National Institute for Health and Care Excellence

Final

Type 2 diabetes: prevention in people at high risk

[A] Evidence reviews for interventions for people at high risk of type 2 diabetes

NICE guideline PH38

Evidence reviews

September 2017

These evidence reviews were developed by the NICE guideline updates team

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Review question 1

What is the effectiveness of providing intensive face to face lifestyle-change programs, digitally delivered lifestyle-change programmes or metformin in preventing type 2 diabetes in adults with fasting plasma glucose concentrations of 5.5 – 6.9 mmol/L or HbA1c of 42 – 47 mmol/L (6.0% to 6.4%)?

Introduction

The previous version of the NICE guideline on the prevention of type 2 diabetes recommends that an intensive lifestyle modification programme is offered to people who are at high risk of developing type 2 diabetes, with fasting plasma glucose concentrations of 5.5 – 6.9 mmol/L or HbA1c of 42 – 47 mmol/L (6.0% to 6.4%). The aim of the update was to assess the clinical and cost effectiveness of intensive lifestyle modification programmes among subgroups of this high risk population to enable commissioners to target the intervention to those who will derive most benefit. A second aim was to assess the clinical and cost effectiveness of metformin or digitally delivered lifestyle interventions among the same population subgroups. In order to assess the clinical and cost effectiveness across subgroups, a health economic decision model was produced, in which subgroups were modelled. The aim of the clinical reviews was to provide key inputs to this decision model. The specific aim of review question 1 was to assess the effectiveness of intensive lifestyle interventions, metformin and digitally delivered lifestyle interventions for the prevention of type 2 diabetes.

PICO table

Population	Adults aged 18 years and over with fasting plasma glucose in the range 5.5 – 6.9 mmol/L or HbA1c in the range 42 – 47 mmol/mol (6.0% – 6.4 %)' or a history of gestational diabetes.
Intervention	• Intensive lifestyle change programme • Digitally delivered lifestyle change programme • Metformin
Comparison	• Any of the interventions described above • No treatment, usual care, placebo
Outcomes	• Progression to type 2 diabetes • Change in weight from baseline • Change in HbA1c levels from baseline • Change in Fasting plasma glucose from baseline • Adverse events and side effects (limited to gastrointestinal intolerance) • Systolic blood pressure • Total cholesterol

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

A systematic review of the literature was conducted, as specified in the review protocol in Appendix A.1. The protocol was developed in consultation with the topic expert members, and then reviewed by the core Committee members, before the review was carried out.

Several sources were used to identify articles for inclusion:

- A systematic review commissioned by Public Health England (https://www.gov.uk/government/publications/diabetes-prevention-programmes-evidence-review) was identified that partly matched the criteria in the review protocol. Studies from this review were considered for inclusion.
- A systematic search was conducted (see appendix B) to identify articles on intensive lifestyle modification that had been published since the systematic review by Public Health England (above) and studies on digital lifestyle modification programmes (which were not included in the Public Health England review.
- A systematic search was conducted (see appendix B) to identify articles on metformin.
- Studies included in the evidence review for the previous version of the NICE guideline on diabetes prevention on lifestyle modification or metformin were also considered for inclusion.

The titles and abstracts were screened and full-text version of articles that were identified as potentially relevant were obtained and reviewed against the criteria specified in the review protocol (appendix A.1).

For the outcome 'progression to type 2 diabetes', the majority of studies reported dichotomous data at a fixed timepoint. A minority of studies reported the number of cases of type 2 diabetes per 100 person years. In order to allow data to be compared across studies, these data were converted to dichotomous data by estimating the number of person years for each study group based on the mean follow up period. This was possible based on the assumption that type 2 diabetes could develop in each individual only once. We chose to convert rate data to dichotomous data (rather than vice versa) because fewer studies reported rate data, and so this required the least conversion.

Continuous outcomes in the review protocol were specified as change from baseline (for example, change in weight from baseline). Change scores were therefore preferred over endpoint scores when extracting data from studies. However, if a study reported an endpoint score but not a change score from baseline, these data were used in the analysis (see the Cochrane handbook for a discussion on combining change and endpoint data).

One study on Indian men (Ramachandran et al. 2013) reported change in BMI, but not change in weight as an outcome. Change in weight was estimated in this case by assuming a height of 164.7cm (the mean height for Indian men reported in a population study by Mamidi et al. 2011).

When more than one study assessed an outcome for a given comparison, data were combined using pair-wise meta-analyses. Five studies were included in the evidence review, but were not included in the primary analysis (see the 'included studies' section for details).

Meta-analysis was implemented using review manager (version 5.3). The Mantel-Haenszel and inverse variance methods were used for dichotomous and continuous outcomes, respectively. One study reported only relative effects between intervention groups (Ackermann 2015) and one study was a cluster randomised controlled trial (Davies 2016), which reported relative effects adjusted for baseline characteristics and clustering. The generic inverse variance data type was used for outcomes reported by these studies to allow these data to be correctly incorporated into the analysis. A random effects model was chosen

because the treatment effects were unlikely to be identical across studies due to differences in interventions across studies (the contents of lifestyle change programmes differed across studies). The I^2 and tau^2 statistics were calculated to assess heterogeneity. Forest plots showing the outcome of these meta-analyses are shown in appendix E.

Where possible, subgroup analysis was conducted according to the subgroups identified in the review protocol. Relevant subgroup data was reported by one trial (the US Diabetes prevention programme, Knowler 2002) for the metformin vs control comparison, and these data are shown in Appendices E 1.1 and E.1.2, respectively. Additionally, for the comparison of intensive lifestyle medication vs control and the outcomes 'change in weight' and 'change in HbA1c', across trials subgroup analyses were conducted based on mean baseline characteristics of the study populations. Across-trials analyses were not conducted for other comparisons and outcomes because of the very small number of trials in each subgroup. Results of the across trial subgroup analyses are shown in Appendix E.1.4.

Clinical evidence

Included studies

Fifteen randomised controlled trials were included in the review. One trial compared metformin, an intensive lifestyle programme and control, 2 trials compared metformin with control and 11 trials compared an intensive lifestyle programme with control. One trial compared a digital lifestyle intervention (text messaging) with control. A summary of the included studies is shown in Table 1. Full evidence tables are shown in appendix D.

Ten studies were included in the primary analysis. Four studies (Fontbonne 2009, Nilsen 2011, Van Name 2016, Yeh 2016) were not included in the primary analysis because data were based on completers only. The committee agreed that these studies may overestimate treatment effects because they did not take into account attrition from interventions in the study. Ramachandran 2006 was not included in the primary analysis because the dose of metformin given in this trial was 500mg/d, which the committee agreed was too low to be representative of practice in the UK, and much lower than the other trials in the review. The US diabetes prevention programme trial was included in the primary analysis comparing metformin with control, but was not included in the analysis comparing intensive lifestyle intervention with control because the Committee considered that the lifestyle intervention that was used in this trial was substantially more intensive than other trials in the review, and current UK practice. Studies that were included in the review, but not in the primary analysis are shown in the forest plots in Appendix D, but were assigned zero weight in the meta-analyses.

Excluded studies

Excluded studies (with reasons for exclusion) are shown in appendix K.

Table 1: Summary of clinical studies included in the evidence review

Study id	Primary publication	N	Intervention(s)	Reported outcomes
Metformin vs Intensive lifestyle programme vs Control				
US DPP 2002-2013	Knowler WC, Barrett-Connor E, Fowler SE et al. (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England Journal	3234	1700mg/d metformin 16 individual lessons in first 24 weeks then monthly group or	Progression to type 2 diabetes Change in weight HbA1c Fasting plasma glucose

Study id	Primary publication	N	Intervention(s)	Reported outcomes
	of Medicine 346(6), 393-403		individual sessions for reinforcement	Adverse events (gastrointestinal symptoms) Systolic blood pressure Total cholesterol
Metformin vs Control				
Ramachandran 2006	Ramachandran A, Snehalatha C, Mary S, Mukesh B, et al. (2006) 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 49(2), 289-97	269	500mg/d metformin	Progression to type 2 diabetes
Fontbonne 2009	Fontbonne A, Diouf I, Baccara-Dinet M, et al. (2009) Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: A post-hoc analysis of the BIGPRO1 trial. Diabetes and Metabolism 35(5), 385-91	101	1700mg/d metformin	Change in weight Change in fasting plasma glucose Change in systolic blood pressure Change in total cholesterol
Intensive lifestyle programme vs Control				
Ackermann 2015	Ackermann Rt, Liss Dt, Finch Ea, et al. (2015) A Randomized Comparative Effectiveness Trial for Preventing Type 2 Diabetes. American Journal of Public Health 105(11), 2328-34	509	16 group lessons in first 24 weeks then monthly support meetings	Change in weight Change in HbA1c Change in systolic blood pressure Change in total cholesterol
Davies 2016	Davies MJ, Gray LJ, Troughton J, et al. (2016) 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 84: 48-56.	880	Six hours of group sessions plus 3hr refresher sessions at 12 and 24 months and a 15 minute phone call every 3 months	Progression to type 2 diabetes Change in weight Change in HbA1c Change in fasting plasma glucose Change in systolic blood pressure Change in total cholesterol

