTT for population aged 45 yrs with at least 1 risk factor for T2DM)	Screening for T2DM only	Not stated	50 year simulation	Cost per QALY: £14150 (£8681/QALY undiscounted) Cost per LYG: £23710 (£11460/LYG undiscounted)		QALY and LYG
						Screening for T2DM and IGT and treatment with lifestyle program	Not stated	50 year simulation	Cost per QALY: £6242 (£2863/QALY undiscounted) Cost per LYG: $10900 (£4179 undiscounted)		QALY and LYG
						Screening for T2DM and IGT and treatment with metformin	Not stated	50 year simulation	Cost per QALY: £7023 (£3429/QALY undiscounted) Cost per LYG: £11690 (£4786/LYG undiscounted)		QALY and LYG
Colagiuri	**2008**	Australia	Simulation using the Diabetes Cost Benefit model, including cost benefit analysis and cost utility analysis ($/DALY)	Whole Australian population	Screening for undiagnosed T2DM and prediabetes (IGT and IFG) in Australians aged 55-74 years and those who were 45-54 years with a	Screening (risk factor assessment), FPG for those at high risk, OGTT for those with FPG 5.9-6.6 mmol/l	10 years	10 year simulation		$53,955/DALY in 45-54 year olds $48,386/DALY in 55-74 year olds $49,713/DALY 45-74 year olds	DALY

					BMI>=30, family history of T2DM and/or hypertension						
STUDIES INCLUDING SCREENING +INTERVENTION <2 YEARS DURATION											
Irvine	**2011**	UK	Trial-based cost-utility analysis	177 participants in trial, 118 allocated to intervention	IFG and T2DM (FPG screening of 45-70 years olds with elements of metabolic syndrome)	UEA-IFG lifestyle program	Control: 6.69 months Intervention: 7.28 months	1 year	£67,163/QALY		QALY
STUDIES INCLUDING NO SCREENING AND OTHER INTERVENTIONS											
Smith	**2010**	US	Markov model (TreeAgePro) based on findings of non-randomised prospective trial	Not stated	55 year old men with BMI>=25kg/m2 and at least 3 signs of metabolic syndrome	Modified DPP designed for distinct populations	12-14 weeks	3 years		$3,420/QALY	QALY

Feldman	**2013**	Sweden	Markov microsimulation model	142	People in primary care with evidence of metabolic syndrome	Primary care - based lifestyle program (Kalmar Metabolic Syndrome Program)	1 year	Simulation until 65 years of age	Men: Low risk: Euro 11,213/QALY Medium risk: Euro 2,052/QALY High risk: Euro 3,305/QALY Women: Low risk: Euro 10,698/QALY Medium risk: Euro 7,379/QALY High risk: Euro 18,739/QALY	Men: Low risk: Euro 7,276/QALY Medium risk: Cost saving High risk: Cost saving Women: Low risk: Euro 7,337/QALY Medium risk: Euro 3,608/QALY High risk: Euro 18,191/QALY	QALY
STUDIES INCLUDING NO SCREENING + UNSPECIFIED LIFESTYLE INTERVENTION											
Jacobs Van Der Brugge n	**2007**	Netherlands	Markov model	Dutch population 2004 (16.3 million) for community intervention	Whole adult population for community intervention	Community intervention	5 years community intervention	70 years	Community intervention: Euro 3100-3900/QALY	-	QALY
				200,000	Obese adults aged 30-70 years for healthcare intervention	Healthcare intervention: Lifestyle program	3 years healthcare intervention	70 years	Healthcare intervention: Euro 3900-5500/QALY	-	QALY

APPENDIX 2: COST OF LIFESTYLE PROGRAMS IN INCLUDED STUDIES

US DIABETES PREVENTION PROGRAM - COSTS OF LIFESTYLE PROGRAM (37)													
Activity	Staff type	YEAR 1				YEAR 2				YEAR 3			
		Volume of contact	Time per contact (hrs)	Staff cost per hour	Total cost p.a.	Volume of contacts	Time per contact (hrs)	Staff cost per hour	Total cost p.a.	Volume of contacts	Time per contact (hrs)	Staff cost per hour	Total cost p.a.
Baseline history and physical examination	GP	1	1	£ 162.00	£ 162.00				£ -				£ -
Annual nurse review and blood tests	District nurse					1	0.33	0.3	£ 11.67	1	0.33	0.3	£ 11.67
Core curriculum	Care manager (Band 5)	16	1	£ 45.00	£ 720.00				£ -				£ -
Supervised activity session	Care manager (Band 5)	2.562	1	£ 45.00	£ 115.29	2.562	1	£ 45.00	£ 115.29	2.562	1	£ 45.00	£ 115.29
	Trainer (Band 5)	1.708	1	£ 45.00	£ 76.86	1.708	1	£ 45.00	£ 76.86	1.708	1	£ 45.00	£ 76.86
Lifestyle group sessions	Care manager (Band 5)	0.36	1.25	£ 45.00	£ 20.25	0.72	1.25	£ 45.00	£ 40.50	0.72	1.25	£ 45.00	£ 40.50
In-person visits	Care manager (Band 5)	7.65	0.58	£ 45.00	£ 199.67	12.33	0.58	£ 45.00	£ 321.81	12.33	0.58	£ 45.00	£ 321.81
Phonecalls	Care manager (Band 5)	2.32	0.25	£ 45.00	£ 26.10	2.66	0.25	£ 45.00	£ 29.93	2.66	0.25	£ 45.00	£ 29.93
Reminder phone calls	Secretary (Band 4)	29.41	0.08	£ 36.25	£ 85.29	17.45	0.08	£ 36.25	£ 50.61	17.45	0.08	£ 36.25	£ 50.61
Materials					£ 9.61				£ -				£ -
Tool box					£ 102.00				£ 105.00				
Intervention cost p.a.					**£ 1,517.06**				**£ 751.66**				**£ 646.66**

Total intervention cost													**£ 2,915.39**
INDIAN DIABETES PREVENTION PROGRAM - COSTS OF LIFESTYLE PROGRAM (64)													
		YEAR 1				YEAR 2				YEAR 3			
Activity	Staff type	Volume of contacts	Time per contact (hrs)	Staff cost per hour	Total cost p.a.	Volume of contacts	Time per contact (hrs)	Staff cost per hour	Total cost p.a.	Volume of contacts	Time per contact (hrs)	Staff cost per hour	Total cost p.a.
Visits	GP	4	0.5	£ 162.00	£ 324.00	4	0.5	162.0	£ 324.00	4	0.5	162.0	£ 324.00
	Social worker	4	0.75	£ 62.86	£ 188.57	4	0.75	£ 62.86	£ 188.57	4	0.75	£ 62.86	£ 188.57
	Dietician	4	0.75	£ 62.86	£ 188.57	4	0.75	£ 62.86	£ 188.57	4	0.75	£ 62.86	£ 188.57
	Helper	4	0.5	£ 36.25	£ 72.50	4	0.5	£ 36.25	£ 72.50	4	0.5	£ 36.25	£ 72.50
	Technician	2	0.16	£ 36.25	£ 11.60	2	0.16	£ 36.25	£ 11.60	2	0.16	£ 36.25	£ 11.60
Phone calls – inbound	Social worker	5.4	0.25	£ 62.86	£ 84.86	2.25	0.25	£ 62.86	£ 35.36	2.2	0.25	£ 62.86	£ 34.57
	Dietician	4.8	0.25	£ 62.86	£ 75.43	1.8	0.25	£ 62.86	£ 28.29	1.6	0.25	£ 62.86	£ 25.14
Phone calls - outbound	Social worker	8	0.41	£ 62.86	£ 206.17	8	0.41	£ 62.86	£ 206.17	10	0.41	£ 62.86	£ 257.71
	Dietician	8	0.41	£ 62.86	£ 206.17	8	0.41	£ 62.86	£ 206.17	10	0.41	£ 62.86	£ 257.71
Reminder calls	Secretary	12	0.05	£ 36.25	£ 21.75	12	0.05	£ -	£ -	12	0.05	£ -	£ -
Intervention cost p.a.					**£ 1,380**				**£ 1,261**				**£ 1,360**
Total intervention cost													**£ 4,001**

APPENDIX 3: BENEFITS OF PREVENTION PROGRAMS

Study	Type of intervention	DALYs averted	Increase in QALYs	Method of calculating QALYs	Years free of diabetes	Increased life years gained (years)	Number needed to treat to prevent 1 case of diabetes
Herman, 2005 - DPP	a. Lifestyle		0.57	Self-administered Quality of Wellbeing Index	11	0.5	
	b. Metformin		0.13		3	0.2	
Eddy, 2005	a. DPP lifestyle (in those with IGT and IFG)		0.159 (0.276 undiscounted)	Quality of Wellbeing Index		0.288	
	b. DPP metformin		NR				
Diabetes Prevention Programme (DPP) Research Group, 2012	a. Lifestyle		0.12 (0.14 undiscounted)	Self-administered Quality of Wellbeing Index			
	b. Metformin		0.02 (0.02 undiscounted)				
Ackermann, 2006	DPP lifestyle intervention at either age 50 of 65yrs of target population		0.59 (lifestyle intervention provided to 50 year olds) 0.27 (lifestyle intervention provided to 65 year olds)	Self-administered Quality of Wellbeing Index			
Palmer, 2004	a. Intensive lifestyle change (US DPP)				1.77-1.82	0.06-0.16 (0.21-0.23 undiscounted)	
	b. Metformin				0.86-0.89	0.03-0.07 (0.10-0.11 undiscounted)	
Palmer, 2012	a. Intensive lifestyle change (US DPP)		0.39	NA	5.71	0.69	
	b. Metformin		0.12	NA	2.47	0.3	

Png, 2014	1. Lifestyle (US DPP)		0.05	Self-administered Quality of Wellbeing Index (used in US DPP)			
	2. Metformin		0.01				
Lindgren, 2007	Lifestyle intervention (FDPS)		0.2	EQ-5D		0.18	
Caro, 2004	a. Lifestyle program (based on FDPS)					0.31	
	b. Metformin					0.14	
	c. Acarbose					0.2	
Ramachandran, 2007	1. Lifestyle management						6.4
	2. Metformin						6.9
	3. Lifestyle management and metformin						6.5
Hoerger, 2007	1. Screening and DPP lifestyle program for IFG and IGT		0.040 per screened subject 0.099 per subject with prediabetes			0.043 (undiscounted) per screened subject 0.106 (undiscounted) per subject with prediabetes	
	2. Screening and DPP for IFG or IGT or IFG and IGT		0.118 per screened subject 0.290 per subject with prediabetes			0.122 (undiscounted) per screened subject 0.300 (undiscounted) per subject with prediabetes	
Icks, 2007	1. Screening and DPP lifestyle program						4.3

	2. Screening and metformin						27.9
Schaufler, 2010	1. Screening and US DPP lifestyle program		2.91 (undiscounted)	Self-Administered Quality of Wellbeing Index			
	2. Screening and metformin		2.83 (undiscounted)	Self-Administered Quality of Wellbeing Index			
Mortaz, 2012	3-yearly screening with FPG and USDPP lifestyle intervention or metformin		0.306	EQ-5D			
Liu, 2012	a. Screening with diet intervention		Initiation age 25 yrs: 3.33 Initiation age 40 yrs: 2.59 Initiation age 60 yrs: 0.56			Initiation age 25 yrs: 1.7 Initiation age 40 yrs: 0.5 Initiation age 60 yrs: 0.1	
	b. Screening with exercise intervention		Initiation age 25 yrs: 3.33 Initiation age 40 yrs: 2.58 Initiation age 60 yrs: 0.56			Initiation age 25 yrs: 1.7 Initiation age 40 yrs: 0.5 Initiation age 60 yrs: 0.1	
	c. Screening with diet and lifestyle intervention		Initiation age 25 yrs: 3.33 Initiation age 40 yrs: 2.59 Initiation age 60 yrs: 0.56			Initiation age 25 yrs: 1.7 Initiation age 40 yrs: 0.5 Initiation age 60 yrs: 0.1	
	d. Screening alone		Initiation age 25 yrs: 2.40 Initiation age 40 yrs: 1.37 Initiation age 60 yrs: 0.33			Initiation age 25 yrs: 1.2 Initiation age 40 yrs: 0.1 Initiation age 60 yrs: 0	

Gilles, 2008	1. Screening for T2DM only		0.03 (-0.02-0.09) Undiscounted: 0.07 (-0.03-0.18)	EQ-5D		0.02 (-0.01 - 0.05) Undiscounted: 0.06 (0.02-0.12)	
	2. Screening for T2DM and IGT and lifestyle intervention		0.09 (0.03-0.17) Undiscounted: 0.22 (0.08-0.36)		0.17 (0.[illegible]-0.23) Undiscounted: 0.33 (0.[illegible]-0.43)	0.05 (0.03-0.08) Undiscounted: 0.15 (0.08-0.22)	
	3. Screening for T2DM, IGT and treat with metformin		0.07 (0.01-0.15) Undiscounted: 0.17 (0.03-0.32)		0.11 (0.[illegible]-0.19) Undiscounted: 0.20 (0.[illegible]-0.37)	0.05 (0.02-0.07) Undiscounted: 0.13 (0.06-0.20)	
Colagiuri, 2008	Screening + lifestyle intervention	0.10 per person with IGT or IFG					
Bertram, 2010	a Diet plus exercise	0.05					
	b. Exercise	0.04					
	c. Diet	0.02					
	d. Acarbose	0.06					
	e. Metformin	0.04					
	f. Orlistat	0.07					
	g. Metformin plus diet and exercise	0.01					
Neumann, 2011	Group lifestyle intervention		30 years of age: Men: 0.02, Women: 0.03 50 years of age: Men: 0.03, Women: 0.02	SF-6D and EQ-5D			

			70 years of age: Men: 0.02, Women: 0.02				
Smith, 2010	Modified DPP		0.01	Not specified			
Feldman, 2013	Primary care -based lifestyle program (Kalmar Metabolic Syndrome Program)		0.05-0.14	Not specified		0.3	
Jacobs Van der Bruggen, 2007	1. Community intervention		0.006-0.039	Not specified		0.007-0.043	1500-300
	2. Healthcare intervention		0.27-1.17	Not specified		0.32-1.35	30-7
Irvine, 2011	Lifestyle intervention (UEA-IFG)		0.003	EQ-5D			
Sagarra, 2013	Individual and group lifestyle program		0.12	15D			
Zhuo, 2012	Community based lifestyle intervention (PLAN4WARD)		0.03 per participant identified as prediabetic 0.053 per person participating in lifestyle program			0.04 per participant identified as prediabetic 0.08 per person participating in lifestyle program	14.24
Herman, 2013	1. USDPP and USDPPOS lifetsyle program		0.15	Self-administered Quality of Wellbeing Index			
	2. Metformin and USDPPOS lifestyle program		0.09				
Dall, 2015	DPPOS		0.39 using ADA screening criteria 0.41 using	EQ-5D		0.36 using ADA screening criteria	3.9 using the ADA screening criteria 4.2 using the USPSTF criteria