Study id	Primary publication	N	Intervention(s)	Reported outcomes
Katula 2011	Katula JA, Vitolins MZ,; Rosenberger EL, et al. (2011). One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. Diabetes Care 34: 1451-7.	301	Weekly group sessions in first 6 months, 3 individual sessions at months 1, 3 and 6. One group session and 1 telephone contact in months 7-12.	Progression to type 2 diabetes Weight Fasting plasma glucose
Kulzer 2009	Kulzer B, Hermanns N, Gorges D, et al. (2009). Prevention of diabetes self-management program (PREDIAS): effects on weight, metabolic risk factors, and behavioral outcomes. Diabetes Care 32: 1143-6.	182	Twelve group lessons (one per week for 8 weeks, then 4 bi-monthly booster sessions).	Change in weight Change in HbA1c Change in fasting plasma glucose Change in systolic blood pressure Change in total cholesterol
Lindstrom 2003	Lindstrom J, Louheranta A, Mannelin M, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6	522	Eight individual sessions in first 9 months, then 3 per year for rest of study. Voluntary group sessions, lectures, exercise and cookery classes also available	Progression to type 2 diabetes Change in weight Change in HbA1c Change in fasting plasma glucose Change in systolic blood pressure Change in total cholesterol
Ma 2013	Ma J, Yank V, Xiao L, et al. (2013) Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Internal Medicine 173: 113-21.	160	Twelve weekly group lessons followed by email or phone contact every 2-4 weeks for rest of study	Progression to type 2 diabetes Change in weight Change in fasting plasma glucose Change in systolic blood pressure Change in total cholesterol
Mensink 2003	Mensink M, Blaak EE, Corpeleijn E, et al. (2003) Lifestyle intervention according to general recommendations improves glucose tolerance. Obesity research 11(12), 1588-96	114	14 group or individual sessions scheduled over course of study, with weekly physical activity classes offered	Progression to type 2 diabetes Change in weight Change in HbA1c Change in fasting plasma glucose Change in systolic blood pressure Change in total cholesterol
Nilsen 2011	Nilsen V ; Bakke PS ; Gallefoss F (2011) Effects of lifestyle intervention in	113	Six group day-long sessions over 6 weeks, with an	Weight HbA1c

Study id	Primary publication	N	Intervention(s)	Reported outcomes
	persons at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 11: 893		additional session after 12 weeks	Fasting plasma glucose Systolic blood pressure Total cholesterol
Oldroyd 2006	Oldroyd JC, Unwin NC, White M, et al. (2006) Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance. Diabetes research and clinical practice 72(2), 117-27	78	Twelve individual review appointments over 24 months, and 80% discount on use of public leisure facilities	Change in weight Change in fasting plasma glucose Change in total cholesterol
Van Name 2016	Van Name MA, Camp AW, Magenheimer EA, et al. (2016) Effective translation of an intensive lifestyle intervention for Hispanic women with prediabetes in a Community Health Center setting. Diabetes Care 39: 525-31.	122	Fourteen weekly group sessions, and access to exercise class 2-3 nights per week	Progression to type 2 diabetes Change in weight Change in HbA1c Change in fasting plasma glucose Change in systolic blood pressure Change in total cholesterol
Yeh 2016	Yeh M-C, Heo M, Suchday S, et al. (2016) Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City. Diabetic Medicine 33: 547-51.	60	12 bi-weekly group sessions then 6 monthly followup sessions	Change in weight Change in HbA1c Change in fasting plasma glucose Change in systolic blood pressure Change in total cholesterol
Digital lifestyle programme (text messaging) vs Control				
Ramachandran 2013	Ramachandran A, Snehalatha C, Ram J, et al. (2013) 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 1(3), 191-8	537	Text messaging intervention – received 2 to 4 messages per week throughout the study providing information on diet and physical activity and prompts to start physical activity and healthy dietary habits.	Progression to type 2 diabetes Weight Systolic blood pressure Total cholesterol

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The quality of evidence for each included study was assessed using the Cochrane risk of bias checklist (for the risk of bias assessment for each study, see the full evidence tables in

appendix D). The quality of evidence for each outcome for each comparison was appraised using the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (for full GRADE profiles, see appendix F). All included studies were randomised controlled trials. The criteria that were used to assign a rating of 'no serious', 'serious' or 'very serious' uncertainty for each domain are shown in Table 2.

The GRADE default minimally important differences were used for dichotomous outcomes (a relative risk of 0.75 and 1.25). For continuous outcomes, minimally important differences of -0.5 and 0.5 standard deviations differences were used. Published minimally important differences were sought for all outcomes via an internet search and through consulting the topic expert members, but none were found.

Table 2: Criteria for GRADE quality assessment

	No serious	Serious	Very serious
Risk of bias	<33% weight from studies judged high risk of bias	33-66% weight from studies judged high risk of bias	>66% weight from studies judged high risk of bias
Indirectness	<33% weight from studies not directly applicable to population, intervention, comparison and outcomes	33-66% weight from studies not directly applicable to population, intervention, comparison and outcomes	>66% weight from studies not directly applicable to population, intervention, comparison and outcomes
Inconsistency*	I^2 <40%	I^2 = 40-75%	$I^2 \geq 76\%$
Imprecision**	Confidence intervals do not cross minimum important harm or benefit	Confidence intervals incorporate minimum important harm or benefit and no important difference (as defined by the minimum important difference)	Confidence intervals incorporate minimum important harm and benefit
Other	No other serious uncertainty not captured above (including publication bias)	Serious uncertainty not captured above	Very serious uncertainty not captured above

** Not assessed when only a single study contributed to outcome*
*** Not assessed for outcomes feeding into health economic model, as uncertainty incorporated into probabilistic sensitivity analysis*

Economic evidence

Included studies

Nine economic studies were included in the review. Of these, 7 were cost–utility analyses comparing both lifestyle intervention and metformin with control. Two studies only compared lifestyle intervention with control but were included as 1 considered intervention at a range of fasting plasma glucose thresholds and the other was a UK study conducted from the perspective of the NHS, and were therefore both relevant to the review question.

Excluded studies

Excluded studies (with reasons for exclusion) are shown in appendix K.

Summary of studies included in the economic evidence review

Evidence from the 9 economic studies included in the review is summarised in Table 3 below and displayed in full in appendix H.

Seven studies assessed the cost–utility of lifestyle intervention or metformin compared with control in patients at high risk of diabetes, all of which found lifestyle intervention to generate the highest number of QALYs overall.

Of these, 3 studies reported in-trial economic analyses of DPP or DPP and DPPOS datasets. Diabetes Prevention Program (2003) conducted an evaluation using DPP data over a 3-year time horizon, and reported ICERs of USD $31,512 and $99,171 (around £25,400/QALY and £79,800/QALY – xe.com/currencyconverter – accessed 11/04/17) for lifestyle intervention versus placebo and metformin versus placebo, respectively, meaning metformin was extendedly dominated by lifestyle intervention and control. Diabetes Prevention Program (2012) conducted an evaluation using DPP and DPPOS data over a 10-year time horizon, and reported ICERs of USD $10,037 and $13,420 (around £8,100 and £10,800) for lifestyle intervention versus placebo and lifestyle intervention versus metformin, respectively. Herman et al. (2013) conducted an evaluation using DPP and DPPOS data over a 10-year time horizon for patients who were adherent to their assigned treatment. In the base case, this analysis reported that both lifestyle intervention and metformin dominate placebo, and lifestyle intervention has an ICER of $14,213/QALY (around £11,400/QALY) compared with metformin.

Four studies used modelling approaches to assess the cost effectiveness of lifestyle intervention and metformin. Herman et al. (2005) used a Markov model to extrapolate outcomes of the DPP over a lifetime time horizon, and reported ICERs of USD $1,124 and $31,286 (around £900 and £25,200) for lifestyle intervention versus placebo and metformin versus placebo, respectively, meaning metformin was extendedly dominated by lifestyle intervention and control. Palmer et al. (2012) used a Markov model to extrapolate the outcomes of the DPP over a lifetime time horizon in an Australian setting, using country-specific unit costs and utility scores. This analysis found that lifestyle intervention dominates control, and that metformin is extendedly dominated by lifestyle intervention and control.

Png et al (2014) used a decision tree to extrapolate the results of the DPP to a Singaporean population over a 3 year time horizon. This analysis reported ICERs of USD $16,920 and $28,100 (around £13,600 and £22,600) for lifestyle intervention versus placebo and metformin versus placebo, respectively, meaning metformin was extendedly dominated by lifestyle intervention and control. Eddy et al. (2005) used an individual patient simulation model (the Archimedes model) to predict outcomes for a patient population comparable to participants in the DPP. This analysis also included a strategy of only offering lifestyle intervention to patients if their FPG rose to above 125mg/dL. Results show that this strategy is associated with an ICER of USD $24,523 (around £19,700) compared with control, while a strategy of offering lifestyle intervention as per the DPP trial is associated with an ICER of $201,818/QALY (around £162,400/QALY) compared with intervening in patients with FPG >125mg/dL, while metformin was dominated.

Two included studies only compared lifestyle intervention with control. Zhuo et al (2013) used a modelling approach based on DPP and DPPOS effectiveness data to estimate the cost effectiveness of providing lifestyle intervention to patients at a variety of minimum FPG thresholds. This analysis showed that ICERs were inversely related to FPG threshold, with a threshold of 120mg/dL giving an ICER of USD $30,100 (around £24,200) and a threshold of 90mg/dL giving an ICER of $115,800 (around £93,200). Gillett et al (2012) used a modelling approach to evaluate the cost effectiveness of lifestyle intervention compared with control for

a UK population from the perspective of the NHS. Results showed that lifestyle intervention is associated with an ICER of £1,819/QALY.