			USPSTF criteria			0.45 using USPSTF criteria	
APPENDIX 4: ASSESSMENT OF QUALITY, RELEVANCE AND CREDIBILITY							
QUESTIONS	**HELPER QUESTIONS**	**SPECIFIC ELEMENTS EXAMINED**	**Herman, 2005**	**Eddy, 2005**	**DPPRG 2012**	**Ackermann, 2006**	**Palmer 2004**
ASSESSMENT OF RELEVANCE							
1. Is the population relevant?	Are the demographics similar?	Age, ethnicity, gender	45% members of minority groups Age >25 years 68% women	Not reported	45% members of minority groups Age >25 years 68% women	50 years of age	Population based on the USDPP: Mean age 50.6 years 32.2% men Mean BMI 34kg/m2
	Are risk factors similar?	Type of pre-diabetes, BMI	IGT *and* IFG, BMI>24kg/m2	IGT and IFG, BM>24kg/m2	IGT *and* IFG, BMI>24kg/m2	IGT	IGT

	Are behaviors similar?	Compliance with intervention	72% participants took at least 80% of required metformin	Not reported	Years 1-3: 72% participants took at least 80% of required metformin Years 4-15: 58% of metformin and 57% of placebo participants attended at least one session	10% p.a. drop out rate modelled in sensitivity analysis	Data drawn from USDPP Additional non-participation/non-adherence not modelled
	Is the medical condition similar?		Yes	Yes	Yes	Yes	Yes
2 Are any critical interventions missing?	Does the intervention analyzed in the model match the intervention you are interested in?	Type of intervention	1. Lifetsyle intervention (duration 2.8 years, USDPP)) 2. Metformin 3. Placebo	1. Lifetsyle intervention over 2.8 years (USDPP) 2. Metformin 3. Usual care	1. Lifestyle intervention over 10 years (USDPP/DPPOS) 2. Metformin 3. Usual care	1. Lifestyle intervention 2. Usual care	1. Lifestyle intervention (based on USDPP) 2. Metformin 3. Usual care
	Have all relevant comparators been considered?		Yes	Yes	Yes	No, metformin not included	Yes

	Does the background care in the model match yours?		US healthcare system	US healthcare system	US healthcare system	US healthcare system	Australia, France, Germany, Switzerland and the United Kingdom's health systems
3 Are any relevant outcomes missing?	Are the health outcomes relevant to you considered?		Yes, QALYs	Yes, QALYs	Yes, QALYs	Yes, QALYs	Yes, LYG
	Are the economic end points relevant to you considered?		Yes, $/QALY	Yes, $/QALY	Yes, $/QALY	Yes, $/QALY	Yes, $/LYG
4. Is the context (settings and circumstances) applicable?	Is the geographic location similar?		US	US	US	US	Australia, France, Germany, Switzerland and the United Kingdom
	Is the time horizon applicable to your decision?		Yes, lifetime simulation	Yes, 30 years	Yes, 10 years	Yes, lifetime simulation	Yes, lifetime
	Is the analytic perspective appropriate to your decision problem?	Health system or societal perspective	Health system perspective	Health system and societal perspective	Health system and societal perspective	Health system perspective	Health system perspective
ASSESSMENT OF CREDIBILITY							
Validation							

Is external validation of the model sufficient to make its results credible for your decision?	Has the model been shown to accurately reproduce what was observed in the data used to create the model?		Not reported	Yes	*Not a modelling study*	Not reported	Not reported
	Has the model been shown to accurately estimate what actually happened in one or more separate studies?		Not reported	Yes		Not reported	Not reported
	Has the model been shown to accurately forecast what eventually happens in reality?		Not reported	Not reported		Not reported	Not reported
Is internal verification of the model sufficient to make its results credible for your decision?	Have the process of internal verification and its results been documented in detail?		Not reported	Yes	*Not a modelling study*	Not reported	Not reported
	Has the testing been performed systematically?		Not reported	Yes		Not reported	Not reported
	Does the testing indicate that all the equations are consistent with their data sources?		Not reported	Yes		Not reported	Not reported
	Does the testing indicate that the coding has been correctly implemented?		Not reported	Yes		Not reported	Not reported

Does the model have sufficient face validity to make its results credible for your decision?	Does the model contain all the aspects considered relevant to the decision?		Yes	Yes	*Not a modelling study*	Yes	Yes
	Are all the relevant aspects represented and linked according to the best understanding of their characteristics?		Yes	Not reported		Yes	Yes
	Have the best available data sources been used to inform the various aspects?		Yes	Not reported		Yes	Yes
	Is the time horizon sufficiently long to account for all relevant aspects of the decision problem?		Yes, lifetime simulation	Yes, 30 years		Yes - lifetime simulation	Yes, lifetime simulation
	Are the results plausible?		Yes	No		Yes	Yes
	If others have rated the face validity, did they have a stake in the results?		Rating of face validity not reported	Rating of face validity not reported in detail		Rating of face validity not reported	Rating of face validity not reported
Design							

Is the design of the model adequate for your decision problem?	Was there a clear, written statement of the decision problem, modeling objective, and scope of the model?		Yes	Yes	*Not a modelling study*	Yes	Yes
	Was there a formal process for developing the model design (e.g. influence diagram, concept map)?		Not reported - pre-existing model utilised	Not reported - pre-existing model utilised		Not reported - pre-existing model utilised	Not reported
	Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context?		Yes	Yes		Yes	Yes
	Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem?		Yes	Not reported		No - assumption that relative risk reduction continues as long as lifestyle intervention continues (until participant gets T2DM or dies)	No-reversion from IGT to normoglycaemia not modelled
	Is the choice of model type appropriate?		Yes	Yes		Yes	Yes

	Were key uncertainties in model structure identified and their implications discussed?		Yes	Yes		Yes	Yes
Data							
Are the data used in populating the model suitable for your decision problem?	All things considered, do you agree with the values used for the inputs?	Duration and extent of impact of lfestyle intervention	Relative risks of T2DM from USDPP Lifetsyle intervention provided **until onset of T2DM** and assumed health and QOL benefits associated with interventions remain constant and persist until diabetes onset	Lifestyle program and metformin assumed to continue to impact T2DM incidence as long as they were provided (up to and after diagnosis with T2DM)	Relatives of of T2DM from USDPP and USDPP OS	Lifetsyle intervention provided until onset of T2DM and that health and QOL benefits associated with interventions remain constant and persist until diabetes onset	Lifestyle intervention provided for 3 years and benefts in terms of reduction in incidence of T2DM only lasts for 3 years (ie. For duration of intervention)
		Source of cost data	USDPP	USDPP	USDPP, USDPP OS	USDPP	Costs of intervention from USDPP Other costs from published data

		Source of outcome data	USDPP	Not reported	USDPP/USDPP OS	USDPP	USDPP
		Discount rate	3% for costs and QALYs	3% costs and QALYs	3% for [illegible] and QALYs	3% for costs and QALYs	5% for costs and LYG in Australian, German, Swiss and French analysis 1.5% for health outcomes and 6% for costs in UK analysis
Analysis							
Were the analyses performed using the model adequate to inform your decision problem?			Yes	Yes	Yes	Yes	Yes

Was there an adequate assessment of the effects of uncertainty?		Key sensitivity analyses	Sensitivity analyses: 1. Group lifestyle programme 2. Generic metformin 3. Reduced effectiveness of interventions to 20% and 50% of USDPP to reflect reduced adherence 4. Discount rates	Sensitivity analyses: 1. Intervention effect 2. Size of the health plan 3. Discount rate 4. Cost of diabetes care 5. Turnover of the health plan	No sensitivity analyses as was a within trial analysis	Sensitivity analyses: 1. Group lifestyle programme 2. Reduced effectiveness of interventions to 50% of USDPP 3. Adherence reduced by 10% each year	Sensitivity analyses: 1. Total costs +/- 10% 2. Life expectancy +/- 10% 3. Rank order stability assessment 4. Discount rates (range 0-6%) 5. Relative risk T2DM 6. Effect duration of intervention 7. Relative risk of mortality for IGT and T2DM 8. Relative costs of IGT and T2DM 9. Intervention costs (80-300% of base case)
Reporting							
Was the reporting of the model adequate to inform your decision problem?	Did the report of the analyses provide the results needed for your decision problem?		Yes	Yes	Yes	Yes	Yes
	Was adequate nontechnical documentation freely accessible to any interested reader?		Yes	Yes	Yes	Yes	Yes

	Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?		Yes	No	Yes	Yes	Yes
Interpretation							
Was the interpretation of results fair and balanced?			Yes	Yes	Yes	Yes	Yes
Conflict of interests							
Were there any potential conflicts of interest?			No	No	No	No	No
If there were potential conflicts of interest, were steps taken to address these?			NA	NA	NA	NA	NA

APPENDIX 4 CONTINUED:

QUESTIONS	HELPER QUESTIONS	SPECIFIC ELEMENTS EXAMINED	Palmer, 2012	Png, 2014	Lingsma, 2007	Caro, 2004	Ramachandran, 2007
ASSESSMENT OF RELEVANCE							
1. Is the population relevant?	Are the demographics similar?	Age, ethnicity, gender	Not reported	Not reported	Age, 69 years	Mean age: 54.5 years 50% male	Indian office workers aged 35-55
	Are risk factors similar?	Type of pre-diabetes, BMI	IGT or IFG, overweight or obese	IGT and IFG	IFG BMI>25kg/m2	IGT	IGT

	Are behaviors similar?	Compliance with intervention	Compliance with metformin 68-76% Adherence with lifestyle programs: 14-58%	Not reported	No drop-out was assumed Participation rate of 87.5% in Canadian training sessions	Non-compliance not explicitly modelled	Compliance measured within intervention
	Is the medical condition similar?		Yes	Yes	Yes	Yes	Yes
2 Are any critical interventions missing?	Does the intervention analyzed in the model match the intervention you are interested in?	Type of intervention	1. Lifestyle intervention (based on USDPP) 2. Metformin 3. Usual care	1. Lifestyle intervention (based on USDPP) 2. Metformin 3. Usual care	1. Lifestyle intervention (based on 6-year Finnish DPS) 2. Usual care	1. Lifestyle intervention (based on 6-year Finnish DPS) 2. Metformin 3. Acarbose 4. Usual care	1. Lifestyle intervention (3 year Indian DPP) 2. Metformin 3. Usual care
	Have all relevant comparators been considered?		Yes	Yes	No metformin not considered	Yes	Yes
	Does the background care in the model match yours?		Australian health system	Singaporean health system	Swedish health system	Canadian health system	Indian health system

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3 Are any relevant outcomes missing?	**Are the health outcomes relevant to you considered?**		**Yes, QALYs**	**Yes, QALYs**	**Yes, QALYs**	**Yes, LYG**	**No, QALYs or DALYs not considered**
	Are the economic end points relevant to you considered?		**Yes, $/QALY**	**Yes, $/QALY**	**Yes, Euro/QALY**	**Yes, $/LYG**	**No, $/QALY or DALY not considered**
4. Is the context (settings and circumstances) applicable?	**Is the geographic location similar?**		**Australia**	**Singapore**	**Sweden**	**Canada**	**India**
	Is the time horizon applicable to your decision?		**Yes, lifetime**	**No - 3 year time horizon**	**Yes, lifetime simulation**	**Yes, 10 year time horizon**	**No, 3 year analysis**
	Is the analytic perspective appropriate to your decision problem?	**Health system or societal perspective**	**Health system perspective**	**Health system and societal perspective**	**Societal perspective**	**Health system perspective**	**Health system perspective**
ASSESSMENT OF CREDIBILITY							
Validation							
Is external validation of the model sufficient to make its results credible for your decision?	**Has the model been shown to accurately reproduce what was observed in the data used to create the model?**		Not reported	Not reported	Not reported	Not reported	*Not a modelling study*
	Has the model been shown to accurately estimate what actually happened in one or more separate studies?		Not reported	Not reported	Not reported	Not reported	

	Has the model been shown to accurately forecast what eventually happens in reality?		Not reported	Not reported	Not reported	Not reported	
Is internal verification of the model sufficient to make its results credible for your decision?	**Have the process of internal verification and its results been documented in detail?**		Yes	Not reported	Not reported	Not reported	*Not a modelling study*
	Has the testing been performed systematically?		Yes	Not reported	Not reported	Not reported	
	Does the testing indicate that all the equations are consistent with their data sources?		Not reported	Not reported	Not reported	Not reported	
	Does the testing indicate that the coding has been correctly implemented?		Not reported	Not reported	Not reported	Not reported	
Does the model have sufficient face validity to make its results credible for your decision?	**Does the model contain all the aspects considered relevant to the decision?**		Yes	Yes	Yes	Yes	*Not a modelling study*
	Are all the relevant aspects represented and linked according to the best understanding of their characteristics?		Yes	Yes	Yes	Yes	

	Have the best available data sources been used to inform the various aspects?		Yes	Yes	Yes	Yes	
	Is the time horizon sufficiently long to account for all relevant aspects of the decision problem?		Yes	No - 3 year horizon modelled	Yes	Yes, 10 years	
	Are the results plausible?		Yes	Yes	Yes	Yes	
	If others have rated the face validity, did they have a stake in the results?		Rating of face validity not reported	Rating of face validity not reported	Rating of face validity not reported	Rating of face validity not reported	
Design							
Is the design of the model adequate for your decision problem?	**Was there a clear, written statement of the decision problem, modeling objective, and scope of the model?**		Yes	Yes	Yes	Yes	Not a modelling study
	Was there a formal process for developing the model design (e.g.		Not reported	Not reported	Not reported	Not reported	

	influence diagram, concept map)?						
	Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context?		Yes	Yes	Yes	Yes	
	Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem?		Yes	Yes	No: Reversion from IFG to NG not modelled	Yes	
	Is the choice of model type appropriate?		Yes	Yes	Yes	Yes	

	Were key uncertainties in model structure identified and their implications discussed?		Yes	Yes	Yes	Yes	
Data							
Are the data used in populating the model suitable for your decision problem?	**All things considered, do you agree with the values used for the inputs?**	**Duration and extent of impact of lfestyle intervention**	Benefits of lifestyle intervention persist once intervention ends at 10 years	Benefits of lifestyle intervetion persist for 3 years which is the duration of the model	No effect of lifestyle intervention assumed after intervention ended	Yes - Assumes 100% benefit for 5 years of intervention but increasing underlying risk of transitioning to T2DM (reaching 20% at 10 years)	Yes - Benefits of lifestyle intervetion persist for 3 years which is the duration of the model
		Source of cost data	DPPOS, Medical Benefits Schedule Australia	Costs of implementing USDPP obtained from National University Hospital Cost Repository Data from Household Expenditure Survey for indirect costs of intervention	Finnish DPS and other literature	Finnish DPS for intervention costs Physician fee schedues, drug formularies, lab fee schedules and published literature for other costs	Indian DPP

		Source of outcome data	DPPOS	USDPP	Literature	Finnish DPS and US DPP	Indian DPP
		Discount rate	No discounting	3% for costs and QALYs	3% for costs and utilities	5% for costs and utilities	No discounting of costs
Analysis							
Were the analyses performed using the model adequate to inform your decision problem?			Yes	Yes	Yes	Yes	No, only NNT not QALYs or DALYs assessed

Was there an adequate assessment of the effects of uncertainty?		**Key sensitivity analyses**	Sensitivity analyses: 1. All parameter values +/-10% 2. PSA with distributions in the following parameters: costs of T2DM, transition probablities, relative risk of mortality in IGT and T2DM, health state utilities	Sensitivity analyses: 1. Incremental QALYs associated with metformin and lifestyle intervention	No sensitivity analyses reported	Sensitivity analyses: 1. Baseline transition probablity to T2DM, returning to NGT or reverting to IGT 2. Risk reduction of each intervention 3. Cost of lifstyle intervention 4. prevalence of IGT 5. Cost of screening 6. Time horizon of analysis 7. Duration of treatment 8. Discount rate 9. Long-term risk of diabetes and impact of treatment	No senstivity analyses, not a modelling study
Reporting							
Was the reporting of the model adequate to inform your decision problem?	**Did the report of the analyses provide the results needed for your decision problem?**		Yes	Yes	Yes	Yes	Yes

	Was adequate nontechnical documentation freely accessible to any interested reader?		Yes	Yes	No	Yes	Yes
	Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?		Yes	Yes	No	No	Yes
Interpretation							
Was the interpretation of results fair and balanced?			Yes	Yes	Yes	Yes	Yes
Conflict of interests							
Were there any potential conflicts of interest?			No	No	No	Yes	No

If there were potential conflicts of interest, were steps taken to address these?			NA	NA	NA	Yes	NA

APPENDIX 4 CONTINUED:

QUESTIONS	**HELPER QUESTIONS**	**SPECIFIC ELEMENTS EXAMINED**	**Hoerger, 2007**	**Icks, 2007**	**Schaufler, 2010**	**Mortaz, 2012**	**Herman, 2013**
ASSESSMENT OF RELEVANCE							
1. Is the population relevant?	**Are the demographics similar?**	**Age, ethnicity, gender**	Age: 45-74yrs	Age: 60-74 years	Age: 35-75 years	Age: 40 years	45% members of minority groups Age >25 years 68% women
	Are risk factors similar?	**Type of pre-diabetes, BMI**	IFG and or IGT BMI>=25kg/m2	IFG and IGT BMI>=24kg/m2	IGT	IFG Overweight	IGT *and* IFG, BMI>24kg/m2

	Are behaviors similar?	**Compliance with intervention**	No lack of compliance modelled (50% non entry into intervention from screening modeled in sensitivity analysis)	30% attend screening test, 40% participate in lifestyle intervention, 59% comply with meformin	30% participation in screening Participation in or compliance with intervention not stated	Non-compliance with intervention and non-attendance of screening not specified	Only adherent participants included
	Is the medical condition similar?		Yes	Yes	Yes	Yes	Yes
2 Are any critical interventions missing?	**Does the intervention analyzed in the model match the intervention you are interested in?**	**Type of intervention**	1. Lifestyle intervention (US DPP) 2. Usual care	1. Lifestyle intervention (US DPP) 2. Metformin 3. Usual care	1. Lifestyle intervention (US DPP) 2. Metformin 3. Usual care	1. Lifestyle intervention (US DPP) 2. Metformin 3. Usual care	1. Lifestyle intervention (US DPP) 2. Lifestyle intervention (USDPP in groups format) 3. Metformin 4. Usual care
	Have all relevant comparators been considered?		Metformin considered in sensitivity analysis	Yes	Yes	Yes	Yes
	Does the background care in the model match yours?		US health system	German health system	German health system	Canadian health system	US health system

3 Are any relevant outcomes missing?	**Are the health outcomes relevant to you considered?**		Yes, QALY, LYG and cumulative diabetes incidence	No, only report cost per case of T2DM avoided	Yes	Yes	Yes, QALY
	Are the economic end points relevant to you considered?		Yes, $/QALY	No	Yes	Yes	Yes, $/QALY
4. Is the context (settings and circumstances) applicable?	**Is the geographic location similar?**		US	Germany	Germany	Canada	US
	Is the time horizon applicable to your decision?		Yes, lifetime simulation	No, 3 year model	Yes, lifetime	Yes, 10 years	Yes, 10 years
	Is the analytic perspective appropriate to your decision problem?	**Health system or societal perspective**	Health system perspective	Health system and societal perspective	Health system perspective	Health system perspective	Health system and modified societal perspective
ASSESSMENT OF CREDIBILITY							
Validation							
Is external validation of the model sufficient to make its results credible for your decision?	**Has the model been shown to accurately reproduce what was observed in the data used to create the model?**		Used previously published diabetes model, additional validation not reported	Not reported	Yes	Not reported	*Not a modelling study*
	Has the model been shown to accurately estimate what actually happened in one or more separate studies?		Not reported	Not reported	Yes	Not reported	

	Has the model been shown to accurately forecast what eventually happens in reality?		Not reported	Not reported	Not reported	Not reported	
Is internal verification of the model sufficient to make its results credible for your decision?	**Have the process of internal verification and its results been documented in detail?**		Used previously published diabetes model, additional validation not reported	Not reported	Yes	Not reported	*Not a modelling study*
	Has the testing been performed systematically?		Not reported	Not reported	Yes	Not reported	
	Does the testing indicate that all the equations are consistent with their data sources?		Not reported	Not reported	Not reported	Not reported	
	Does the testing indicate that the coding has been correctly implemented?		Not reported	Not reported	Yes	Not reported	
Does the model have sufficient face validity to make its results credible for your decision?	**Does the model contain all the aspects considered relevant to the decision?**		Yes	Yes	Yes	Yes	*Not a modelling study*
	Are all the relevant aspects represented and linked according to the best understanding of their characteristics?		Yes	Yes	Yes	*Yes*	

	Have the best available data sources been used to inform the various aspects?		Yes	Yes	Yes	*Yes*	
	Is the time horizon sufficiently long to account for all relevant aspects of the decision problem?		Yes	No, 3 years	Yes, lifetime	Yes, 10 years	
	Are the results plausible?		Yes	Yes	Yes	*Yes*	
	If others have rated the face validity, did they have a stake in the results?		Rating of face validity not reported	Rating of face validity not reported	Rating of face validity not reported	Rating of face validity not reported	
Design							
Is the design of the model adequate for your decision problem?	**Was there a clear, written statement of the decision problem, modeling objective, and scope of the model?**		Yes	Yes	Yes	Yes	*Not a modelling study*
	Was there a formal process for developing the model design (e.g.		Not reported	Not reported	Not reported	Not reported	

	influence diagram, concept map)?						
	Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context?		Yes	No, transition back to NGT not modelled	No, transition back to NGT not modelled	No, transition back to NGT not modelled	
	Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem?		Continuation of lifestyle intervention as long as participant has prediabetes , assumption that risk reduction continues as long as intervention continues	Yes	Yes	Unclear how different interventions (lifestyle and metformin) are modelled	
	Is the choice of model type appropriate?		Yes	Yes	Yes	Yes	

	Were key uncertainties in model structure identified and their implications discussed?		Yes	Yes	Yes	No, limited sensitivity analyses relating mainly to frequency of screening	
Data							
Are the data used in populating the model suitable for your decision problem?	**All things considered, do you agree with the values used for the inputs?**	**Duration and extent of impact of lfestyle intervention**	No - Duration and extent of impact likley overstated: maintained at 55.8% relative risk reduction as long as intervention continues (which is as long as the participant has pre-diabetes)	Duration of impact: 3 years in line with US DPP	Extent of impact based on literature review Duration of impact not stated	No, Duration of impact not stated	Duration and extent of impact based on US DPP/DPPOS. However group-based lifetsyle program was assumed to be as effective as the individual program
		Source of cost data	USDPP	USDPP, German healthcare system	USDPP Doctors fee scale for the German SHI and pharmaceutical prices and German cost of illness study	Report for the Ontario Ministry of Health and Long-term Care	USDPP/DPPOS
		Source of outcome data	USDPP	USDPP	USDPP	USDPP Not stated fot QALYs	USDPP/DPPOS

		Discount rate	3% for costs and QALYs	No discounting	5% costs, no discounting of QALYs	3% for costs and benefits	3% for costs and benefits in health system perspective Societal perspective undiscounted
Analysis							
Were the analyses performed using the model adequate to inform your decision problem?			Yes	Yes	Yes	Yes	Yes
Was there an adequate assessment of the effects of uncertainty?		**Key sensitivity analyses**	Sensitivity analyses: 1. Prevalence of pre-diabetes 2. Different age groups 3. Repeated screening every 3 years 4. Screening and diagnostic test costs 5. Different diagnostic test cut-offs 6. Metformin 7. Group lifestyle program 8. 20% less relatiev risk reduction of lifestyle program 9. 50%	Sensitivity analyses: 1. Participation rates in screening and intervention 2. Prevalence of IGT and T2DM 3. relatiev risk of T2DM in control group 4. Costs of patient time	Sensitivity analyses: 1. Cost of screening and intervention 2. Discount rate for costs 3. Discount rate for utilities 4. Participation in intervention 5. No effect of early detection on disease progression 6. Metformin	Sensitivity analyses: 1. Frequency of screening	No sensitivity analyses reported

			enrollment in intervention				
Reporting							
Was the reporting of the model adequate to inform your decision problem?	**Did the report of the analyses provide the results needed for your decision problem?**		Yes	Yes	Yes	Yes	Yes
	Was adequate nontechnical documentation freely accessible to any interested reader?		Yes	Yes	Yes	No	In previous publications from the same trial, but not in this publication

	Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?		No	Yes	No	No	No
Interpretation							
Was the interpretation of results fair and balanced?			Yes	Yes	Yes	Yes	Yes
Conflict of interests							
Were there any potential conflicts of interest?			No	No	No	No	Not stated
If there were potential conflicts of interest, were steps taken to address these?			NA	NA	NA	NA	NA

APPENDIX 4 CONTINUED:

QUESTIONS	HELPER QUESTIONS	SPECIFIC ELEMENTS EXAMINED	Liu, 2013	Gilles, 2008	Colaguiri, 2008	Bertram, 2010	Neumann, 2011
ASSESSMENT OF RELEVANCE							
1. Is the population relevant?	**Are the demographics similar?**	**Age, ethnicity, gender**	Age: 25-74 years Chinese population	Age 45 years UK population	55-74 years Australian population and 45-54 year old people with BMI >25 kg/m2	Age >55 years or age >45 years with risk factors (BMI, blood pressure, family history of T2DM etc.) or high risk groups	Based on population in Saxony, Germany
	Are risk factors similar?	**Type of pre-diabetes, BMI**	IGT	IGT	IFG & IGT	IFG and IGT	FINDRISK score 11-20 or FINDRISK >=21 and no diagnosis of T2DM

	Are behaviors similar?	**Compliance with intervention**	100% compliance assumed in base case, 60% and 80% modelled in sensitivity analyses	100% compliance with screening and intervention in base case, modelled 70% and 50% compliance in sensitivity analyses	Assumed only 25-50% would participate in screening and intervention	Non-compliance not explicitly modelled	Non-compliance not explicitly modelled
	Is the medical condition similar?		Yes	Yes	Yes	Yes	Yes
2 Are any critical interventions missing?	**Does the intervention analyzed in the model match the intervention you are interested in?**	**Type of intervention**	1. Lifestyle intervention (Da Qing) 2. Usual care	1. Lifestyle intervention 2. Metformin 3. Usual care	1. Lifestyle intervention (unspecified) 2. Usual care	1. Diet and exercise 2. Exercise 3. Diet 4. Acarbose 5. Metformin 6. Orlistat 7. Usual care	1. Lifestyle program (based on PREDIAS and SDPP) 2. Usual care
	Have all relevant comparators been considered?		No, metformin not considered	Yes	No, metformin not modelled	Yes	No, metformin not modelled
	Does the background care in the model match yours?		Chinese health system	UK health system	Australian health system	Austrlian health system	German health system

3 Are any relevant outcomes missing?	**Are the health outcomes relevant to you considered?**		Yes, QALY	Yes, QALYs and LYG	Yes, QALY	Yes, DALYs	Yes, QALYs
	Are the economic end points relevant to you considered?		Yes, $/QALY	Yes, £/QALY	Yes, $/QALY	Yes, $/DALY	Yes, Euro/QALY
4. Is the context (settings and circumstances) applicable?	**Is the geographic location similar?**		China	UK health system	Australia	Australia	Germany
	Is the time horizon applicable to your decision?		Yes, 40 years	Yes, 50 year simulation	Yes, 1 year model	Yes, until age 100 years or death	Yes, lifetime simulation
	Is the analytic perspective appropriate to your decision problem?	**Health system or societal perspective**	Societal perspective	Health system perspective	Societal perspective	Health system perspective	Societal perspective
ASSESSMENT OF CREDIBILITY							
Validation							
Is external validation of the model sufficient to make its results credible for your decision?	**Has the model been shown to accurately reproduce what was observed in the data used to create the model?**		Not reported	Not reported	Used previously published diabetes model	Not reported	No external validation possible as German cohort data not available
	Has the model been shown to accurately estimate what actually happened in one or more separate studies?		Not reported	Not reported	Not reported	Not reported	No external validation posisble as German cohort data not available