Table 3: Summary of evidence from economic review

Study, comparators, currency	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	QALYs	ICER	
Diabetes prevention program, 2003 Lifestyle intervention v metformin v control USA (USD)	Partially applicable	Potentially serious limitations	In-trial analysis of DPP with 3 year time horizon Healthcare system perspective	Lifestyle intervention v control: $2,296 Metformin v control: $2,191	Lifestyle intervention v control: 0.072 Metformin v control: 0.022	Lifestyle intervention v control: $31,512 Metformin v control: $99,171	One-way sensitivity analyses show that the ordering of results is robust. Implementing a 50% reduction in personnel cost and making the assumption that lifestyle intervention is delivered as a group (with the same effectiveness) substantially reduces the ICER of lifestyle intervention.
Diabetes prevention program, 2012 Lifestyle intervention v metformin v control USA (USD)	Partially applicable	Minor limitations	In trial analysis of DPP and DPPOS with 10 year time horizon Healthcare system perspective	Lifestyle intervention v control: $1,226 Metformin v control: -$159	Lifestyle intervention v control: 0.12 Metformin v control: 0.02	Lifestyle intervention v control: $10,037 Metformin v control: dominates	One-way sensitivity analysis also reports ICERs without discounting. Lifestyle intervention v control: $6,651 Metformin v control: dominates

Study, comparators, currency	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	QALYs	ICER	
Eddy et al., 2005 Lifestyle intervention as per DPP v lifestyle intervention in patients with FPG>125mg/dL v metformin v control USA (USD)	Partially applicable	Minor limitations	Individual patient simulation model (Archimedes model) with 30 year time horizon Societal perspective	Lifestyle intervention in patients >125mg/dL: $3,066 DPP lifestyle intervention: $6,903 Metformin: dominated	Lifestyle intervention in patients >125mg/dL: 0.125 DPP lifestyle intervention: 0.034 Metformin: dominated	Lifestyle intervention in patients >125mg/dL: $24,523 DPP lifestyle intervention: $201,818 Metformin: dominated	Using a healthcare system perspective, DPP lifestyle intervention is associated with an ICER of around $143,000/QALY compared to control
Gillett et al., 2012 Lifestyle intervention v control UK (GBP)	Partially applicable	Minor limitations	Individual patient simulation model with lifetime time horizon Healthcare system perspective	Lifestyle intervention v control: £121	Lifestyle intervention v control: 0.0663	Lifestyle intervention v control: £1,819	One-way sensitivity analysis showed that, even under pessimistic assumptions, the ICER of lifestyle intervention remains cost effective

Study, comparators, currency	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	QALYs	ICER	
Herman et al., 2005 Lifestyle intervention v metformin v control USA (USD)	Partially applicable	Minor limitations	Markov model with lifetime time horizon Healthcare system perspective	Lifestyle intervention v control: $635 Metformin v control: $3,922	Lifestyle intervention v control: 0.57 Metformin v control: 0.13	Lifestyle intervention v control: $1,124 Metformin v control: $31,286	One-way sensitivity analysis shows that both treatments are more cost effective in younger patients (although lifestyle intervention remains clearly cost effective in any age group. Making the assumption that lifestyle intervention is delivered as a group therapy (with the same effectiveness) results in lifestyle intervention dominating both other interventions. Reducing the effectiveness of lifestyle intervention by 50% increases the ICER versus placebo to $7,886/QALY.

Study, comparators, currency	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	QALYs	ICER	
Herman et al., 2013 Lifestyle intervention v metformin v control in patients adherent to their assigned treatment USA (USD)	Partially applicable	Minor limitations	In-trial analysis with 10 year time horizon Healthcare system perspective	Lifestyle intervention v control: -$210 Metformin v control: -$1,086	Lifestyle intervention v control: 0.14 Metformin v control: 0.08	Lifestyle intervention v control: dominates Metformin v control: dominates	Discounting at 3% per year results in an ICER of $19,988 for lifestyle versus placebo, and an ICER of $20,183 for metformin versus placebo. Making the assumption that lifestyle intervention is delivered as group treatment (with the same effectiveness) results in lifestyle dominating placebo with no discounting and an ICER of $9,688/QALY versus placebo with a discount rate of 3% per year.

Study, comparators, currency	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	QALYs	ICER	
Palmer et al., 2012 Lifestyle intervention v metformin v control Australia (AUD)	Partially applicable	Minor limitations	Markov model with lifetime time horizon Healthcare system perspective	Lifestyle intervention v control: -$289 Metformin v control: $1,217	Lifestyle intervention v control: 0.39 Metformin v control: 0.12	Lifestyle intervention v control: dominates Metformin v control: $10,142	Setting the rate of progression to diabetes to the average rate over DPP and DPPOS trials and increasing cost of interventions by 20% and results in lifestyle intervention no longer dominating placebo. However, the ICER remains sufficiently low that lifestyle intervention is still clearly a cost effective treatment. Probabilistic sensitivity analysis shows that, at a threshold of $50,000/QALY, the probability of metformin and lifestyle intervention being cost effective is 78% and 100%, respectively.
Png et al., 2014 Lifestyle intervention v metformin v placebo Singapore (USD)	Partially applicable	Potentially serious limitations	Decision tree with 3 year time horizon Healthcare system perspective	Lifestyle intervention v control: $846 Metformin v control: $281	Lifestyle intervention v control: 0.05 Metformin v control: 0.01	Lifestyle intervention v control: $16,920 Metformin v control: $28,100	Deterministic sensitivity analyses were carried out in which the QALYs associated with each intervention were varied, and showed that ICERs were inversely related to QALY gain.

Study, comparators, currency	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost	QALYs	ICER	
Zhuo et al., 2013 Lifestyle intervention at varying thresholds of FPG USA (USD)	Partially applicable	Minor limitations	Markov model with lifetime time horizon Healthcare system perspective	FPG threshold for intervention (mg/dL): 120: - 115: $300 110: $600 105: $900 100: $1,400 95: $1,800 90: $1,700	FPG threshold for intervention (mg/dL): 120: - 115: 0.01 110: 0.02 105: 0.02 100: 0.03 95: 0.02 90: 0.01	FPG threshold for intervention (mg/dL): 120: - 115: $30,100 110: $32,900 105: $42,300 100: $60,700 95: $81,800 90: $115,800	A number of alternative scenarios were tested via one-way sensitivity analysis. Scenarios which had a considerable effect on ICERs were: • Using a lower-cost, lower-effectiveness intervention (PLAN4WARD) reduced ICERs • Considering only participants 45-49 years old reduced ICERs • Using cost and effectiveness data from the DPPOS as well as DPP increased ICERs • Making the assumption that interventions are 50% less effective after year 3 increased ICERs

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Economic model

The de novo economic analysis for this update was developed by the School of Health and Related Research (ScHARR) at the University of Sheffield, with input from the guideline committee. The modelling methodology and results are summarised below, with the full report displayed in appendix I.

Introduction & Aims

The previous NICE PH38 guideline indicates that all individuals at risk of type 2 diabetes, defined by a fasting plasma glucose level (FPG) of 5.5-6.9 mmol/L or HbA1c of 6-6.4% (42-48 mmol/mol) should be offered an intensive lifestyle intervention, with those who are unable to take up such an intervention being offered metformin. NHS England, Public Health England (PHE) and Diabetes UK have developed the NHS Diabetes Prevention Programme (NHS DPP) based upon NICE PH38 recommendations. The NHS DPP interventions are commissioned centrally by NHS England. The NHS DPP has different lifestyle change intervention characteristics, and do not correspond to the recommendations in the previous PH38 guideline, as these were based on the findings of a later systematic review.

Given that it has been estimated that there are 5 million individuals at risk of type 2 diabetes in England, and that the NHS DPP interventions will be available to only 100,000 individuals annually, there is a need to identify and prioritise those individuals who are expected to benefit most from the intervention. It is also important to determine whether metformin could be a cost-effective alternative to intensive lifestyle intervention in a wider group of individuals than those currently indicated in the NICE PH38 guidelines.

A subgroup cost-effectiveness analysis of the NHS DPP has already been carried out as part of work commissioned by PHE using the School for Public Health Research (SPHR) Diabetes Prevention model. However, this analysis did not include individuals identified through an FPG test, only looked at a set of non-mutually exclusive subgroups defined using a single population characteristic, and did not analyse the cost-effectiveness of metformin for diabetes prevention. The aim of this new analysis therefore was to model the clinical and cost effectiveness of intensive lifestyle-change programmes or metformin in preventing type 2 diabetes in a wider range of high risk population subgroups than previously analysed. This analysis was carried out with the help of a new NICE clinical effectiveness review and the input of the NICE guidelines committee.

Methods

The analysis was performed using an adaptation of the SPHR Diabetes Prevention model version 2.3, which takes the perspective of the NHS and personal social services over a lifetime horizon. The baseline population was taken from the Health Survey for England (HSE) 2011. Given that HSE 2011 does not include measurements of FPG, a statistical model was developed based upon analysis of the LEADER dataset, to derive an estimate of baseline FPG for each individual dependent upon other personal characteristics including HbA1c, BMI, gender, ethnicity, smoking status and total cholesterol.

Intervention effectiveness data was taken from the NICE clinical effectiveness review, which summarised available data on reduction in weight, HbA1c, systolic blood pressure, total cholesterol and diabetes incidence for each intervention compared to control (either no intervention or brief lifestyle advice), at one year and three year time points post intervention implementation. Three year diabetes incidence risk reduction data were not directly used as inputs in the model – the effectiveness of interventions in reducing the risk of diabetes was modelled as a function of reduction in weight, HbA1c, systolic blood pressure, and

cholesterol. Instead, these data were used to validate the model's HbA1c trajectory-based predicted diabetes incidence. Where necessary, the data were also used to calibrate the effectiveness of interventions in reducing HbA1c through trial and error to enable the model to approximate the observed diabetes incidence reduction. All 8 studies included in the NICE review for intensive lifestyle intervention, and the 1 study included for metformin, were intention to treat analyses, and therefore it was assumed that relevant adherence rates were incorporated in the effectiveness estimates. Initial uptake of the intervention was not modelled in this analysis; it was assumed that all eligible individuals had been previously identified as high risk based on a blood glucose measure and willing to at least initially take up the intervention.

Alternative scenarios were modelled in order to explore uncertainty around extent of intervention effectiveness, duration until waning of effect and stratification of effectiveness in terms of HbA1c reduction for subgroups defined by personal characteristics. Three intensive lifestyle intervention effectiveness scenarios were modelled: optimistic, conservative and pessimistic, depending upon whether the effectiveness estimates included results from both the US Diabetes Prevention Programme (US DPP) and Finnish Diabetes Prevention Study (DPS) (optimistic); Finnish DPS but not US DPP (conservative) or neither study (pessimistic); These studies had higher intensity interventions and a greater maintenance element in the years after the initial intervention than expected in the NHS DPP. Initial weight loss estimates in these three scenarios ranged from 2.97kg in the optimistic scenario to 2.15kg in the pessimistic scenario. Equally, two scenarios were modelled for the metformin intervention: optimistic, based on data from the US DPP in which initial weight loss was 2.27kg; and conservative, based on a proportional reduction in effectiveness in line with that seen in the conservative lifestyle intervention, in which initial weight loss was 1.84kg. Each of these five intervention scenarios was modelled under a set of four different conditions that depended upon whether or not the HbA1c effect was stratified by baseline age, BMI and FPG; and whether the HbA1c three year effect was assumed to persist until death/diabetes diagnosis, or return to baseline in line with weight regain. This resulted in twelve different intensive lifestyle intervention scenarios and eight different metformin intervention scenarios. In all scenarios, the duration of weight regain was estimated by linear projection of the regain slope between the year one and year three effectiveness data, which resulted in weight regain periods ranging between six and ten years. All scenarios also included stratification of weight loss by baseline BMI.

NHS England provided an updated estimate of the cost of the NHS DPP at £223 per person incurred as a one-off cost in the first year, incorporating expected participant retention rates. Metformin treatment was estimated at £138 in the first year; incorporating medication costs, additional blood tests and healthcare staff time, dropping to £54, £48 and £42 in years two, three and four onwards, to take account of a lower requirement for blood tests and staff time following treatment stabilisation from year two, and participant drop-out between years one and four.

Probabilistic sensitivity analysis (PSA) was carried out for each of the 20 intervention scenarios, plus the control scenario. 2000 PSA runs were performed on each of the 2,594 high risk individuals from HSE 2011, and per person results calculated following weighting of results to represent the population of England. The model collected a series of outcomes including total costs, quality-adjusted life years (QALYs) and diabetes incidence over time. All costs and QALYs were discounted at 3.5% per annum in the base case scenario and 1.5% per annum as a sensitivity analysis. Outcomes were collected for a total of 22 univariate subgroups defined as follows:

- Socioeconomic status (IMD quintiles 1-5)
- Age (<40; 40-59; 60-74; 75+)
- Gender (male; female)

- Ethnicity (white; BME)
- Baseline BMI (<25 kg/m2; 25-29.9 kg/m2; 30-34.9 kg/m2; 35+ kg/m2 in white individuals OR <23 kg/m2; 23-27.4 kg/m2; 27.5-34.9 kg/m2; 35+ kg/m2 in BME individuals)
- Baseline HbA1c (6-6.1%; 6.2-6.4%)
- Baseline FPG (5.5-5.9 mmol/L; 6-6.4 mmol/L; 6.5-6.9 mmo/L)

Outcomes for 24 combinatorial subgroups were also obtained, which included nine mutually exclusive subgroups defined through HbA1c criteria and 13 mutually exclusive subgroups defined through FPG criteria.

Results

The results indicate that the intensive lifestyle intervention is cost-effective compared to control in all scenarios and all subgroups tested. For the patient population overall, results also indicate that lifestyle intervention results in smaller lifetime costs and a higher number of lifetime QALYs than control. The net monetary benefit produced by lifestyle intervention compared to control for the total population at a threshold of £20,000 per QALY ranged from £223 to £4,897, depending on assumptions used in scenarios.

Optimistic scenarios always produce more benefit than conservative scenarios, which in turn produce more benefit than pessimistic scenarios. Assuming the HbA1c effect is persistent produces around five times as much benefit as assuming it returns to baseline in line with weight regain, whilst assuming the HbA1c effect is stratified has little impact upon the overall cost-effectiveness results. Whilst the relative cost-effectiveness of intervening in different subgroups does not vary depending upon whether optimistic, conservative or pessimistic estimates of intervention effectiveness are used, it does depend strongly upon whether the HbA1c intervention effects are assumed to be stratified and/or persistent.

In general, although results indicate that lifestyle intervention is cost effective across all subgroups, the results suggest that it is more cost-effective to intervene in individuals with high baseline HbA1c or FPG than individuals with lower baseline HbA1c or FPG, and individuals of BME rather than white ethnic backgrounds. However, in contrast to the previous PHE commissioned work, the finding that it is more cost-effective to intervene in individuals with high BMI than those with lower BMI, depends upon which judgement is made surrounding the assumptions around HbA1c effect stratification and persistence. If persistence is not assumed and there is no stratification then high BMI groups gain more net benefit than low BMI groups. If stratification is assumed or if lifetime persistence of HbA1c effect is assumed then this effect is lost and low BMI groups gain net benefit similar to or even higher than high BMI groups. This is because:

1. The applied BMI-dependent stratification of weight loss is smaller in the current analysis than in the previous PHE work because it is based on updated effectiveness data;
2. The high risk population includes a high proportion of individuals defined by FPG criteria, whose HbA1c is < 6% and who are at low risk of diabetes in the model;
3. The BMI-dependent stratification of HbA1c effect, when applied in certain scenarios, actually gives a greater effect to those with lower BMI.

The age groups that are predicted to benefit most from the intensive lifestyle intervention vary depending upon the assumptions around HbA1c persistence of effect, with young individuals benefitting particularly highly if it is assumed that HbA1c effects are persistent over the lifetime, whilst middle aged individuals benefit most if it is assumed that HbA1c effects return to baseline in line with weight regain. There is little difference in net benefit between the socioeconomic quintiles.

Cost-effectiveness results for metformin versus no intervention in different subgroups follow a similar set of patterns as those for intensive lifestyle intervention. Optimistic scenarios always produce more benefit than conservative scenarios, whilst assuming that the HbA1c effect is persistent produces six to eighteen fold as much benefit as assuming it returns to baseline. Unlike intensive lifestyle intervention, metformin is not predicted to be cost-effective in all subgroups unless HbA1c effect is persistent, with no benefit accruing to individuals of low BMI and, if HbA1c effect is stratified, those of high age.

In general, the ordering of subgroups for metformin mirrors that of the intensive lifestyle intervention, with individuals of higher HbA1c or FPG generally accruing more benefit than those of lower HbA1c or FPG. However, differences are seen if the HbA1c effect is assumed to be stratified due to the opposite impacts that metformin and intensive lifestyle intervention have on stratification of HbA1c effect by baseline BMI or age. This means that, when stratification is assumed, whilst having a higher BMI does not confer any increased benefits for the intensive lifestyle intervention, it does confer greater benefits with metformin treatment than having a lower BMI. Similarly, when stratification is assumed, those of young age tend to benefit more with metformin treatment compared to control than they do with intensive lifestyle intervention compared with control.

Comparison of total population results indicates that optimistic or conservative intensive lifestyle intervention scenarios tend to produce more QALYs and save more costs than the equivalent optimistic or conservative metformin interventions. Across all scenarios, there is a correlation between costs saved and QALYs gained, which means that scenarios and interventions which produce more QALYs for individuals tend to also produce more financial savings for the NHS.

In terms of diabetes incidence, the model estimates that without intervention, around 40% of the population identified at high risk of diabetes would succumb to diabetes within 10 years. This figure could be substantially reduced in individuals participating in an intensive lifestyle intervention or taking metformin, with the extent of reduction being dependent upon scale and persistence of HbA1c effect assumptions.

Conclusions

The relative cost-effectiveness of giving an intensive lifestyle intervention or metformin to different population subgroups has been analysed. There are some consistent patterns regarding which subgroups could produce the most net monetary benefit. In most scenarios, prioritising individuals with the highest baseline HbA1c or FPG for intensive lifestyle intervention or for metformin has a high probability (close to 100%) of yielding more benefits than intervening in those with lower baseline HbA1c or FPG. Those from BME groups also tend to benefit more than those of white ethnicity, although the relative cost-effectiveness is less pronounced than for HbA1c and FPG, is not consistent across all scenarios, and is likely to be a result of a lower mean age for this subgroup.

However, the results differ substantially for some subgroups depending upon two sets of issues: a) whether to assume intervention effect on HbA1c is stratified by baseline age, BMI and FPG , and b) whether to assume lifetime persistence of HbA1c effect or otherwise. The persistence may be dependent on the degree to which individuals adhere to the NHS DPP lifestyle changes (or metformin treatment), and are able to maintain these in the long term, which in turn may depend upon the extent of follow-up support to those individuals from the NHS DPP providers and other NHS services. In contrast with the previous PHE work, which found that prioritising individuals with the highest baseline BMI for intensive lifestyle intervention would yield more benefit than intervening in those with lower baseline BMI, this work shows that there are scenarios in which persistence or stratification is assumed that could switch this around and result in lower BMI subgroups receiving more benefit. This

uncertainty does not apply to metformin where it appears to be more likely that those with high BMI will benefit more than those with low BMI across all the scenarios. Which age group benefits most is also dependent upon the assumption around persistence of intervention effect, with those scenarios that assume a persistent lifetime HbA1c effect, preferentially benefitting the young, whilst those scenarios that assume HbA1c effect wanes over time in line with weight loss benefitting the middle aged.

A key limitation of this analysis is the limited quality and in some cases lack of statistical significance of the available subgroup effectiveness data. This could be improved considerably through efforts to facilitate a well-designed future evaluation and analysis of the NHS DPP. Direct comparison of intensive lifestyle intervention against metformin is difficult given that the scenarios analysed here suggest it would depend upon which assumptions around intervention effectiveness, stratification and duration of effect are most likely to reflect reality in England. Further primary research investigating the effectiveness of metformin as a first line prevention intervention in parallel to the NHS DPP would help to answer this question.