	Has the model been shown to accurately forecast what eventually happens in reality?		Not reported	Not reported	Not reported	Not reported	Not reported
Is internal verification of the model sufficient to make its results credible for your decision?	**Have the process of internal verification and its results been documented in detail?**		Not reported	Not reported	Used previously published diabetes model	Not reported	Not reported
	Has the testing been performed systematically?		Not reported	Not reported	Not reported	Not reported	Not reported
	Does the testing indicate that all the equations are consistent with their data sources?		Not reported	Not reported	Not reported	Not reported	Not reported
	Does the testing indicate that the coding has been correctly implemented?		Not reported	Not reported	Not reported	Not reported	Not reported
Does the model have sufficient face validity to make its results credible for your decision?	**Does the model contain all the aspects considered relevant to the decision?**		Yes	Yes	Yes	Yes	Yes
	Are all the relevant aspects represented and linked according to the best understanding of their characteristics?		Yes	Yes	Yes	Yes	Yes

	Have the best available data sources been used to inform the various aspects?		Yes	Features of the lifestyle intervention modelled are unclear	Type of lifestyle intervention unclear	Yes	Patients are identified based on FINDRISK score, but transition probabilities are used from studies where participants identified using FPG and OGTT
	Is the time horizon sufficiently long to account for all relevant aspects of the decision problem?		Yes, 40 years	Yes, 50 years	Yes, 50 years	Yes, until 100 years or dead	Yes, lifetime
	Are the results plausible?		Yes	Yes	Yes	Yes	Yes
	If others have rated the face validity, did they have a stake in the results?		Rating of face validity not reported	Rating of face validity not reported	Rating of face validity not reported	Rating of face validity not reported	Rating of face validity not reported
Design							
Is the design of the model adequate for your decision problem?	**Was there a clear, written statement of the decision problem, modeling objective, and scope of the model?**		Yes	Yes	Yes	Yes	Yes

	Was there a formal process for developing the model design (e.g. influence diagram, concept map)?		Not reported	Not reported	Not reported	Not reported	Not reported
	Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context?		Yes	No, transition back to NGT not modelled	No, transition back to NGT not modelled	Yes	Yes
	Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem?		No - assumption regarding duration of impact of this intervention is not stated	No - duration and extent of benefit of lifestyle intervention and metformin is unclear	Yes	Yes	Yes
	Is the choice of model type appropriate?		Yes	Yes	Yes	Yes	Yes
	Were key uncertainties in model structure identified and their		Partially	Yes	Yes	Yes	Yes

	implications discussed?						
Data							
Are the data used in populating the model suitable for your decision problem?	**All things considered, do you agree with the values used for the inputs?**	**Duration and extent of impact of lfestyle intervention**	No - assumption regarding duration of impact of this intervention is not stated	Duration of impact not explicit	Extent of impact were from DPP and FINDRS (risk reduction of 60% at 3 yrs and 30% at 6 yrs) and impact modelled unchanged for 10 years as intervention last for 10 years	Effect of lifestyle change will decay by 10% per year, whereas effect of medications will remain constant Lifestyle intervention continues as long as patient has pre-diabetes	Lifestyle program continues for 5 years and benefits of program are modelled for 6 years, declining linearly from year 1 to year 6
		Source of cost data	Literature	Literature review	Unspecified intervention costing A$500	Systematic review and meta-analysis	Saxon Diabetes Prevention Programme, CODE-2 study
		Source of outcome data	Literature	Literature review	Literature (FDPS and UKPDS)	Literature	Finnish DPS, and literature review

		Discount rate	3% costs and QALYs	3.5% costs and QALYs	3% for costs	3% costs	3% costs and QALYs
Analysis							
Were the analyses performed using the model adequate to inform your decision problem?			Yes	Yes	Yes	Yes	Yes
Was there an adequate assessment of the effects of uncertainty?		**Key sensitivity analyses**	Sensitivity analyses: 1. Positive rates of screening 2. Incidence of IGT and T2DM 3. Incidence of maortality and diabetes related complications 4. Treatment of diabetes-related disorders 5. Utilities of all health states	Sensitivity analyses: 1. Prevalence 2. Compliance 3. Sensitivity of screening tests 4. Cost of interventions 5. Cost of diabetes 6. Effectiveness of interventions 7. Time horizon	Sensitivity analyses: 1. 70% take up of lifestyle program 2. Lower complication rates of T2DM 3. Reduce impact of intervention 4. Increasing cost of intervention ($1,000 pa.) 5. Increasing proportion of undiagnosed diabetes 6. Increasing proportion of population screened	Sensitivity analysis: 1. Second screening OGTT	Probabilistic sensitivity analysis including: 1. All transition probabilities 2. Cost of NGT, IGT and T2DM 3. Cost of intervention

					7. Prevalence 8. Discount rate		
Reporting							
Was the reporting of the model adequate to inform your decision problem?	**Did the report of the analyses provide the results needed for your decision problem?**		Yes	Yes	Yes	Yes	Yes
	Was adequate nontechnical documentation freely accessible to any interested reader?		Yes	Yes	No	Yes	Yes

	Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?		No	No	No	No	Yes
Interpretation							
Was the interpretation of results fair and balanced?			Yes	Yes	Yes	Yes	Yes
Conflict of interests							
Were there any potential conflicts of interest?			No	No	Not stated	No	No
If there were potential conflicts of interest, were steps taken to address these?			NA	NA	NA	NA	NA

APPENDIX 4 CONTINUED:

QUESTIONS	HELPER QUESTIONS	SPECIFIC ELEMENTS EXAMINED	Smith, 2010	Feldman, 2013	Jacobs Van Der Bruggen, 2007	Irvine, 2011	Sagarra, 2013
ASSESSMENT OF RELEVANCE							
1. Is the population relevant?	Are the demographics similar?	Age, ethnicity, gender	US population, 55 yrs age 27.1% African American	Not reported	Age: 30-60 years	Age: 40-70 years BMI>=25kg/m 2 First degree relative with T2DM or waist circumference >94cm men and >80 cm women, history of coronary heart disease, IFG or gestational diabetes	Age: 45-75 years
	Are risk factors similar?	Type of pre-diabetes, BMI	BMI >=25kg/m2 and metabolic syndrome	Participants with metabolic syndrome recruited (central obesity, high triglyceride and HDL, high blood pressure, impaired fasting glucose or previously diagnosed T2DM). 34% of participants had T2DM	Intensive intervention for obese adults Community intervention for the whole population	IFG and T2DM	IGT, IFG or IGT and IFG

	Are behaviors similar?	Compliance with intervention	47% who screened positive enrolled in intervention	Non compliance not modelled, participation rates based on Kalmar Metabolic Syndrome Program	50% compliance with intensive lifestyle intervention	Compliance with intervention included (57-97% in different activities)	Failure to attend screening (20%), failure to attend confirmatory blood test (42% of total population), failure to enrol in intervention (11.5%)
	Is the medical condition similar?		Yes	Yes	Yes	Yes	Yes
2 Are any critical interventions missing?	Does the intervention analyzed in the model match the intervention you are interested in?	Type of intervention	1. Lifestyle program (modified US DPP, less sessions and group format) 2. Usual care	1. Lifestyle program (Kalmar Metabolic Syndrome Program) 2. Usual care	1. Intensive lifestyle program (3 years) 2. Community-wide nutrition and exercise program 3. Usual care	1. Lifestyle program (UEA-IFG) 2. Usual care	1. Individual lifestyle program (DE-PLAN-CAT) 2. Group lifestyle program (DE-PLAN-CAT) 3. Usual care
	Have all relevant comparators been considered?		No, metformin not modelled	No, metformin not modelled	No, metformin not modelled	No, metformin not included	Metformin not included
	Does the background care in the model match yours?		US health system	Swedish health system	The Netherlands health system	UK health system	Spanish health system

3 Are any relevant outcomes missing?	Are the health outcomes relevant to you considered?		Yes, QALY	Yes, QALYs	Yes, QALYs	No, impact on diabetes incidence not considered	Yes, QALYs
	Are the economic end points relevant to you considered?		Yes, $/QALY	Yes, Euro/QALY	Yes, Euro/QALY	Yes, £/QALY	Yes, Euro/QALY
4. Is the context (settings and circumstances) applicable?	Is the geographic location similar?		US	Sweden	The Netherlands	The UK	Spain
	Is the time horizon applicable to your decision?		No, 3 year analysis	Yes, until 85 years of age	Yes, 70 years	No, less than 1 year	No, 4 year analysis
	Is the analytic perspective appropriate to your decision problem?	Health system or societal perspective	Health system perspective	Health system and Societal perspective	Health system perspective	Health system perspective	Health system perspective
ASSESSMENT OF CREDIBILITY							
Validation							
Is external validation of the model sufficient to make its results credible for your decision?	Has the model been shown to accurately reproduce what was observed in the data used to create the model?		Used previously published diabetes model	Not reported	Not reported	*Not a modelling study*	*Not a modelling study*
	Has the model been shown to accurately estimate what actually happened		Not reported	Not reported	Not reported		

	in one or more separate studies?						
	Has the model been shown to accurately forecast what eventually happens in reality?		Not reported	Not reported	Not reported		
Is internal verification of the model sufficient to make its results credible for your decision?	Have the process of internal verification and its results been documented in detail?		Used previously published diabetes model	Not reported	Based on previously published model (National Institute for Public Health and the Environment (RIVM) chronic disease model (CDM)	*Not a modelling study*	*Not a modelling study*
	Has the testing been performed systematically?		Not reported	Not reported	Not reported		
	Does the testing indicate that all the equations are consistent with their data sources?		Not reported	Not reported	Not reported		
	Does the testing indicate that the coding has been correctly implemented?		Not reported	Not reported	Not reported		
Does the model have sufficient face validity to make its results credible for your decision?	Does the model contain all the aspects considered relevant to the decision?		Yes	Yes	Yes	*Not a modelling study*	*Not a modelling study*

	Are all the relevant aspects represented and linked according to the best understanding of their characteristics?		Yes	Yes	Yes		
	Have the best available data sources been used to inform the various aspects?		Yes	Yes	Yes		
	Is the time horizon sufficiently long to account for all relevant aspects of the decision problem?		No, 3 year analysis	Yes	Yes		
	Are the results plausible?		Yes	Yes	Yes		
	If others have rated the face validity, did they have a stake in the results?		Rating of face validity not reported	Rating of face validity not reported	Rating of face validity not reported		
Design							

Is the design of the model adequate for your decision problem?	Was there a clear, written statement of the decision problem, modeling objective, and scope of the model?		Yes	Yes	Yes	Not a modelling study	Not a modelling study
	Was there a formal process for developing the model design (e.g. influence diagram, concept map)?		Not reported	Not reported	Not reported		
	Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context?		Yes	Yes	Yes		
	Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem?		Yes	Yes	Yes		

	Is the choice of model type appropriate?		Yes	Yes	Yes		
	Were key uncertainties in model structure identified and their implications discussed?		Yes	Yes	Yes		
Data							
Are the data used in populating the model suitable for your decision problem?	All things considered, do you agree with the values used for the inputs?	Duration and extent of impact of lfestyle intervention	Extent of impact: based on community based USDPP in Pennsylvania for year 1, then placebo arm of the USDPP for years 2 and 3	Improvements in risk profile seen following lifstyle program remain constant for 12 months after intervention (2 years in total), then decline annually, with no additional benefit modelled from the 5th year onwards	Community intervention: BMI decrease 0.05kg/m2 and 15% inactive individuals increase activity Intensive intervention: BMI decrease by 0.3kg/m2 1.5kg/m2 and 50-75% inactive individuals increase activity	Within-trial analysis	Yes, in-trial analysis
		Source of cost data	Community-based, modified USDPP, UKPDS, Framingham Heart Study	Kalmar Metabolic Syndrome Program	Two Dutch trials (HeartHealth Limburg, Lifstyel Intervention and Impaired Glucose Tolerance Maastricht)	UK trial (UEA-IFG)	Collection of cost data in DE-PLAN-CAT trial

		Source of outcome data	Community-based modified USDPP in Pennsylvania	Kalmar Metabolic Syndrome Program, literature	Literature	UK trial (UEA-IFG)	15D questionaire in DE-PLAN-CAT trial
		Discount rate	3% for costs and QALYs	3% costs and QALYs	4% cost and 1.5% effects	No discounting, analysis <1 year	No discounting due to short analytical time frame
Analysis							
Were the analyses performed using the model adequate to inform your decision problem?			Yes	Yes	Yes	Yes, but short timeframe limits applicability	Yes

Was there an adequate assessment of the effects of uncertainty?		Key sensitivity analyses	Probabilistic sensitivity analyses including: 1. Transition probabilities 2. Enrllment 3. Screening true positive rate 4. Utilities	Sensitivity analyses include: 1. Discount rate 2. Duration of relatiev risk reduction following lifetsyle program 3. Grouping by gender or risk factor	Sensitivity analyses: 1. Intervention costs 2. Discount rates	Sensitivity analyses: 1. Including costs of screening 2. IFG participants only 3. T2DM participants only 4. Only include participants with >4 months follow-up 5. Complete case results only 6. Excluding trainer costs	Sensitivity analyses: 1. Costs 2. Effectiveness of intervention
Reporting							
Was the reporting of the model adequate to inform your decision problem?	Did the report of the analyses provide the results needed for your decision problem?		Yes	Yes	Yes	Yes	Yes
	Was adequate nontechnical documentation freely accessible to any interested reader?		Yes	Yes	Yes	Yes	Yes, not a modelling study

	Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?		Yes	Unclear, supplementary material created but no longer available online	No	Yes	NA
Interpretation							
Was the interpretation of results fair and balanced?			Yes	Yes	Yes	Yes	Yes
Conflict of interests							
Were there any potential conflicts of interest?			Not stated	No	Not stated	No	No
If there were potential conflicts of interest, were steps taken to address these?			NA	NA	NA	NA	NA

APPENDIX 4 CONTINUED:

QUESTIONS	HELPER QUESTIONS	SPECIFIC ELEMENTS EXAMINED	Zhou, 2012	Dall, 2015
ASSESSMENT OF RELEVANCE				
1. Is the population relevant?	Are the demographics similar?	Age, ethnicity, gender	Age 12-64 years, 65-84 yrs US national population	Adults in US population (from NHANES)
	Are risk factors similar?	Type of pre-diabetes, BMI	Obesity and FPG or HbA1c	Elevated HbA1c
	Are behaviors similar?	Compliance with intervention	50-60% uptake of lifetsyle intervention modelled	Non-compliance not modelled

	Is the medical condition similar?		Yes	Yes
2 Are any critical interventions missing?	Does the intervention analyzed in the model match the intervention you are interested in?	Type of intervention	1. Lifestyle program (Group-based translation of USDPP) 2. Usual care	1. Lifestyle program (based on DPPOS) 2. Usual care
	Have all relevant comparators been considered?		No, metformin not included	No, metformin excluded
	Does the background care in the model match yours?		US health system	US health system
3 Are any relevant outcomes missing?	Are the health outcomes relevant to you considered?		Yes, QALYs	No, only report net savings
	Are the economic end points relevant to you considered?		Yes, $/QALY	No
4. Is the context (settings and circumstances) applicable?	Is the geographic location similar?		US	US
	Is the time horizon applicable to your decision?		Yes, 25 years	Yes, 10 years
	Is the analytic perspective appropriate to your decision problem?	Health system or societal perspective	Health system perspective	Societal perspective
ASSESSMENT OF CREDIBILITY				
Validation				

Is external validation of the model sufficient to make its results credible for your decision?	Has the model been shown to accurately reproduce what was observed in the data used to create the model?		Yes, used a previously published and validated model	Not reported
	Has the model been shown to accurately estimate what actually happened in one or more separate studies?		Yes, used a previously published and validated model	Not reported
	Has the model been shown to accurately forecast what eventually happens in reality?		Yes, used a previously published and validated model	Not reported
Is internal verification of the model sufficient to make its results credible for your decision?	Have the process of internal verification and its results been documented in detail?		Not reported	Yes
	Has the testing been performed systematically?		Not reported	Yes
	Does the testing indicate that all the equations are consistent with their data sources?		Not reported	Yes
	Does the testing indicate that the coding has been correctly implemented?		Not reported	Yes
Does the model have sufficient face validity to make its results credible for your decision?	Does the model contain all the aspects considered relevant to the decision?		Yes	Yes

	Are all the relevant aspects represented and linked according to the best understanding of their characteristics?		Yes	Yes
	Have the best available data sources been used to inform the various aspects?		Yes	No, assumes 50% reduction in incidence of T2DM d/t lfestyle programs
	Is the time horizon sufficiently long to account for all relevant aspects of the decision problem?		Yes, 2 years	Yes
	Are the results plausible?		Yes	No, due to assumptions regarding compliance and risk eduction
	If others have rated the face validity, did they have a stake in the results?		Rating of face validity not reported	Rating of face validity not reported
Design				
Is the design of the model adequate for your decision problem?	Was there a clear, written statement of the decision problem, modeling objective, and scope of the model?		Yes	Yes

	Was there a formal process for developing the model design (e.g. influence diagram, concept map)?		Yes	Yes
	Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context?		Yes	Yes
	Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem?		Yes	Assumptions regarding 100% compliance and 50% cumulative reduction in diabetes incidence are ambitious
	Is the choice of model type appropriate?		Yes	Yes
	Were key uncertainties in model structure identified and their implications discussed?		Yes	Yes
Data				

Are the data used in populating the model suitable for your decision problem?	All things considered, do you agree with the values used for the inputs?	Duration and extent of impact of lfestyle intervention	5% 60% reduction in diabetes risk in first 2 years of program, 10-15% in third year, no impact thereafter	41% cumulative reduction in diabetes incidence over 10 years is ambitious
		Source of cost data	Modified USDPP (Promoting a Lifestyle of Activity and Nutrition for Working to Alter the Risk of Diabetes) and DPPOS	Literature and MEPS/NHIS
		Source of outcome data	Claims data	Literature (CDC, UKPDS, Framingham)
		Discount rate	3% for costs and effects	3% for costs and QALYs
Analysis				

Were the analyses performed using the model adequate to inform your decision problem?			Yes	Yes
Was there an adequate assessment of the effects of uncertainty?		Key sensitivity analyses	Sensitivity analyses: 1. Effectiveness of lifestyle intervention 2. Costs of intervention 3. Age of participants 4. Costs of participation in screening test and intervention	Sensitivity analyses: 1. Intervention effect 2. HbA1c 3. BMI 4. Bood pressure 5. Lipid profile 3. Annual probablity of T2Dm and its complications
Reporting				
Was the reporting of the model adequate to inform your decision problem?	Did the report of the analyses provide the results needed for your decision problem?		Yes	Yes
	Was adequate nontechnical documentation freely accessible to any interested reader?		Yes	Yes

	Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?		No	Yes
Interpretation				
Was the interpretation of results fair and balanced?			Yes	Yes
Conflict of interests				
Were there any potential conflicts of interest?			Not stated	Yes
If there were potential conflicts of interest, were steps taken to address these?			No	Unclear

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7/8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Figures p12-22
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures p4-9 and p23-28
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures p11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P12 and p13-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

PRISMA 2009 Checklist

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PREVENTING TYPE 2 DIABETES: SYSTEMATIC REVIEW OF STUDIES OF COST-EFFECTIVENESS OF LIFESTYLE PROGRAMMES AND METFORMIN, WITH AND WITHOUT SCREENING FOR PREDIABETES

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PREVENTING TYPE 2 DIABETES: SYSTEMATIC REVIEW OF STUDIES OF COST-EFFECTIVENESS OF LIFESTYLE PROGRAMMES AND METFORMIN, WITH AND WITHOUT SCREENING, FOR PREDIABETES

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ABSTRACT:
(300 words)

Objective: Explore the cost-effectiveness of lifestyle interventions and metformin in reducing subsequent incidence of type 2 diabetes, both alone and in combination with a screening programme to identify high-risk individuals.

Design: Systematic review of economic evaluations.

Data sources and eligibility criteria: Database searches (Embase, Medline, PreMedline, NHSEED) and citation tracking identified economic evaluations of lifestyle interventions or metformin alone or in combination with screening programmes in people at high risk of developing diabetes. ISPOR's Questionnaire to Assess Relevance and Credibility of Modelling Studies for Informing Healthcare Decision Making used to assess study quality.

Results: 27 studies were included; all had evaluated lifestyle interventions and 12 also evaluated metformin. Primary studies exhibited considerable heterogeneity in definitions of pre-diabetes and intensity and duration of lifestyle programmes. Lifestyle programmes and metformin appeared to be cost-effective in preventing diabetes in high-risk individuals (median ICERs of £7,490/QALY and £8,428/QALY respectively) but economic estimates varied widely between studies. Intervention-only programmes were in general more cost-effective than programmes that also included a screening component. The longer the period evaluated, the more cost-effective interventions appeared. In the few studies that evaluated other economic considerations, budget impact of prevention programmes was moderate (0.13-0.2% of total healthcare budget), financial payoffs were delayed (by 9-14 years), and impact on incident cases of diabetes was limited (0.1-1.6% reduction). There was insufficient evidence to answer the question of 1) whether lifestyle programmes are more cost effective than metformin or 2) whether pragmatic (low-intensity) lifestyle interventions are more cost-effective than the more intensive lifestyle programmes that were tested in trials.

Conclusions: The economics of preventing diabetes are complex. There is some evidence that diabetes prevention programmes are cost-effective, but the evidence base to date provides few clear answers regarding design of prevention programmes because of differences in denominator populations, definitions, interventions and modelling assumptions.

INTRODUCTION:

Diabetes is a global health priority, with 415 million known adult cases worldwide, of which 91% are type 2 diabetes (1). Ageing of the population is predicted to drive substantial increases in prevalence (estimated to 642 million by 2040) (2), with particularly rapid increases in low- and middle-income countries (3). The burden of complications in diabetes is high, including heart disease, stroke, neuropathy, nephropathy and retinopathy (4). Type 2 diabetes develops as a result of genetic, environmental and behavioural factors, including sedentary lifestyle and energy-rich, nutrient-poor diet, both of which predispose to obesity (5).

Diabetes takes a significant toll on health budgets around the world, accounting for 5-20% of total healthcare expenditure in many countries (1). Both absolute costs and proportion of overall health budget for type 2 diabetes are set to increase further in future decades as prevalence rises, in the context of a marked reduction in the proportion of the population who are economically active (e.g. in the UK, the relative economic burden per worker is expected to increase by 40-50% by 2060 (6)). Cost-effective treatment and prevention strategies, with acceptable budget impact, will therefore become increasingly important as resources become stretched.

Types of prediabetes: Type 2 diabetes is often preceded by a phase of abnormal glucose regulation (prediabetes). Prediabetes is a generic term that includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and HbA1c in the 'at risk' range (7). One individual may have one, two or all of these types of prediabetes. Table 1 describes these different prediabetic states, how they are diagnosed and current diagnostic guidelines (8,9,10). The distinction between types of prediabetes is important for a number of reasons. Firstly, different definitions of pre-diabetes are associated with distinct physiological changes. Impaired fasting glucose is associated with reduced hepatic insulin sensitivity, and first phase insulin response; impaired glucose tolerance is associated with reduced peripheral insulin sensitivity and second phase insulin response and HbA1c reflects aggregated blood glucose levels over time (11). Secondly, progression to diabetes ranges from 3.6% to 7.6% annually depending on the type of pre-diabetes (12). Thirdly, impaired glucose tolerance is associated with increased risk of microvascular disease whereas the relationship is less clear for other types of pre-diabetes (7). Finally, there is evidence that people with different types of pre-diabetes respond differently to the same intervention. For example, in a large US trial, the US Diabetes Prevention Program, lifestyle programs were less effective and metformin more effective in participants with IGT *and* HbA1c in the 'at risk range' compared to the entire cohort which were identified on the basis of IGT (13).

Types of screening and prevention programmes: Prediabetes is almost always asymptomatic. It tends to be diagnosed incidentally (when blood tests are performed for other reasons) or as part of a pro-active screening programme delivered either to an entire population or to selected individuals. Most commonly, screening blood tests are offered to people identified as at high risk of developing diabetes based on demographic variables (e.g.

age, ethnicity), survey questions (e.g. family history of diabetes, personal history of gestational diabetes) or biomarkers (e.g. body mass index, blood pressure), typically combined in a 'diabetes risk score' (14). People diagnosed with prediabetes may be offered a lifestyle programme (to encourage a healthy diet and increased physical activity) or metformin. These interventions have been shown to delay or prevent type 2 diabetes in a significant proportion of participants in large randomised trials in the US (15), Europe (16), China (17) and India (18). Lifestyle programmes in these trials were intensive and sustained: 3-10 years of individual and group sessions provided by specialist staff (dieticians or exercise physiologists with annual physician review). Subsequent translation of these findings into large-scale community-based programmes produced interventions that were both shorter (3-12 months) and less intense (e.g. they offered less sessions and were delivered to groups rather than individuals by non-specialist staff such as lay workers or prevention managers). These large-scale community-based programmes have been offered to populations of similar age and BMI to the large trials but with different selection criteria (e.g. selection based on elements of the metabolic syndrome rather than the criteria of impaired glucose tolerance seen in the large trials) (19). There is some evidence that these pragmatic interventions offered to a real-world population deliver more limited and less sustained benefits than were seen with more intensive interventions in trial populations (20).

Given the potential impact on populations and health budgets, the burden of type 2 diabetes is a key issue for policy makers. In response, a number of countries, including the US and UK, are developing (or seeking to develop) national diabetes prevention programmes (21, 22). The design of large-scale prevention programmes incorporates a number of important choices: i) whether to screen a portion of the population for diabetes risk or focus on people who are already known to have prediabetes, ii) if no screening programme is in place, how to identify participants who may benefit from a diabetes prevention programme and iii) the role of different types of interventions (lifestyle programmes or metformin) and iv) the optimum intensity and duration of the programme.

This study was designed to help inform decision-making by local and national policy makers and health insurers in countries with a high and/or rising incidence of type 2 diabetes. Our research question were:

1. What is the evidence on cost-effectiveness of lifestyle programmes or metformin in diabetes prevention?
2. What is the impact of the following factors on the cost-effectiveness of these interventions?
    a. Type of pre-diabetes (IFG, IGT or 'at risk' HbA1c)
    b. Intensity of lifestyle intervention: Including three different measures of intensity, each of which was examined separately: i) frequency of contact in initial 'core' teaching/coaching sessions, ii) duration of core and maintenance intervention and iii) group or individual format of sessions)
    c. Inclusion of screening: Intervention-only studies on a predefined prediabetic *or* high-risk population or screening for prediabetes followed by intervention
    d. Years of follow-up to evaluate diabetes incidence: less than 10 years and more than 25 years.

3. What are the implications of these findings for policy makers and health insurers?

A number of systematic reviews of economic evaluations of diet and exercise in diabetes prevention have been undertaken in the last 10 years (23-27). This paper is the first review to consider the cost-effectiveness of metformin and the first review to examine intervention-only and screening-plus-intervention studies separately. In addition, this paper adds to previous reviews by updating the dataset with two new primary studies not included in previous systematic reviews (28,29) and evaluating studies' relevance for decision making by policy makers and health insurers.

METHODS:

Search strategy and inclusion criteria: A database search (covering Embase, PreMedline, Medline and NHS EED) for peer-reviewed articles on pre-diabetes and diabetes prevention between 2004 (the year before the publication of the first cost-effectiveness review of the US Diabetes Prevention Program) and 2014 identified 3833 papers. Search terms are outlined in Appendix 1. Citation tracking and screening of references (in included studies and review articles) identified a further 23 papers up to April 2016. We included studies that reported full economic evaluation (cost-effectiveness, cost-utility or cost benefit analysis) of i) lifestyle programmes, ii) metformin or iii) screening in combination with lifestyle programmes and/or metformin against a base case of usual care or no intervention.

To meet our inclusion criteria, economic evaluations needed to have:

1. Evaluated the treatment of prediabetes with either metformin and/or lifestyle programmes (that addressed diet *and* physical activity);
2. Included 12 months or more of intervention and follow up;
3. Quantified outcomes (such as change in quality adjusted life years, disability adjusted life years, life years gained or numbers needed to treat to prevent one case of type 2 diabetes);
4. Described the method used to classify people as high-risk of developing type 2 diabetes (hence eligible for interventions), including blood tests for pre-diabetes (any in Table 1); screening questionnaires, diabetes risk algorithms or presence of particular risk factors.

Review articles were excluded as were articles focusing only on women with a history of gestational diabetes.

Full papers meeting the above criteria were reviewed; data were extracted from included papers (by SR) and data extraction for a third of papers was checked by a second reviewer (EB).

Quality assessment: A checklist developed by the International Society for Pharmaco-economics and Outcomes Research (the ISPOR-AMCP-NCP questionnaire (30)) was used to evaluate the relevance and credibility of modelling studies for decision-making by policy makers.