Clinical evidence statements

Metformin compared with either placebo or no treatment

- Three randomised controlled trials compared metformin with either placebo or no treatment, although only a single large study was included in the primary analysis (2,155 participants). Progression to diabetes was lower in the metformin group and reductions in weight, Hba1C and fasting plasma glucose (FBG) and adverse events (gastrointestinal symptoms) were higher. The difference in adverse events was clinically important. Systolic blood pressure and total cholesterol were indistinguishable between metformin and placebo groups. [Moderate quality evidence]

Metformin – subgroup data

- One randomised controlled trial (2,155 participants) provided subgroup data on the outcome ‘progression to type 2 diabetes’ for metformin relative to placebo. There was evidence to suggest that metformin was more effective for those with a BMI greater than 35 compared with those with a lower BMI, more effective for those with a baseline fasting plasma glucose (FPG) of more than 6.1 mmol/L than those with a lower FPG, and more effective for those with a history of gestational diabetes compared with parous women with no history of gestational diabetes. There was no clinically significant evidence for differences across age and ethnicity subgroups. [Moderate quality evidence – based on quality ratings for full population above]

Intensive lifestyle modification programme compared with usual care or no treatment

- Twelve randomised controlled trials compared an intensive lifestyle modification programme with usual care or no treatment, and 8 of these studies were included in the primary analysis (2,516 participants). Progression to diabetes was lower in the intensive lifestyle groups and reductions in weight, Hba1c and fasting plasma glucose, systolic blood pressure and total cholesterol were higher. However, differences in systolic blood pressure, total cholesterol and blood glucose in the long term (over 24 months) were indistinguishable. Differences in progression to diabetes were considered clinically important in the short and long term. [Low to high quality evidence]

Intensive lifestyle modification programme – subgroup data

- Across-trial subgroup analyses based on mean baseline characteristics for the outcomes ‘change in weight’ and ‘change in HbA1c’ also found no robust evidence for differences across the following subgroups: age, baseline BMI, baseline fasting plasma glucose, baseline HbA1c. [Low to high quality evidence – based on quality ratings for full population above]

Text messaging lifestyle intervention

- One randomised controlled trial (527 participants) compared a text messaging lifestyle intervention with usual care. The text messaging intervention showed a beneficial effect over usual care for progression to type 2 diabetes, but not other reported outcomes (change in weight, systolic blood pressure and total cholesterol). [Very low to low quality evidence]

Economic evidence statements

- Seven studies assessed the cost–utility of lifestyle intervention and metformin compared with control in patients at high risk of diabetes. Intensity of lifestyle intervention in all of these analyses was equivalent to that of the intervention in the DPP. All analyses found that lifestyle intervention was associated with the highest number of QALYs. Analyses with longer time horizons reported more favourable ICERs for both lifestyle intervention and metformin compared with control. Five of the 7 studies reported an ICER for lifestyle intervention which indicated that it is unambiguously the most cost-effective option (with an ICER sufficiently small to overcome any reasonable doubts regarding model assumptions and applicability to the NHS setting). One study reported an ICER of ambiguous cost effectiveness for lifestyle intervention compared with control (USD $31,512/QALY [around £25,300/QALY – xe.com/currency converter accessed 11/04/17]), although this analysis used a short time horizon of 3 years. One study reported an ICER of USD $115,800 (around £92,200/QALY) for lifestyle intervention in patients at risk of diabetes compared with a strategy of only offering lifestyle intervention to patients once FPG reached >125mg/dL. These studies were assessed as being partially applicable, due to being conducted for non-UK populations and not stratifying patients by subgroup, and ranged from having minor limitations to potentially serious limitations.
- One study assessed the cost–utility of offering lifestyle intervention at a range of different FPG thresholds and reported ICERs ranging from USD $30,100/QALY (around £24,200/QALY) at a threshold of 120mg/dL to $115,800/QALY (around £93,200/QALY) at a threshold of 90mg/dL). This study was assessed as being partially applicable, due to being conducted in a non-UK population, and was categorised as having minor limitations.
- One study assessed the cost–utility of lifestyle intervention compared with control based on a UK population from the perspective of the NHS, and reported an ICER of £1,819/QALY. Intervention in this analysis was assumed to be equivalent to that provided in the Finnish DPS. This study was assessed as being partially applicable as it did not stratify patients by subgroup, and was categorised as having minor limitations.
- The de novo economic analysis assessed the cost effectiveness of lifestyle intervention and metformin across various patient subgroups. Results showed both interventions were more cost effective in patients with higher HbA1c and higher FBG levels. Metformin was also shown to be more cost effective in patients with a higher BMI. In the majority of scenarios lifestyle intervention was more cost effective than metformin, but this varied across subgroups, and according to assumptions. This analysis was assessed as being directly applicable to the review question, as it was conducted in a UK population and stratified patients by subgroup appropriately. It was categorised as having only minor limitations due to an appropriately long time horizon, appropriately sourced data, and extensive sensitivity analysis.

Review question 2

What is the uptake of intensive face to face lifestyle-change programs, digitally delivered lifestyle-change programmes and metformin for impaired glucose regulation amongst those for whom it is offered?

Introduction

The aim of review question 2 was to provide key inputs to the health economic decision model based on update and adherence rates for metformin, intensive lifestyle change programmes and digital lifestyle change programmes.

PICO table

Population	Adults aged 18 years and over with fasting plasma glucose or HbA1c in the following range 5.5 – 6.9 mmol/L or HbA1c 42 – 47 mmol/mol (6.0% – 6.4 %)' or a history of gestational diabetes.
Intervention	• Intensive lifestyle change programme • Digitally delivered lifestyle change programme • Metformin
Comparison	• Any of the interventions described above • Non-comparative data was also eligible for inclusion in the review
Outcomes	• Uptake • Adherence

Methods and process

This evidence review was developed using the methods and process described in 'Developing NICE guidelines: the manual'. Methods specific to this review question are described in the review protocol in appendix A.2.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

A systematic review of the literature was conducted, as specified in the review protocol in Appendix A.2. The protocol was developed in consultation with the topic expert members, and then reviewed by the core Committee members, before the review was carried out. A systematic search was conducted (see 0). The systematic search was designed to identify observational studies meeting the review criteria. In addition, all of the randomised controlled trials included in the review for review question 1 were considered for inclusion. The titles and abstracts were screened and full-text version of articles that were identified as potentially relevant were obtained and reviewed against the criteria specified in the review protocol (appendix A.2).

Clinical evidence

Included studies

No non-randomised studies met the inclusion criteria for the review. Thirteen of the randomised controlled trials that were included in review question 1 were included (2 studies provided no data on uptake or adherence). One trial provided data on metformin and intensive lifestyle programmes, and 11 trials provided data on intensive lifestyle programme only. One trial provided data on a digital lifestyle intervention (text messaging). Usual

care/placebo was not specified as a relevant comparator for this review question, and therefore data were not extracted from the control arms of these trials.

A summary of included studies is shown in Table 4. Uptake was not reported by any study, and so is not included in the summary table. Adherence was reported differently across studies. The definition of adherence and adherence rates reported by each study are shown in the summary table together with the dropout rate for each intervention when reported (this measure was extracted as an indirect measure of adherence as it was more widely reported).

The data were not suitable for meta-analysis because of the large degree of heterogeneity in the way that outcomes were reported; the definitions used by studies for adherence varied widely, and dropout rates (an indirect measure of adherence) were reported at different time points across studies. Subgroup analysis was therefore also not possible.

Full evidence tables are shown in appendix D.

Excluded studies

Excluded studies (with reasons for exclusion) are shown in appendix K.

Table 4: Summary of clinical studies included in the evidence review

Study id	Primary publication	N	Adherence definition	Adherence	Dropout rate
Metformin					
Fontbonne 2009	Fontbonne A, Diouf I, Baccara-Dinet M, et al. (2009) Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: A post-hoc analysis of the BIGPRO1 trial. Diabetes and Metabolism 35(5), 385-391	49	-	Not reported	21/49 (43%)
Ramachandran 2006	Ramachandran A, Snehalatha C, Mary S, Mukesh B, et al. (2006) 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 49(2), 289-97	133	-	Not reported	5/133 (3.8%)
US DPP 2002	Knowler WC, Barrett-Connor E, Fowler SE et al. (2002) Reduction in	1073	Took >=80% of prescribed dose	72%	106/1073 (9.8%)

Study id	Primary publication	N	Adherence definition	Adherence	Dropout rate
	the incidence of type 2 diabetes with lifestyle intervention or metformin.. The New England journal of medicine 346(6), 393-403				
Intensive lifestyle programme					
Ackermann 2015	Ackermann Rt, Liss Dt, Finch Ea, et al. (2015) A Randomized Comparative Effectiveness Trial for Preventing Type 2 Diabetes. American journal of public health 105(11), 2328-34	257	Completion of 9 or more intervention lessons	103/257 (40.0%)	44/257 (17%)
Davies 2016	Davies M J; Gray L J; roughton J et al. (2016) 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 84: 48-56.	447	Attended first educational lesson	346/447 (77.4%)	114/447 (26%)
Katula 2011	Katula JA ; Vitolins MZ ; Rosenberger EL et al. (2011). One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. Diabetes Care 34: 1451-7.	151	-	Not reported	15/151 (10%)
Mensink 2003	Mensink M, Blaak EE, Corpeleijn E et al. (2003) Lifestyle intervention according to general recommendations improves glucose tolerance. Obesity research 11(12), 1588-96	55	Reaching two of three dietary goals and participation for at least 1 hour per week of supervised exercise during the 2 years of intervention.	10/52 (19.2%)	14/55 (25.5%)
Nilsen 2011	Nilsen V ; Bakke PS ; Gallefoss F (2011) Effects of lifestyle intervention in persons	109	-	Not reported	17/109 (15.6%)

Study id	Primary publication	N	Adherence definition	Adherence	Dropout rate
	at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 11: 893				
Oldroyd 2006	Oldroyd JC, Unwin NC, White M et al. (2006) Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance. Diabetes research and clinical practice 72(2), 117-27	39	Attended all appointments	12/39 (36%)	5/39 (12.8%)
Tuomilehto 2001	Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. The New England journal of medicine 344(18), 1343-50	265	-	Not reported	24/265 (9.1%)
US DPP 2002	Knowler WC, Barrett-Connor E, Fowler SE et al. (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England journal of medicine 346(6), 393-403	1079	At least 150 minutes of physical activity per week at last visit	58%	107/1079 (9.9%)
Van Name 2016	Van Name MA, Camp AW, Magenheimer EA et al. (2016) Effective translation of an intensive lifestyle intervention for Hispanic women with prediabetes in a Community Health Center setting. Diabetes Care 39: 525-531.	66	Attended at least 14 classes	42 (68%)	4/65 (6.2%)
Yeh 2016	Yeh M-C ; Heo M ; Suchday S et al. (2016)	30	-	Not reported	0/30 (0%)

Study id	Primary publication	N	Adherence definition	Adherence	Dropout rate
	Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City. Diabetic Medicine 33: 547-51.				
Digital lifestyle programme (text messaging)					
Ramachandran 2013	Ramachandran A, Snehalatha C, Ram J et al. (2013) 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 1(3), 191-8	271	-	Not reported	10/271 (3.7%)

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The quality of evidence for each included study was assessed using the Cochrane risk of bias checklist (for the risk of bias assessment for each study, see the full evidence tables in appendix D). The quality of evidence for each outcome for each intervention was appraised using a modification of the approach recommended by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group (for full GRADE profiles, see appendix F). A modification of the standard approach was needed as the data for this review question was from single arms of randomised controlled trials, and was therefore non-comparative (no data was identified from studies other than randomised controlled trials). Using GRADE, non-comparative single arm data from RCTs also started as low quality evidence. Risk of bias was assessed by considering whether the design of studies contributing to the evidence had limitations which may impact uptake and adherence. When more than 1 study was included, inconsistency was assessed by considering whether the range of results across studies could plausibly be accounted for by chance. Indirectness was assessed by considering whether the estimates of uptake and adherence in the included studies was likely to be applicable to a population at risk of developing type 2 diabetes in the UK, in particular whether the intervention in the study was judged to be sufficiently similar to the UK diabetes prevention programme (DPP). Imprecision was assessed by considering whether the sample size of the included studies was sufficient to provide a reliable estimate of uptake and adherence.