Assumptions and calculations: All the economic evaluations included in this review were cost-effectiveness analyses (including cost-utility analyses), which measure both the cost of

the intervention and the impact of the intervention on participants' quality and/or length of life (31). No full cost-benefit analyses were identified. Cost effectiveness analyses report their results as ratios of incremental costs divided by incremental benefits; in an incremental cost effectiveness ratio (ICER). Resources to spend on healthcare are finite, so policy makers set a 'willingness to pay' threshold against which a treatment's incremental cost-effectiveness ratio is compared. Historically, the National Institute for Clinical Excellence in the UK has approved new technologies below the willingness to pay threshold of £20,000 – £30,000/QALY (32), the US has used a threshold of $50,000/QALY (33) and the WHO has recommended cost less than the per capita gross domestic product of the relevant country per disability adjusted life year as the threshold (34). For this review we used a willingness to pay threshold of £20,000/QALY. This means that if an intervention is below the willingness to pay threshold (costs less than £20,000 per quality adjusted life year), the intervention is considered *cost-effective.* If the intervention costs more than the willingness to pay threshold, it is considered not cost-effective. An intervention is only *cost-saving* if it is more effective *and* costs less than current treatment.

Costs are reported in British pounds 2015 using purchasing power parity and currency exchange rates from the CCEMG - EPPI-Centre Cost Converter (35). Costs of lifestyle interventions were calculated in 2015 British pounds where sufficient data was available on constituent activities and staff involved, drawing on the Personal Social Services Research Unit (36) for UK staff cost estimates.

Incremental Cost Effectiveness Ratios (ICERs) are reported separately for each outcome measure: as either cost saving or £/Quality adjusted life year gained (£/QALY), £/disability adjusted life year averted (£/DALY) or £/life year gained (£/LYG).

Definitions of measures of effectiveness used in included studies (37, 38):

Quality adjusted life year (QALY): A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.

Disability adjusted life year (DALY): A measure of the impact of a disease or injury in terms of healthy years lost.

Life years gained (LYG): A measure of the impact of a disease or treatment on the length of life. Years of life are not adjusted to reflect health or disability.

Incremental cost-effectiveness ratios (ICERs) are reported from two different perspectives: health system and societal perspective. The health system perspective includes only direct medical costs such as: i) staff, facilities, medication and consumables costs required for provision of the intervention, and ii) general healthcare of participants. In addition, studies of cost effectiveness from a societal perspective include some or all elements of i) indirect costs of the intervention (e.g. exercise equipment, food preparation equipment), ii)

participant time (travelling to and participating in intervention's activities), iii) lost productivity due to absence from work and iv) disability benefits payments.

Studies were grouped on a number of dimensions to identify key drivers of differences through subgroup analysis. Subgroups examined included: type of prediabetes, intensity of lifestyle intervention (defined by number of sessions in 'core' intervention, duration of core and maintenance program, group vs. individual format), inclusion of screening, years of follow-up to evaluate diabetes incidence. Sub-group medians could not be derived for the type of prediabetes, as the majority of studies used impaired glucose tolerance to identify eligible participants (with or without impaired fasting glucose), and there were 2 or less studies that reported £/QALY using each of the remaining methods of identification. Therefore, in order to understand the potential significance of the type of prediabetes we undertook a meta-analysis of randomised controlled trials of lifestyle programmes for diabetes prevention. Data was extracted from the 22 primary studies that reported diabetes incidence as an end-point that were included in three recent systematic reviews of lifestyle programmes in diabetes prevention (39,40,41). Data was analysed in RevMan (Review Manager version 5.3). Due to the heterogeneity of the primary studies we used a random-effects model and analysed subgroups defined by the trials' inclusion criteria (IFG, IGT, HbA1c or risk score) and duration of the intervention. Forest plots were generated to illustrate the relative risk of diabetes following a lifestyle programme for each of these groups compared to no intervention.

Patient and public involvement: This review was conceptualized by a multi-disciplinary group, including lay members, in Newham, East London. The authors attended regular project meetings of this group, reporting back the results of the review to the rest of the team. Findings of this review are being used to inform the evaluation of a large voluntary-sector led prevention initiative in this borough.

RESULTS

42 full papers were reviewed and 15 were excluded for reasons outlined in Figure 1.

In total, 27 studies of diabetes prevention programmes with economic evaluations have been published from 15 countries between 2004 and 2016 (28,29,42-66). 6 of the economic evaluations were within-trial cost-utility analyses and 21 were modelling studies (16 Markov models, two simulation models, two decision trees and one combination Markov model and decision tree). Within the modelling studies there were a wide range of model structures, parameters and parameter values which in part drive the variability observed in study results (67).

Type of intervention: All 27 studies evaluated lifestyle interventions and 12 also evaluated metformin (Appendix 2). 13 reported interventions in a population previously identified as prediabetic (people with IFG, IGT or high HbA1c) and 14 reported screening of a broader population and subsequent intervention on those identified as high risk of developing type 2 diabetes. The majority of studies evaluated intensive trial-based interventions, although there was a great deal of heterogeneity in the type of lifestyle interventions evaluated.

Table 2 describes some of the dimensions on which lifestyle programmes differed: frequency of contact, duration, staff providing intervention, individual vs group interventions and frequency of contact.

3 studies (56, 61, 47) did not specify the details of their lifestyle interventions.

Intensive trial-based lifestyle programmes: 18 of the 24 studies that did describe in detail the lifestyle intervention being evaluated were based on intensive trial-based lifestyle interventions (8 based on the US Diabetes Prevention Program, 4 on the US Diabetes Prevention Program together with the US Diabetes Prevention Program Outcome Study, 3 on the Finnish Diabetes Prevention Study, one on the Da Qing study, one on the Indian Diabetes Prevention Programme and one on DE-PLAN-CAT) and 3 were based on community translation of these intensive interventions lasting 3-5 years. The primary studies were generously resourced, large (300-3000 participants) and provided lengthy interventions (3-10 years' duration) including 7-16 initial contacts in the 'core program' delivered by specialist staff (dieticians, exercise physiologists and annual medical review). Two within-trial studies (42,66) reported intensive trial-based lifestyle programme costs in sufficient detail for costs to be reconstituted on an activity based costing basis (Appendix 3). The costs in 2015 British pounds of these interventions were as follows: £2,915 per participant over 3 years for the USDPP lifestyle program, £4,001 per participant over 3 years for the Indian DPP lifestyle programme (excluding staff travel costs).

Translational community-based programmes: 3 of the 24 studies were based on community translation of these intensive interventions lasting 3-5 years and 3 studies were based on other published studies covering much smaller populations (<150 participants) and providing less intensive interventions (ranging from 12 weeks to 1 year in duration), delivered by non-specialist staff (diabetes prevention facilitators and lay workers).

Target population – demographics and type of pre-diabetes: The target population for 16 of the 27 studies were overweight individuals with impaired glucose tolerance (IGT), with or without impaired fasting glucose (IFG). 4 used IFG alone (44, 54, 58, 65), 2 used IGT *or* IFG (46, 53), 1 used IFG or HbA1c (55), 1 used HbA1c alone (29) and 3 used other methods of screening (such as diabetes risk algorithms, BMI or other elements of metabolic syndrome) (43,45,47). 17 out of 27 studies included participants based on a BMI greater than or equal to 24kg/m^2, 3 included participants based on a BMI greater than or equal to 30mg/kg2 and the remainder did not state a BMI cut-off for participation. A wide range of ages (from 18 years and older) were included.

Benefits of interventions: The primary benefit of diabetes prevention programmes is reduction in incidence of type 2 diabetes and its associated complications, measured in the number needed to treat to delay or prevent a case of diabetes or improvements in quality adjusted life years (QALYs), disability adjusted life years (DALYs) and life years gained (LYG), as summarised in Appendix 4.

Lifestyle interventions: 21 studies reported change in quality-adjusted life-years associated with lifestyle interventions with a median 0.159 (range: 0.003-2.91) increase in Q ALYs and 13 reported life-years gained with a median increase of 0.30 (range: 0.04-0.84) increase relative to usual care. This is equivalent to a median increase in 110 days of life or 58 days of life in optimal health for lifestyle programmes. Four studies reported numbers needed to treat with lifestyle programmes to prevent 1 case of type 2 diabetes with results ranging from 4.2-30.

Metformin: 8 studies measured change in quality-adjusted life-years associated with metformin therapy with a median of 0.105 (range: 0.01-2.83) increase in QALYs and 5 studies reported increase in life-years gained with a median gain of 0.14 (range: 0.05 to 0.3). This is equivalent to a median increase of 51 days of life and 38 days of life in optimal health for metformin. Two studies reported number needed to treat with metformin to prevent 1 case of type 2 diabetes as 6.9 and 27.9.

Side effects of screening or intervention: The impact of screening and intervention on length of quality of life was included as a change in incremental QALYs in a number of studies (51,52,53), and three studies modelled the impact of adverse effects explicitly (42,49,59).

'Value for money': Policy makers may consider a range of economic factors when considering a new programme: cost-effectiveness, budget impact, effect on incident cases of the disease and equity of healthcare provision (68). All studies included in this review considered cost effectiveness, reporting incremental cost-effectiveness ratios, 5 described budget impact, 2 modelled impact on incident cases of diabetes and none considered impact on equity of healthcare provision.

Cost-effectiveness: Overall, lifestyle interventions and metformin appeared to be cost effective in preventing diabetes in high-risk individuals, as summarised in Table 3, though there was wide variation in economic estimates between studies. Substantial differences in participant selection and intervention design, which reflect the different types of pre-diabetes and different types of interventions, as well as differences in model structure, parameters and parameter values make comparison between studies difficult.

There is insufficient evidence to suggest that lifestyle interventions or metformin will be cost saving. Out of 27 studies, lifestyle interventions were found to be cost saving in 2 studies from a health system perspective (55,59), cost saving from a health system perspective in some countries but not others in 1 study (49) and cost saving from a societal perspective in 3 studies (54,58,64). Of the 12 studies evaluating metformin, 2 studies concluded metformin was cost saving from a health system perspective (42,48), 1 study concluded metformin was cost saving from a health system perspective in some countries but not others (49) and 2 concluded metformin was cost saving from a societal perspective (42,63).

Lifestyle programmes appear to be cost effective. Of the 16 studies measuring effectiveness as £ per quality adjusted life years (£/QALY), the median incremental cost effectiveness ratio (ICER) from a health system perspective was £7,490/QALY (range: cost saving to £134,420/QALY) (Figure 2). Only 2 studies reported lifestyle interventions that were not cost

effective (costing more than £20,000 per quality-adjusted life-year); of these, one used a model substantially different in structure to other modelling studies included (the Archimedes model, which analyses changes in biological variables, such as insulin resistance, rather than transitions between disease states, such as prediabetes, which are used by other models) (50) and the other included analysis lasting only 1 year therefore the benefits of reduced incidence of diabetes were not included (44).

Metformin also appears to be cost effective from a health system perspective. Of the 7 studies measuring effectiveness as £ per quality-adjusted life-years (£/QALY), the median incremental cost effectiveness ratio (ICER) from a health system perspective was £8,428/QALY (range: cost saving to £32,430/QALY). 2 studies reported metformin to not be cost effective (costing more than £20,000 per quality-adjusted life-year): of these, one used a model substantially different in structure to other modelling studies included (the Archimedes model) (50) and the other was the first economic model of the US Diabetes Prevention Programme (51). The subsequent models based on the US Diabetes Prevention Programme and its follow up study have found metformin to be cost saving or cost effective (42).

Twelve studies compared lifestyle programmes and metformin directly. From a health system perspective, neither intervention appears more cost-effective than the other with 6 studies reporting lifestyle programmes more cost effective than metformin (48, 51, 59, 56, 60, 62), 5 studies (45, 42, 29, 49, 57) reporting metformin more cost effective than lifestyle programmes and one (64) showing less than 1% difference in cost effectiveness between the two. However, from a societal perspective, metformin appears more cost-effective than lifestyle programmes, with four (64,42, 50, 60) out of the five studies undertaking this analysis finding metformin more cost effective. This is because the cost of participants' time travelling to and attending lifestyle programme sessions is included in most calculations of cost from a societal perspective, but not from a health system perspective.

Given the range of screening and lifestyle interventions provided, and the range of cost effectiveness ratios, studies which reported ICERS as £/QALY from a health system perspective were grouped on a number of dimensions to identify key drivers of differences. The analyses revealed that:

1) Screening plus intervention studies tended to be less cost-effective than intervention-only studies on average, but both approaches were associated with a wide range of ICERs highlighting current uncertainties. Of the 10 studies that reported £/QALY from a health system perspective for intervention-only studies the median ICER was £4,606/QALY (range: cost saving to £134,420/QALY). And the median ICER for the 8 screening-plus-intervention studies was £7,814/QALY (range: £573 - £76,566/QALY).
2) In general, the longer the period evaluated the more cost-effective the interventions appeared. Studies that measured cost-effectiveness over a period of 25 years or more appeared more cost effective (median ICER: £2,976/QALY) than studies that measured cost effectiveness over 10 years or less (median ICER: £10,416).

3) There was insufficient evidence to conclude whether lifestyle programmes with a duration of less than 2 years, 2-6 years or more than 6 years were more or less cost-effective: Of the 9 studies that included lifestyle programs with a duration of more than 2 years and less than 6 years the median ICER was £3,275/QALY (range: cost saving to £134,420/QALY). Three studies included interventions less than 2 years' duration with a wide variety of results (ICERs of £3,215 [43], £10,471 [45] and £76,566 [44]). And three reported interventions of more than six years' duration with a median ICER of £7,628/QALY (range: cost-saving to £15,191/QALY).
4) There was insufficient evidence to conclude whether higher frequency of contact during 'core sessions' was more or less cost-effective: Of the 11 studies that included lifestyle programs with 16 or more core sessions the median ICER was £7,628/QALY (range: cost saving to £134,420/QALY). Three studies reported £/QALYs for lifestyle programs with <16 core sessions with widely varying results (ICERs of £3,215 [43], £3,275 [46] and £76,566 [44]).
5) There was insufficient evidence to conclude whether group or individual core sessions were more or less cost-effective: Of the 11 studies that included the core component of the lifestyle programme delivered on an individual basis the median ICER was £7,628/QALY (range: cost saving to £134,420/QALY). Three studies included lifestyle programs where the core component was delivered in groups with a wide range of results (ICERs of -£6,214 [55], £3,215 [43], £3,275 [46] and £76,566 [44]).

There were insufficient studies in each group to conduct cost-effectiveness sub-group analysis by type of pre-diabetes. However, our meta-analysis of intervention trials suggests that this may be an important factor. Meta-analysis of intervention trials (15-18, 68-88) (Figure 2) showed that lifestyle interventions greater than or equal to 3 years' duration for participants with IGT reduced the relative risk of developing diabetes by 45% (95% CI 28-57%). Lifestyle interventions lasting less than 3 years in participants with IGT showed a 26% (95% CIs 0 to 45%) relative risk reduction. There were insufficient studies to divide participants identified by other diagnostic criteria by duration of intervention. But for all studied that identified participants by IFG alone, IFG or IGT and presence of risk factors the relative risk of diabetes was reduced by 37% (95% CI 12%-55%), 23% (95% CI 5%-38%) and 11% (95% CI -0.2-22%) respectively. No studies used HbA1c alone as the diagnostic criteria for selecting participants.