Economic evidence

Included studies

No economic studies were identified for this review question.

Excluded studies

Excluded studies (with reasons for exclusion) are shown in appendix K.

Clinical evidence statements

All studies were a single arm from a randomised control trial and all evidence was of very low quality

- One study (1,073 participants) found that adherence to metformin, (defined as taking >80% of the prescribed dose) was 72%.
- Three studies (1,255 participants) reported dropout rates for metformin, which ranged from 3.8 to 43%.
- Six studies (1,943 participants) reported adherence rates to intensive lifestyle interventions ranging from 19.2% to 77.4%. Definitions of adherence varied across studies.
- 10 studies (2,498 participants) reported dropout rates for intensive lifestyle intervention, which ranged from 0 to 26%.
- One study (271 participants) reported that the dropout rate for digital lifestyle intervention was 3.7%.
- No studies reported uptake rates for any intervention.

Recommendations

This section contains recommendations from both review questions in this evidence review.

A.1 For people confirmed as being at high risk (a high risk score and fasting plasma glucose of 5.5–6.9 mmol/l or HbA1c of 42–47 mmol/mol [6.0–6.4%]):

- Tell the person they are currently at high risk but that this does not necessarily mean they will progress to type 2 diabetes. Explain that the risk can be reduced. Briefly discuss their particular risk factors, identify which ones can be modified and discuss how they can achieve this by changing their lifestyle.
- Offer them a referral to a local, evidence-based, quality-assured intensive lifestyle-change programme (see recommendations 1.8.1-1.10.2). In addition, give them details of where to obtain independent advice from health professionals. **[2017]**

A.2 When commissioning local or national services to deliver intensive lifestyle-change programmes (see recommendations 1.8.1-–1.10.2), where the availability of places is limited, prioritise people with a fasting plasma glucose of 6.5–6.9 mmol/l or HbA1c of 44–47 mmol/mol [6.2–6.4%]). **[2017]**

A.3 Ensure that intensive lifestyle-change programmes are designed to help as many people as possible to access and take part in them (see sections 1.15 and 1.16 for recommendations on providing information and services, and supporting lifestyle change in people who may need particular support). **[2017]**

A.4 Use clinical judgement on whether (and when) to offer metformin[a] to support lifestyle change for people whose HbA1c or fasting plasma glucose blood test results have deteriorated if:

[a] The large study of metformin included in the evidence review and on which this recommendation is based (the US Diabetes Prevention Programme) used standard-release metformin. At the time of publication (September 2017), one modified-release metformin product, Glucophage SR, had recently extended its marketing authorisation to include reducing the risk or delaying the onset of type 2

- this has happened despite their participation in intensive lifestyle-change programmes, **or**
- they are unable to participate in an intensive lifestyle-change programme

particularly if they have a BMI greater than 35. **[2017]**

Research recommendation

Digitally delivered lifestyle change programmes

What is the effectiveness of providing digitally delivered intensive lifestyle-change programmes in preventing type 2 diabetes in adults at high risk of type 2 diabetes?

Why is this important

There is a lack of good quality evidence on the effectiveness of digitally delivered intensive lifestyle-change programmes in preventing type 2 diabetes.

Specification for research recommendation

PICO	**Population:** Adults aged 18 years and over with fasting plasma glucose in the range 5.5 – 6.9 mmol/L or HbA1c in the range 42 – 47 mmol/mol (6.0% – 6.4 %)' or a history of gestational diabetes. **Intervention:** • Digitally delivered intensive lifestyle change programme **Comparison:** No treatment, usual care, placebo **Outcomes:** • Progression to type 2 diabetes • Change in weight from baseline • Change in HbA1c levels from baseline • Change in Fasting plasma glucose from baseline • Systolic blood pressure • Total cholesterol
Current evidence base	There is a lack of good quality evidence on the effectiveness of digitally delivered intensive lifestyle-change programmes in preventing type 2 diabetes.
Study design	RCT

diabetes in overweight adults with impaired glucose tolerance and/or fasting glucose, and/or increased HbA1c who are at high risk of overt type 2 diabetes and are progressing towards this despite intensive lifestyle change for 3-6 months. Other standard-release and modified-release metformin products may similarly extend their marketing authorisations in the future. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for information on off-label prescribing.

Rationale and impact

Why the committee made the recommendations

A health economic model showed that lifestyle-change programmes are cost-effective for all people at high risk of diabetes, providing support to the existing recommendation to offer the intervention to this group of people. The model also showed that lifestyle-change programmes are particularly cost-effective for people with higher HbA_{1c} or fasting plasma glucose levels. Therefore, the committee determined that, in instances where offering the intervention to all high risk people is not possible due to capacity constraints, lifestyle-change programmes should be prioritised for people with a fasting plasma glucose of 6.5–6.9 mmol/l or HbA_{1c} of 44–47 mmol/mol. The committee also agreed that people should be given information about their diabetes risk because this was recommended in the previous version of NICE guidance on type 2 diabetes prevention based on the expert view of the previous committee.

The committee also recognised that people with mental illness or dementia often have poorer physical health and would therefore benefit from testing and, if needed, intervention to reduce their risk of type 2 diabetes. Therefore an additional recommendation was made to ensure that intensive lifestyle-change programmes are designed to help as many people as possible to access and take part in them.

The results of the economic modelling also showed that, in the high-risk population overall and in most subgroups, lifestyle-change programmes are more clinically and cost effective than metformin. They also showed that, compared with control alone, metformin is cost effective in the high-risk population overall, and for most subgroups. Therefore, the committee agreed that metformin could be used in support of lifestyle change when blood test results have deteriorated despite someone taking part in these programmes or if they can't take part for some reason. They also agreed that metformin could be used for people whose BMI is over 35 when their blood test results have deteriorated because the model showed that metformin is particularly clinically and cost effective for this group.

Impact of the recommendations on practice

The 2012 version of this guideline recommended that intensive lifestyle-change programmes should be offered to people at high risk of type 2 diabetes. Intensive lifestyle-change programmes should also be designed to help as many people as possible to access and take part in them. However, providing these programmes to all these people has a large resource impact. To make the most of resources commissioners may need to prioritise subsets of the population.

The NHS Diabetes Prevention Programme is currently being implemented throughout England in response to the 2012 recommendations in this guideline. Implementing the 2017 recommendation will allow this programme to be initially targeted at groups of the population who will benefit most, in a way that is consistent across the UK.

The updated recommendation on metformin reflects current practice, so the committee noted that it shouldn't have an impact.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

With the exception of adverse events, the outcomes in the clinical review formed the basis of the economic model and were used to estimate changes in quality of life. Because this estimate was explicit in the economic model, the committee did not qualitatively weigh up the relative importance of these outcomes, and did not assign outcomes as 'critical' or 'important'. Outcomes were chosen for the clinical review that allowed the health economic model to incorporate important differences in quality of life between interventions. Metabolic outcomes (change in weight, systolic blood pressure and total cholesterol) were included because they are related to cardiovascular risk. The committee acknowledged that the benefits of interventions for preventing diabetes are unlikely to be limited to diabetes specifically, and that measures of cardiovascular risk were also an important consideration for modelling. Adverse events were not included in the economic model but were thought to be important because they can have a large impact on quality of life and are relevant for people considering treatments. The committee agreed that adverse events were particularly important when considering metformin as an intervention for preventing type 2 diabetes because this is a long-term intervention, and adverse events may have a large impact on adherence.

The quality of the evidence

The evidence comparing metformin with control was of moderate quality (not considering imprecision/uncertainty, which is captured in the health economic model). However, all of the evidence from the primary analysis came from a single large randomised controlled trial, and therefore it was not possible to assess the consistency of evidence across trials. The committee noted that adherence rates were high for metformin in this trial. But this was unlikely to be reflected in practice because the trial included intensive follow-up to encourage adherence that would not be routinely available. As a result the evidence was downgraded for indirectness in the GRADE tables (Appendix F).

The evidence comparing intensive lifestyle interventions was of low to high quality (not considering imprecision/uncertainty, which is captured in the health economic model). The main factor limiting quality was the inconsistency in the magnitude of effect across trials, with high heterogeneity for many outcomes that could not be explained by planned subgroup analysis or exploratory sensitivity analysis.

Only one study (the US diabetes prevention programme) compared metformin and lifestyle head to head, but the lifestyle intervention arm of this trial was excluded from the primary analysis because the committee thought that it did not reflect UK practice. Therefore, no UK relevant data were available directly comparing the effectiveness of lifestyle interventions with metformin.

Very low to low quality evidence from a single randomised controlled trial was found comparing digitally delivered lifestyle interventions with control. The committee agreed that this trial could not be used to inform UK practice because the intervention (text messaging) did not reflect current digitally delivered lifestyle-change programmes in development. Also, the population (Indian men with a relatively low BMI) was not representative of the population at high risk of diabetes in the UK. Due to this lack of high quality evidence, the committee made a new research recommendation.