Other measures impacting the 'value for money' judgement: Cost-effectiveness analysis only measures cost and benefit of an intervention for an individual participant. Policy makers, who are responsible for overall health budgets and the health of the population as a whole, may consider other measures (such as budget impact, impact on equity and impact on incident cases of the disease) when evaluating the impact of an intervention. In terms of budget impact, three studies (47, 61, 62) estimated the cost of implementing a national diabetes prevention programme to be between 0.13 and 0.2% of annual national health expenditure in the Netherlands, Germany and Australia. Two studies (61, 55) modelled annual expenditures for lifestyle programmes, showing that net savings only exceeded net expenditures 9-14 years after initiating the prevention programme.
Failure to attend screening, enrol in an intervention or comply with an intervention means that the number of cases of diabetes prevented is lower than might be anticipated when

extrapolating from trials. As a result of these factors, as well as the partial and finite impact of interventions, two studies (47, 62) estimated that only 0.1-1.6% of cases of diabetes would be prevented by a population-wide programme in the Netherlands and a region of Germany. As an example of how this population-wide impact is calculated, Icks (62) calculated that 29% of incident cases of diabetes in 3 years would be due to people with pre-diabetes (defined as impaired glucose tolerance in this study). Of this pre-diabetic population, 30% of people would attend the screening test (OGTT), 40% and 59% would participate in the lifestyle intervention and metformin respectively. 32% of these would develop diabetes in 3 years with no intervention and 9.3% and 28.8% would develop diabetes with lifestyle and metformin respectively which resulted in 0.2% of incident cases of diabetes being prevented by metformin and 0.8% by lifestyle programmes. These rates of attendance and enrolment are based on best estimates, a recent systematic review found significant variation in participation rates seen in studies of lifestyle programmes (89).

Quality, relevance/applicability and credibility of existing economic evaluations for current healthcare decision making: Evaluation of studies against ISPOR's Questionnaire to Assess Relevance and Credibility of Modelling studies for Healthcare Decision Making (30) (Appendix 5) raised a number of issues. The most important of these for policy makers are outlined below. No studies were excluded on the basis of this evaluation.

Relevance/applicability of included studies (Table 4): Given the variety of lifestyle programmes and range of different types of prediabetes, we examined the extent to which the included studies reflect national guidance in the UK (90, 91) and the US (9,21), and the areas in which they differ.

Health system context: 24 out of 27 studies were undertaken in high-income, predominantly Caucasian nations. Only two studies (64,66) were undertaken in developing countries, China and India.

Target population: Only 6 (44, 54, 55, 58, 65, 29) out of 27 studies used diagnostic tests for prediabetes that are in line with current UK guidance, that is HbA1c and fasting plasma glucose. The majority of studies, 16 out of 27 included participants with a positive oral glucose tolerance test (with or without fasting blood glucose). Prevalence differs between different types of pre-diabetes, with the potential to have a large impact on budgets. For example, one study in this review (53) compared the cost-effectiveness of different diagnostic tests and found that expanding the definition of pre-diabetes from IGT *and* IFG to IFG *or* IGT increased the number of eligible participants three-fold, with the savings from reduced diabetes incidence insufficient to offset the increase in cost, with a resulting small reduction in cost-effectiveness.

Type of intervention: 21 of the 27 studies evaluated intensive trial-based interventions or intensive translations of trial interventions, which reflect current ADA guidance (lifestyle interventions modelled on the USDPP, targeting 7% weight loss) (9). However, reviews of community translations of the US DPP trial showed that whilst these translational programs cost less to implement they were also less effective (19,20). The modelling studies based on the USDPP trial data may therefore not be relevant comparators for a USDPP-based community programme. In contrast, the National Institute of Clinical Excellence in the UK

and the Community Preventative Services Task Force in the US advocate a more pragmatic approach to lifestyle programmes. Only 3 studies (45, 43, 44) in this review are relevant comparators in terms of duration and intensity of lifestyle intervention and they report a wide range of cost effectiveness (from £3,215/QALY to £76,566/QALY). One study (44) (ICER £76,566) was an in-trial cost utility analysis over 1 year, therefore was unable to quantify the impact of the prevention programme on diabetes incidence. And one (43) assumed treatment effects equivalent to those seen in a trial of an intensive lifestyle programme.

Credibility of included studies: Two key issues emerged with the assessment of the credibility of the modelling studies included in this review: i) areas where updated evidence is available that may impact the evaluation and ii) areas where uncertainty persists and a range of assumptions are observed.

Availability of updated meta-analyses: 12 of the 21 modelling studies assumed reductions in diabetes incidence equivalent to that achieved in the US Diabetes Prevention Programme or Finnish Diabetes Prevention Study trials (relative risks of 0.50 at 3 years [15] and 0.40 at 6 years [16] respectively). However, two recent meta-analyses of randomised controlled trials (39,40), have shown a relative risk of diabetes of 0.59 and 0.64. And a meta-analysis of pragmatic lifestyle interventions (41) excluding large trials showed a relative risk of 0.74. The higher the relative risk, the less the effect of the intervention; therefore, these recent meta-analyses suggest that models based on DPP or DPS trial data will over-state the impact of interventions.

Key uncertainties regarding modelling assumptions: Firstly, uncertainty remains over the extent to which the reduction in diabetes incidence persists once the intervention has ended. Studies included in this review made a wide range of assumptions on this point, ranging from no effect after the intervention ended to effects persisting until the participant developed type 2 diabetes or died. One recent meta-analysis (39), showed relative risks of 0.80 at up to 20 years follow up. However, this analysis includes predominantly the large trials (US DPP, FDPS and Da Qing) as long term follow up data is not available on community-based translational studies. Therefore, this relative risk likely overstates the long term benefits of interventions outside the trial context. Secondly, uncertainty persists over the percentage of people that fail to enrol in lifestyle interventions following screening. Reflecting this uncertainty, 5 studies included in this review assumed 100% enrolment, 2 assumed between 50 and 99% and 5 assumed less than 50% enrolment. A recent systematic review (89) found that enrolment in interventions varies widely (from 0.28% to 100%) depending on method of communication, setting, and type of intervention. Finally, based on included studies, the relationship between the type of prediabetes and cost-effectiveness of the study is unclear. A factor which may be important given the differences in relative risk reductions illustrated by our meta-analysis.

DISCUSSION:

Principal findings: This systematic review of economic evaluations of diabetes prevention programmes has produced seven major findings. First, that numerous economic evaluations have been undertaken in fifteen different countries and produced diverse results, due to differences in model structure and parameter values and to differences in

health systems, types of prediabetes and types of lifestyle interventions included. Second, that the majority of evaluations relate to intensive trial-based interventions in populations in high-income countries identified with the oral glucose tolerance tests. Third, that with these caveats in mind, both metformin and lifestyle interventions in people with prediabetes appear to be cost-effective but not cost saving despite their impact on reducing diabetes incidence, with median ICERs of £8,428/QALY and £7,490/QALY respectively. To place this figure in context, smoking cessation services are estimated by NICE to have ICERs ranging from cost-saving to £984/QALY (92) and breast cancer screening is estimated to have an ICER of £20,800/QALY by the UK Panel on Breast Cancer Screening (93). The fact that diabetes prevention programmes are not cost saving is not due solely to the issue of discounting, as three studies (42, 56, 64) report undiscounted cost-effectiveness ratios with only one of those appearing cost-saving. Fourth, that metformin and lifestyle programmes appear equally cost-effective when only the costs of the health system are taken into account, but metformin is more cost-effective when costs of participants' time (participating in and travelling to programme activities) is taken into account. Fifth, screening-plus-intervention programmes were less cost effective on average than intervention-only programmes. But both approaches were associated with a wide range of cost effectiveness ratios and the population benefit of screening in identifying people with previously undiagnosed prediabetes is not taken into account in a cost-effectiveness calculation. Sixth, there is insufficient evidence to deduce what intensity, duration or format or lifestyle programmes are more cost-effective than others. Finally, programmes that evaluated costs and benefits over 25 years or more were more cost effective than those that looked at 10 years or less.

Implications for policy makers: Both the type of prediabetes and the type of lifestyle program have a substantial impact on the number of cases of diabetes that are delayed or prevented. Guidance in the UK and the US advocate lower intensity pragmatic lifestyle programmes and there is a small amount of evidence that these are cost-effective. In light of recent meta-analyses, historical studies are likely over-stating treatment effects and uncertainty over duration of impact limits accurate long-term modelling. Guidance in the UK advocates the use of fasting plasma glucose or HbA1c in identifying people with pre-diabetes. There is currently insufficient data to conclude that interventions in people identified solely with HbA1c are cost-effective, and no randomised controlled trials with HbA1c as the inclusion criteria to enable estimation of treatment effects. There is insufficient evidence to suggest that metformin is more cost-effective than lifestyle programmes.

Policy makers need to make decisions even when all the evidence is not available, as is the case with the English national diabetes prevention programme (Healthier You: The NHS DPP) (22) which provides low intensity lifestyle programmes to people with IFG and or high HbA1c. In this case, rigorous evaluation alongside policy implementation could add to the evidence base, examining: i) what reduction in relative risk is associated with a large-scale implementation of a low-intensity lifestyle programme?, ii) how does this reduction in risk attenuate over time?, iii) how does reduction in relative risk differ by type of prediabetes?

In addition to these considerations of cost effectiveness, policy makers may need to balance impact on health budgets, incident cases of diabetes and equity of healthcare provision. In

the few studies where these were modelled, budget impact was moderate (prevention programmes required 0.13-0.2% of respective countries total healthcare budget), financial payoffs were delayed (net expenditure on treatment and prevention of diabetes only declined after 9-14 years) and impact on incident cases of diabetes was limited (0.1-1.6% reduction in incident cases). This suggests that other avenues to reducing incident cases of diabetes will need to be explored if substantial inroads are to be made in controlling the diabetes 'epidemic'. These may include population-wide measures to address obesity, a primary determinant of progression to type 2 diabetes in a person with pre-diabetes (94).

Comparison with previous systematic reviews: Our findings confirm those of previous systematic reviews which have shown that lifestyle interventions are generally cost-effective, but with a wide range of cost-effectiveness ratios, reflecting heterogeneity of interventions, target populations and modelling approaches. They have shown that lifestyle interventions appear more cost-effective if group, rather than individual sessions, are provided and a long time-horizon is adopted for analysis. They have raised the issue of the limited number of studies in developing countries, the concern that real-life implementation of programmes will be less effective than trial-based interventions, and the uncertainty that persists regarding long-term efficacy of these interventions. This review has added to previous work in three key areas: evaluation of metformin, comparison of screening-plus-intervention against intervention-only studies and consideration of the relevance and credibility of studies for decision makers.

STRENGTHS AND LIMITATIONS

To our knowledge, this is the largest and most up-to-date summary of economic evaluations of diabetes prevention programmes and the only one to include comparison with metformin and consideration of relevance and credibility for policy makers. We undertook a detailed analysis of assumptions underpinning modelling studies and compared these with findings from clinical trials.

Limitations are the small number of economic evaluations included that reflect prevailing national policy and the preponderance of studies from wealthy developed countries.

SUGGESTIONS FOR FURTHER RESEARCH

This study has identified three areas where further research would be beneficial. Firstly, developing an understanding of how people with different types of prediabetes respond to interventions and the subsequent cost-effectiveness profiles for different diagnostic-treatment combinations. This could be undertaken in both modelling studies, using recent evidence from meta-analyses, or retrospective analysis of existing trial data where different types of pre-diabetes may co-exist (e.g. IGT and HbA1c, IGT and IFG or IGT only participants). Secondly, long-term follow up studies of pragmatic lifestyle intervention programmes are important to understand the duration of impact on diabetes incidence following cessation of studies, uncertainty in this area limits the accuracy of long-term modelling studies. Finally, consideration of the role of broader social and environmental programmes (e.g. sugar tax, increasing walkability of neighbourhoods) on diabetes incidence will be important as, based on studies in this review, individual lifestyle programs and metformin are unlikely to be sufficient to address the vast majority of incident cases of diabetes.

CONCLUSIONS:
National diabetes prevention policy in the UK and US advocates pragmatic lifestyle programmes (less than 3 years in duration), and in the UK the use of HbA1c or fasting plasma glucose is recommended for diagnosing prediabetes. However, the majority of cost-effectiveness studies relate to a different definition of pre-diabetes and a higher intensity of intervention, which limits the direct applicability of findings. In the few studies that evaluated other economic considerations, budget impact of prevention programs was moderate, financial payoffs were delayed and impact on incident cases of diabetes was limited. There remains a need for long-term economic evaluation of programmes that reflect current policy and consideration of the role of broader social and environmental programmes on diabetes incidence.