Within-trial subgroup data from the US diabetes prevention programme was available and considered robust by the committee. These data were used to inform the economic model where possible. Between-trial subgroup analysis was also performed for the intensive lifestyle intervention, but there were very few trials in some subgroups, and so the committee considered that these analyses were not robust or clinically meaningful because the subgroup effects were likely to arise (at least partly) due to differences between trials unrelated to the subgroups of interest.

Evidence on adherence to interventions for the prevention of type 2 diabetes was found based on single arms of randomised controlled trials and was of very low quality. Definitions of adherence varied across studies, introducing inconsistency across studies. Dropout rates were considered as an indirect measure of adherence, but different trial durations introduced additional heterogeneity to this measure. Intervention uptake was not reported in any included study.

Benefits and harms of intensive lifestyle interventions and metformin

The clinical review found that intensive lifestyle interventions were beneficial in terms of diabetes progression, fasting plasma glucose, HbA1c, weight loss, systolic blood pressure and total cholesterol compared with a control, particularly in the short term (12–24 months). No harms of intensive lifestyle-change programmes were found in the evidence review, although the committee noted that programmes may not be suitable for all (for example, those with some physical disabilities). Metformin showed a beneficial effect on blood glucose and weight compared with placebo, but this was countered by an increase in gastrointestinal adverse events. The committee also considered the burden of taking daily medications and the negative effects of medicalisation of people taking metformin for the prevention of diabetes. Therefore the committee agreed that an intensive lifestyle-change programme should be the first choice for treatment offered to people at high risk of diabetes, as recommended by the 2012 version of this guideline, and that metformin should only be offered to support lifestyle change.

The committee noted that the subgroup analysis conducted alongside the US DPP indicated that people with gestational diabetes, a BMI of greater than 35 or a baseline FDG of between 6.11 and 6.94 mmol/l gained larger benefits from metformin than the average for the population in the trial. The committee agreed it was important to consider cost-effectiveness alongside effectiveness when making recommendations about subgroups, and these discussion are described in the section below. The committee agreed that the level of between study heterogeneity meant they were not confident in using the results of the subgroup analyses for lifestyle interventions as part of decision making, and therefore these recommendations were based on the discussions of the economic model detailed below.

Cost effectiveness and resource use

Owing to shortcomings of evidence provided in the economic literature, the committee focused the majority of their discussion on the evidence produced by the new economic modelling.

Because of the large number of possible scenarios produced by varying modelling assumptions, the committee discussed which scenarios were likely to best represent clinical reality. First, the committee discussed whether it was more realistic to assume that the effect of lifestyle intervention and metformin on HbA_{1c} level would be likely to persist over a person's entire lifetime or to assume that HbA_{1c} levels would gradually return to the same level as control at the same rate as weight. The committee agreed that, although clinical evidence suggests that HbA_{1c} level is likely to converge with baseline (i.e. return to the level of the control group) at a slower rate than weight, the assumption that the effect of

intervention on HbA_{1c} persists indefinitely is unrealistic. Therefore the assumption that HbA_{1c} returns to baseline at the same rate as weight was agreed to be closer to clinical reality.

Second, the committee discussed whether model inputs for the effect of interventions on HbA_{1c} should be stratified by age, BMI, and fasting plasma glucose (FPG level), or whether a constant intervention effect should be assumed across all patients. The committee agreed that the effectiveness of interventions would vary between groups. Moreover, it was agreed that the direction of change in effectiveness according to stratification factors made sense clinically – the effectiveness of lifestyle intervention is positively correlated with age and negatively correlated with BMI, whereas the reverse is true for metformin. Although the committee acknowledged that the stratification of effects was based on data from the US Diabetes Prevention programme (DPP), and therefore on an intervention that is more intensive than in the NHS DPP, they concluded that the stratification assumption is still the more plausible of the two.

Third, the committee discussed which studies should be used in estimating the overall effectiveness of lifestyle intervention. Three alternative scenarios were discussed: an 'optimistic scenario', in which data from the US DPP and Finnish Diabetes Prevention Study (DPS) were included; a 'conservative scenario' in which data from the Finnish DPS but not the US DPP were included; and a 'pessimistic scenario', in which data from neither study were included. Selecting a specific assumption from among the 3 alternatives was thought to be less crucial than in the other scenario decisions. This is because, although the data used to estimate effectiveness affect the overall magnitude of cost effectiveness in results, the relative cost effectiveness between patient subgroups remains consistent. Nonetheless, the committee thought that the 'conservative' or 'pessimistic' scenarios were the more realistic of the three, as the lifestyle intervention provided by the NHS is considerably less intensive than the intervention provided in the US DPP.

The scenarios specified by the committee as most plausible showed that lifestyle intervention is likely to be cost effective across all patient subgroups compared with control, providing support for the existing recommendation that all high risk people should be offered the intervention. In particular, lifestyle intervention was most cost effective in people with higher HbA_{1c} and FBC levels. This pattern was also persistent across all other scenarios. For this reason, the committee determined that people in the groups with the highest HbA_{1c} (44–47 mmol/mol [6.2–6.4%]) and the highest FPG (6.5–6.9 mmol/l) levels should be prioritised for lifestyle intervention in cases where capacity constraints prevent the intervention from being offered to the entire high risk population.

The committee discussed the evidence for the relative cost effectiveness of the other subgroups included in the analysis. The scenarios specified by the committee as being the most plausible showed that lifestyle intervention was more cost effective in individuals aged 60-74 compared to individuals in younger or older age groups, in individuals of BMI 25-29 compared to individuals with a higher BMI, and individuals of white ethnicity compared to BME individuals. However, the differences in cost effectiveness of lifestyle intervention between these groups was less pronounced than in subgroups stratified by HbA_{1c} and FBC. Moreover, the committee noted that the direction of these trends reversed in other scenarios. Results showed that lifestyle intervention was relatively more cost-effective in younger or middle-aged patients in scenarios which assumed persistence of intervention effect, due to a longer life expectancy over which health benefits could be accrued. Similarly, lifestyle intervention was more cost effective for patients with high BMI compared to those with low BMI in scenarios in which treatment effect was not stratified. Scenarios in which treatment effect was not stratified and scenarios in which persistence of treatment effect was assumed showed that lifestyle intervention was more cost-effective in BME individuals than in individuals of white ethnicity. The committee determined that, although certain model scenarios were more plausible than others, the considerable variability in the relative cost-

effectiveness of lifestyle intervention across subgroups stratified by age, BMI and ethnicity meant that the evidence lacked the strength to confidently prioritise lifestyle intervention in particular age, BMI or ethnicity subgroups. The committee also discussed results of the combinatorial subgroups, but it was determined that, considering individual subgroups results were too variable to draw firm conclusions, this issue was likely to be compounded in combinatorial groups.

Overall, the results for metformin showed that, in the majority of scenarios, lifestyle intervention produced a higher number of QALYs and was more cost effective than metformin. Furthermore, the committee noted that the de novo analysis did not account for reduction in quality of life associated with metformin adverse events – meaning that the model potentially underestimates the cost-effectiveness of lifestyle intervention compared to metformin. The analysis also showed, compared to control, metformin was cost-effective in the high-risk population overall, and in the majority of subgroups across the majority of scenarios. For these reasons, the committee determined that the current recommendation that metformin should be provided as a second-line option for people at risk of diabetes was appropriate. Subgroup results showed that metformin is expected to be especially cost effective in people with a high BMI (whereas the opposite is true for lifestyle intervention in the scenario in which stratification is assumed). The committee agreed that this finding was consistent with the biological mode of action of metformin and is likely to accurately reflect clinical reality. They therefore decided that metformin should be prioritised for people with a high BMI in the recommendations.

The committee discussed the potential resource impact of the recommendations. They agreed that, because of the very large patient population, if lifestyle intervention was provided to the entire patient population in the highest risk group for HbA1c and FPG, the resource impact would be very significant. However, considering that Public Health England has secured funding for intensive lifestyle intervention in 300,000 patients over the course of 3 years, resource impact will probably be capped according to this predetermined number. Prioritising the patients in whom treatment is the most cost-effective means that people with the highest capacity to gain will be targeted until the funding cap is reached.

Other factors the committee took into account

Recommendation A.1 was part of the previous version of the NICE guideline on diabetes prevention. This recommendation was retained in the current guideline because the evidence reviewed was consistent with the previous recommendation; intensive lifestyle modifications were cost-effective across all subgroups, supporting the recommendation to offer such programmes to people at high risk. The recommendation also states that people at high risk of diabetes should be given information about their diabetes risk. This element of the recommendation was based on the expert opinion of the previous committee and has therefore been retained.

The committee acknowledged that people with South Asian ethnicity may be at higher risk of rapid progression to type 2 diabetes for a given blood glucose level than people of other ethnicities. However, evidence of effectiveness of intensive lifestyle interventions and metformin were not available for this population subgroup, and so this subgroup could not be considered separately in the economic model, and rigorous evidence on the progression to diabetes across ethnicities was not available. The 2012 version of the NICE guideline on prevention of diabetes in people at high risk included a recommendation for research on the effects of ethnicity on the effectiveness of intensive lifestyle lifestyle-change programmes, and the committee agreed that this recommendation should remain. The committee noted that many people at high risk of diabetes are also overweight or obese and that healthcare professionals should follow the recommendations in the NICE guidelines on obesity.

There was limited evidence of the effectiveness of intensive lifestyle interventions and metformin in preventing type 2 diabetes in people with a previous history of gestational diabetes. This evidence could not be incorporated into the economic model due to a lack of data for the required model input parameters. The committee noted that this group may require special consideration and suggested that clinicians should cross refer to the NICE guideline on diabetes in pregnancy when considering diabetes prevention in this group.