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All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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REFERENCES

1. IDF, *International Diabetes Federation Diabetes Atlas*, International Diabetes Federation (IDF), 7th edition, 2015
2. Wild S et al. Global Prevalence of Diabetes: estimates for the year 2000 and Projections for 2030. *Diabetes Care* 27. 5 (2004): 1047-1053
3. WHO Diabetes Fact Sheet. Accessed at http://www.who.int/mediacentre/factsheets/fs312/en/ on 1st June 2016
4. Alberti KGMM, Zimmett P, Shaw International Diabetes Federation. A Consensus on Type 2 Diabetes Prevention. Diabet Med. 2007; 24: 451-63
5. P Zimmet, KG Alberti, J Shaw Global and societal implications of the diabetes epidemic. Nature. 2001; 414 (6865):782-787
6. Bagust A, Hopkinson PK, Maslove L, Currie CJ. The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060.Diabet Med. 2002 Jul;19 Suppl 4:1-5.
7. Yudkin J, Montori VM. The epidemic of pre-diabetes: the medicine and the politics. BMJ. 2014; 349: g4485
8. World Health Organization (2011) Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. World Health Organization, Geneva
9. American Diabetes Association. Standards of Medical Care in Diabetes 2016. Diabetes Care. 2016; 39: Suppl
10. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327– 1334
11. Faerch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired glucose tolerance: does it matter for treatment and prevention of type 2 diabetes. Diabetologica. 2009; 52: 1714-1723
12. Morris DH, Khunti K, Achana F, Srinivasan B, Gray LJ, Davies MJ, Webb D, Progression rates from HbA1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologica. 2013;56: 1489-1493
13. Diabetes Prevention Program Research Group. HbA1c as a Predictor of Diabetes and as an Outcome in the Diabetes Prevention Program: A Randomized Clinical Trial. Diabetes Care. 2014. Suppl. DOI: 10.2337/dc14-0886
14. Noble D, Mathur R, Dent T, Meeds C, Greenhalgh T. Risk models and scores for Type 2 Diabetes: A systematic review. BMJ 2011;343:d7163
15. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393-403.
16. Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, et al, Finnish Diabetes Prevention Study Group. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care. 2003; 26:3230-6.
17. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997; 20:537-44.
18. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian

Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006; 49:289-97.
19. Ali MK, Echouffo-Tcheugui J, Williamson DF. How Effective Were Lifestyle Interventions In Real-World Settings That Were Modeled On The Diabetes Prevention Program? Health Affairs. 2012: 1 (31): 67–75
20. Kahn R, Davidson MB. The reality of Type 2 Diabetes Prevention. Diabetes Care. 2014;37(4):943-949
21. The Community Guide. Diabetes Prevention and Control: Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among People at Increased Risk. Atlanta, GA: Community Preventive Services Task Force; 2014. Accessed on 19th April 2015 at www.thecommunityguide.org/diabetes/supportingmaterials/SScombineddietandpa-econ.html
22. The NHS Diabetes Prevention Program accessed on 19th April 2015 at https://www.england.nhs.uk/ourwork/qual-clin-lead/diabetes-prevention/
23. Alouki K, Delisle H, Bermudez-Tamayo C, Johri M, Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies Journal of Diabetes Research, 2016
24. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. Int J Environ Res Health. 2010 Aug;7(8):3150-95.
25. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010 Aug;33(8):1872-94.
26. Li R, Qu S, Zhang P, Chattopadhyay S, Gregg EW, Albright A, Hopkins D, Pronk NP. Economic Evaluation of Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Ann Intern Med. 2015 Sep 15;163(6):452-60.
27. Radl KI, Ianuale C, Boccia S. A systematic review of the cost-effectiveness of lifestyle modification as primary prevention intervention for diabetes mellitus type 2. Epidemiology Biostatistics and Public Health 2013 (10);2
28. Schaufler TM, Wolff M Cost effectiveness of preventive screening programs for type 2 diabetes mellitus in Germany. Appl Health Econ Health Policy. 2010;8(3):191-202
29. Dall TM, Storm MV, Semilla AP, Wintfield N, O'Grady M, Narayan KM, Value of lifestyle intervention to prevent diabetes and sequelae. Am J Prev Med. 2015 Mar;48(3):271-80
30. Caro J, Eddy DM, Kan H et al. Questionnaire to Assess Relevance and Credibility of Modeling Studies for Informing Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. Value in Health. 2014;17: 174-182
31. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. 2006 Oxford University Press
32. Devlin N, Parkin P. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? Department of Economics Discussion Paper Series, City University. Accessed on 14.10.2016 on https://www.city.ac.uk/__data/assets/pdf_file/0015/90501/0301_devlin-parkin.pdf

33. Groose SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert Rev Pharmacoecon Outcomes Res. 2008;8:165-178
34. World Health Organisation. Macroeconomics and Health: Investing in Health for Economic Development. Geneva.: World Health Organisation; 2001
35. http://eppi.ioe.ac.uk/costconversion/default.aspx. Accessed on the 20th September 2016
36. Curtis B, Burns A. Unit Costs of Health and Social Care 2015. Personal Social Services Research Unit Accessed 14.10.2016 on http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php
37. National Institute of Clinical Excellence. Glossary. Accessed 14.10.2016 on https://www.nice.org.uk/Glossary
38. Robberstad B. QALYs vs DALYs vs LYs gained: What are the differences, and what difference do they make for health care priority setting? Norsk Epidemiologi 2005; 15 (2): 183-191
39. Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Can type 2 diabetes be prevented using screen-and-treat policies? Systematic review and meta-analysis of screening tests and interventions for pre-diabetes. BMJ 2017 4;356:i6538
40. Balk EM et al. Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Annals of Internal Medicine. 2015;163 doi:10.7326/M15-0452
41. Ashra NB, Spong R, Carter P, et al. *A systematic review and meta- analysis assessing the effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes mellitus in routine practice*. London: Public Health England, 2015. Accessed 01.10.15 on https://www.gov.uk/government/publications/diabetes-prevention-programmes-evidence-review
42. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care. 2012; 35:723-30
43. Smith KJ, Hsu HE, Roberts MS, Kramer MK, Orchard TJ, Piatt GA, et al. Cost-effectiveness analysis of efforts to reduce risk of type 2 diabetes and cardiovascular disease in southwestern Pennsylvania, 2005–2007. Prev Chronic Dis. 2010; 7:A109.
44. Irvine L, Barton GR, Gasper AV, Murray N, Clark A, Scarpello T, et al. Cost-effectiveness of a lifestyle intervention in preventing type 2 diabetes. Int J Technol Assess Health Care. 2011; 27:275-82
45. Feldman I, Hellström L, Johansson P. Heterogeneity in cost-effectiveness of lifestyle counseling for metabolic syndrome risk groups—primary care patients in Sweden. Cost Eff Resour Alloc. 2013; 11:19
46. Sagarra R, Costa B, Cabré JJ, Solà-Morales O, Barrio F, el Grupo de Investigación DE-PLAN-CAT/PREDICE. Lifestyle interventions for diabetes mellitus type 2 prevention. Rev Clin Esp (Barc). 2014; 214:59-68
47. Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, Hoogenveen RT, Vijgen SM, Baan CA. Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. Diabetes Care. 2007; 30:128-34
48. Caro JJ, Getsios D, Caro I, Klittich WS, O'Brien JA. Economic evaluation of therapeutic interventions to prevent type 2 diabetes in Canada. Diabet Med. 2004; 21:1229-36

49. Palmer AJ, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland, and the United Kingdom. Clin Ther. 2004; 26:304-21
50. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med. 2005; 143:251-64
51. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al, Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005; 142:323-32
52. Ackermann RT, Marrero DG, Hicks KA, Hoerger TJ, Sorensen S, Zhang P, et al. An evaluation of cost sharing to finance a diet and physical activity intervention to prevent diabetes. Diabetes Care. 2006; 29:1237-41
53. Hoerger TJ, Hicks KA, Sorensen SW, Herman WH, Ratner RE, Ackermann RT, et al. Cost-effectiveness of screening for pre-diabetes among overweight and obese U.S. adults. Diabetes Care. 2007; 30:2874-9
54. Lindgren P, Lindström J, Tuomilehto J, Uusitupa M, Peltonen M, Jönsson B, et al, DPS Study Group. Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective. Int J Technol Assess Health Care. 2007; 23:177-83
55. Zhuo X, Zhang P, Gregg EW, Barker L, Hoerger TJ, Tony Pearson-Clarke, et al. A nationwide community-based lifestyle program could delay or prevent type 2 diabetes cases and save $5.7 billion in 25 years. Health Aff (Millwood). 2012; 31:50-60
56. Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT, et al. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. BMJ. 2008; 336:1180-5
57. Bertram MY, Lim SS, Barendregt JJ, Vos T. Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care. Diabetologia. 2010; 53:875-81
58. Neumann A, Schwarz P, Lindholm L. Estimating the cost-effectiveness of lifestyle intervention programs to prevent diabetes based on an example from Germany: Markov modelling. Cost Eff Resour Alloc. 2011; 9:17
59. Palmer AJ, Tucker DM. Cost and clinical implications of diabetes prevention in an Australian setting: a long-term modeling analysis. Prim Care Diabetes. 2012; 6:109-21
60. Png ME, Yoong JS. Evaluating the cost-effectiveness of lifestyle modification versus metformin therapy for the prevention of diabetes in Singapore. PLoS One. 2014; 9:e107225
61. Colagiuri S, Walker AE. Using an economic model of diabetes to evaluate prevention and care strategies in Australia. Health Aff (Millwood). 2008; 27:256-68
62. Icks A, Rathmann W, Haastert B et a', Clinical and cost-effectiveness of primary prevention of Type 2 diabetes in a real world routine healthcare setting: model based on the KORA survey 2000. Diabetic Med 2007; 24(5):473-80

63. Herman WH, Edelstein SL, Ratner RE et al, Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. Am J Manag Care 2013; 19(3):194-202
64. Liu X, Li C, Gong H et al, An economic evaluation for prevention of diabetes in a developing country: a modelling study. BMC Public Health 2013; 13(279)
65. Mortaz S, Wessman C, Duncan R, Gray R, Badawi A. Impact of screening and early detection of impaired fasting glucose tolerance and type 2 diabetes in Canada: A Markov model simulation. Clinicoecon and Outcomes Research. 2012;4:91-97
66. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial results of the Indian Diabetes Prevention Programme (IDPP). Diabetes Care. 2007 Oct;30(10):2548-52.
67. Sculpher MJ, Pang FS et al. Generalisability in Economic Evaluations studies in healthcare: a review and case studies. Health Technol Assess. 2004;8: 1-192
68. Daniels N, Porteny T, Urritia J. Expanded HTA: Enhancing Fairness and Legitimacy. Int J Health Policy Manag. 2016; 5(1): 1–3
69. Yates T, Davies M, Gorely T, Bull F, Khunti K. 2009. Effectiveness of a pragmatic education program designed to promote walking activity in individuals with impaired glucose tolerance. Diabetes Care, 32, 1404-1410
70. Parikh P, Simon EP, Fei K, Looker H, Goytia C, Horowitz CR. 2010. Results of a pilot diabetes prevention intervention in East Harlem, New York City: project HEED. Am J Public Health, 100, s232-s239.
71. Iqbal Hydrie MZ,Basit A,Shera AS,Hussain A. Effect of intervention in subjects with high risk of diabetes mellitus in Pakistan. J Nutr Metab. 2012;2012:867604. [PMID: 22888411] doi:10.1155/2012 /867604
72. Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, et al. Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. The Lancet Diabetes & Endocrinology. 2013;1(3):191-8
73. Oldroyd JC, Unwin NC, White M, Mathers JC, Alberti K. Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance. Diabetes research and clinical practice. 2006;72(2):117-27
74. Penn L, White M, Oldroyd J, Walker M, Alberti KGM, Mathers JC. 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(1):1
75. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar A, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289-97
76. Roumen C, Corpeleijn E, Feskens EJM, Mensink M, Saris WHM, Blaak EE. Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine. 2008;25(5):597-605
77. Sakane N, Sato J, Tsushita K, Tsujii S, Kotani K, Tsuzaki K, et al. Prevention of type 2 diabetes in a primary healthcare setting: three-year results of lifestyle intervention in Japanese subjects with impaired glucose tolerance. BMC Public Health. 2011;11(1):40

78. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract. 2005 Feb;67(2):152-62
79. Eriksson KF, Lindgarde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. Diabetologia. 1991 Dec;34(12):891-8
80. Katula JA, Vitolins MZ, Morgan TM, Lawlor MS, Blackwell CS, Isom SP, et al. The Healthy Living Partnerships to Prevent Diabetes study: 2-year outcomes of a randomized controlled trial. Am J Prev Med. 2013 Apr;44(4 Suppl 4):S324-32
81. Ma J, Yank V, Xiao L, Lavori PW, Wilson SR, Rosas LG, et al. Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Intern Med. 2013;173:113-21
82. Saito T, Watanabe M, Nishida J, et al. Lifestyle modification and prevention of type 2 diabetes in overweight japanese with impaired fasting glucose levels: A randomized controlled trial. Archives of Internal Medicine. 2011;171(15):1352-60
83. Xu DF, Sun JQ, Chen M, Chen YQ, Xie H, Sun WJ, et al. Effects of lifestyle intervention and meal replacement on glycaemic and body-weight control in Chinese subjects with impaired glucose regulation: a 1-year randomised controlled trial. The British journal of nutrition. 2013 Feb 14;109(3):487-92
84. Bhopal RS, Douglas A, Wallia S, Forbes JF, Lean ME, Gill JM, et al. Effect of a lifestyle intervention on weight change in south Asian individuals in the UK at high risk of type 2 diabetes: a family-cluster randomised controlled trial. The Lancet Diabetes & Endocrinology. 2014;2(3):218-27
85. Davies MJ, Gray LJ, Troughton J, Gray A, Tuomilehto J, Farooqi A, et al. A community based primary prevention programme for type 2 diabetes integrating identification and lifestyle intervention for prevention: The Let's Prevent Diabetes cluster randomised controlled trial. Preventive medicine. 2016 Mar;84:48-56
86. Costa B, Barrio F, Cabre´ JJ, Pin˜ol JL, Cos X, Sole´ C, et al; DEPLAN-CAT Research Group. Delaying progression to type 2 diabetes among high-risk Spanish individuals is feasible in real-life primary healthcare settings using intensive lifestyle intervention. Diabetologia. 2012;55:1319-28
87. Ockene IS, Tellez TL, Rosal MC, Reed GW, Mordes J, Merriam PA, Olendzki BC, Handelman G, Nicolosi R, Ma Y. 2012. Outcomes of a Latino community-based intervention for the prevention of diabetes: the lawrences latino diabetes prevention project. Am J Public Health, 102, 336-342
88. Vermunt PW, Milder IE, Wielaard F, de Vries JH, van Oers HA, Westert GP. Lifestyle counseling for type 2 diabetes risk reduction in Dutch primary care: results of the APHRODITE study after 0.5 and 1.5 years. Diabetes Care. 2011;34:1919-25
89. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programmes: learnings from the last 15 years Implementation Science 2015 10:172
90. National Institute for Health and Care Excellence. Type 2 diabetes: prevention in people at high risk. NICE Guideline PH 38. Accessed at https://www.nice.org.uk/guidance/ph38 on 20.3.16.2012
91. National Institute of Clinical Excellence. Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. Costing template. July 2012. Accessed on 07.09.2016 at https://www.nice.org.uk/guidance/ph38/resources/costing-report-68964013

92. National Institute of Clinical Excellence. Cost effectiveness of Interventions for Smoking Cessation: Final Report. 2007
93. Pharoah P, Sewell B, Fitzsimmons D, Bennett HS, Pashayan N. Cost effectiveness of the NHS breast screening programme: life table model. BMJ 2013;346:f2618
94. Cobiac LJ, Veerman L, Vos T. The Role of Cost-Effectiveness Analysis in Developing Nutrition Policy. Annu Rev Netr 2013;33: 373-93

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Tables/figures appendix pg 12-13
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5/6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables/figures appendix p14-24
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables/figures appendix p6-9 and p27-32
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables/figures appendix p11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Quality assessment: tables/figures appendix p32-90
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified	15

PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

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