Appendices

Appendix A: Review protocols

A.1 Review question 1 – Effectiveness of metformin and lifestyle change programmes for prevention of type 2 diabetes

RQ1: Review Protocol	
Components	**Details**
Review question	What is the effectiveness of providing intensive face to face lifestyle-change programs, digitally delivered lifestyle-change programmes or metformin in preventing type 2 diabetes in adults with fasting plasma glucose concentrations of 5.5 – 6.9 mmol/L or HbA1c of 42 – 47 mmol/L (6.0% to 6.4%)?
Background/ objectives	PH38 'Type 2 diabetes: prevention' recommends an intensive lifestyle-change programme for people with a fasting plasma glucose (FPG of 5.5 – 6.9 mmol/l or HbA1c of 42 – 47 mmol/mol (6.0 – 6.4 %). The Diabetes Prevention Program is being rolled out and this consists of a minimum of 13 education and exercise sessions of one to two hours, at least 16 hours face to face in total. The Diabetes Prevention Program is also looking at the use of apps to deliver this intensive lifestyle change program. The current NICE guideline recommends that standard-release metformin should be offered to people at high risk of type 2 diabetes who meet either of the following criteria. Their blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle change programme. They are unable to participate in lifestyle-change programmes because of disability or for medical reasons There are concerns that the current criteria for offering intensive lifestyle modification programmes are too inclusive and that significant resource would be committed on people at lower risk of developing type 2 diabetes. Therefore, the level of risk needs to be reviewed to identify when it is most appropriate in terms of both individual risk and NHS resources to promote individualised interventions to prevent development of type 2 diabetes. The aim of the review is to determine the effectiveness of metformin and lifestyle modifications in order to populate a health economic model that will assess the cost effectiveness of these interventions for different population subgroups.
Population	Adults aged 18 years and over with fasting plasma glucose or HbA1c in the following range 5.5 – 6.9 mmol/L or HbA1c 42 – 47 mmol/mol (6.0% – 6.4 %)' OR a history of gestational diabetes.
Intervention	Metformin, alone or in addition to other interventions (for example, lifestyle change) provided any other interventions were the same in the comparison group. Lifestyle change programs: Intensive face to face programmes meeting at least 9 of the 12 criteria specified in the NICE diabetes prevention guideline (PH38) Digitally delivered (e.g. online, internet-based, web-based mobile, 'apps')
Comparator	Any of the interventions listed above plus No treatment, usual care, placebo
Outcomes	Progression to type 2 diabetes Change in weight from baseline

RQ1: Review Protocol	
	Change in HbA1c levels from baseline Change in Fasting plasma glucose from baseline Adverse events and side effects (limited gastrointestinal intolerance) The following outcomes will be extracted specifically to feed into the economic model, but will not be treated as outcomes for the clinical review: Systolic blood pressure Total cholesterol Data will be pooled at the following time points: 12 – 24 months post treatment initiation Longer than 24 months post treatment initiation When a study reported at multiple time points within these ranges, data from the latest reported timepoint in the range will be extracted and used for analysis.
Type of review question	Intervention
Types of study to be included	Systematic reviews of RCTs RCTs
Language	English language only
Status	Published papers (full text)
Any other information or criteria for inclusion/exclusion	Studies must have a minimum follow up period of 12 months. The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been wrongly sifted out
Analysis of subgroups or subsets	Fasting plasma glucose at baseline as follows 5.5 - 5.9 mmol/L 6.0 – 6.4 mmol/L 6.5 – 6.9 mmol/L HbA1c at baseline as follows: 42 – 44 mmol/mol [6.0 - 6.1%] 45 – 47 mmol/mol [6.2 - 6.4%] Ethnicity White BME BMI <25 kg/m2 25-29 kg/m2 30-34 kg/m2 35 kg/m2 and above Age <40 40-59 60-74 =>75 Previous history of gestational diabetes

RQ1: Review Protocol	
	Grouping of data across doses and treatment durations will be carried out in discussion with the topic experts, as clinically appropriate
Data extraction and quality assessment	**Sifting** Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the review question (measured against protocol). In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered being not relevant to the topic will be excluded. i) Selection based on titles and abstracts A 10% double-sift of titles and abstracts will be conducted. Included papers will either be systematic reviews of RCTs or RCTs, and we expect only a small number of papers to be included following the search. The review question is straight forward and therefore full double sifting is not warranted. In cases of uncertainty the following mechanisms will be in place: technical analyst will discuss with a support technical analyst comparison with included studies of other current (within 5 years) systematic reviews recourse to members of the committee ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will be conducted (see above). In cases of uncertainty the same mechanisms stated in i) above will be followed. **Data extraction** Relevant information from included studies will be extracted into standardised evidence tables [adapted to suit this particular question] these include: Age Sex Body mass index (BMI) History of gestational diabetes Ethnicity Fasting plasma glucose/HbA1c at baseline Details of the intervention Dose of metformin Frequency of dosing Contents of lifestyle change programme, including number of NICE criteria for lifestyle interventions met Length of treatment period Length of follow up Details of any concomitant treatment Details of the comparison **Critical appraisal** The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual appropriate for the design of each included study. Quality assessment GRADE methodology will be used to assess the quality of evidence on an outcome basis: Risk of bias will be assessed using critical appraisal checklists Inconsistency will be assessed using tau2

RQ1: Review Protocol	
	Indirectness will be assessed after considering the population, intervention and outcomes of included studies, relative to the target population as specified in the review protocol; Imprecision will be assessed using the confidence intervals around point estimates cross the MIDs for each outcome. COMET and published literature including related NICE guidelines will be checked for appropriate minimal important differences (MID) for each outcome. If none are available, the topic experts will be consulted on the appropriateness of using default MIDs as suggested by the GRADE working group. **Quality Assurance:** A full double-scoring quality assessment will not be conducted due to the nature of the review question. Other quality assurance mechanisms will be in place as follows: Internal QA (10%) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. The Committee will be sent the evidence synthesis prior to the committee meeting and will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	If possible a bayesian network meta-analysis of available study data will be carried out to provide a more complete picture of the evidence body as a whole. A random effects model will be used as it is expected that the studies will be heterogeneous in terms of population, which would make a fixed effects model inappropriate. Model fit will be assessed by calculating the total residual deviance and deviance information criteria. Between trial standard deviation will be calculated to assess heterogeneity. If a network meta-analysis is not possible or appropriate, random effects pair-wise meta-analysis will be undertaken. Tau2 will be used to assess heterogeneity in this case. If substantial heterogeneity is identified, the source of this heterogeneity will be explored using subgroup analysis and consideration will be given to the appropriateness of pooling data
Searches	The review will incorporate and update a review by the University of Leicester on lifestyle modifications in diabetes prevention. The search strategy will consist of: An update of the review by the University of Leicester to identify new studies on lifestyle modification that were not incorporated in the University of Leicester review. This search will have a date limit of January 2014 (date of previous review). A search strategy to identify digitally delivered lifestyle modifications (‘apps’) and metformin with no date limit, as these interventions were not included in the University of Leicester review. **Sources to be searched** Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. **Supplementary search techniques** None identified **Limits** Studies reported in English Study design RCT and Systematic Review filters will be applied Animal studies will be excluded from the search results

RQ1: Review Protocol	
	Conference abstracts will be excluded from the search results The update of the University of Leicester review on lifestyle modifications will have a date limit of January 2014. The metformin element of the review will not have a date limit.
Key papers	Gillies, C.L., Abrams, K.R., Lambert, P.C., Cooper, N.J., Sutton, A.J., Hsu, R.T., Khunti, K. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ, doi:10.1136/bmj.39063.689375.55 (published 19 January 2007). Nuzhat B Ashra1, Rebecca Spong1, Patrice Carter1, Melanie J Davies1, Alison Dunkley1, Clare Gillies1, Colin Greaves2, Kamlesh Khunti1, Sarah Sutton3, Thomas Yates1, Dalia Youssef1, Laura J Gray4 A systematic review and metaanalysis assessing the effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes mellitus in routine practice Paper under review- Barry E, Roberts S , Oke Jason, 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. Under review by BMJ.

A.2 Review question 2 – Uptake and adherence to metformin and lifestyle change programmes for prevention of type 2 diabetes

RQ2: Review Protocol	
Components	**Details**
Review question	What is the uptake of intensive face to face lifestyle-change programs, digitally delivered lifestyle-change programmes and metformin for impaired glucose regulation amongst those for whom it is offered?
Background/ objectives	See review question 1 for the objectives of update. This review question has been formulated to provide key inputs to the health economic model that will be created as part of the update. The objective is to determine the uptake of and adherence to intensive face to face lifestyle-change programmes, digitally delivered lifestyle-change programmes and metformin offered for type 2 diabetes prevention. The results of this review will input in the economic model to determine the cost effectiveness of these interventions.
Population	Adults aged 18 years and over with fasting plasma glucose or HbA1c in the following range 5.5 - 6.9 mmol/L or HbA1c 42 – 47 mmol/mol (6.0% - 6.4 %) OR a history of gestational diabetes.
Intervention	• Intensive face to face lifestyle-modification programmes meeting at least 9 of the 12 criteria specified in the NICE diabetes prevention guideline (PH38) • Digitally delivered lifestyle-modification programmes (e.g. telephone, self-help manual, online, video, mobile, web-based mobile) • Metformin
Comparator	• No comparator. Note that data may be extracted from single arms of comparative studies. • Any of the interventions specified above (where interventions are compared head to head)
Outcomes	1. Proportion of people who start an intervention after it is offered 2. Proportion of people who complete an intervention who have started

RQ2: Review Protocol	
Components	**Details**
Type of review question	Descriptive/intervention
Types of study to be included	Observational or interventional (single or multiple arms of RCTs)
Language	English language only
Status	Published papers (full text only) – no date restriction
Any other information or criteria for inclusion/exclusion	**Exclusion** Observational studies with a sample size of less than 250 People with a diagnosis of type 2 diabetes or other forms of diabetes. Pregnant women. The committee will be sent the list of included and excluded studies prior to the committee meeting. The committee will be requested to check whether any studies have been excluded inappropriately, and whether there are any relevant studies they know of which haven't been picked up by the searches or have been wrongly sifted out.
Analysis of subgroups or subsets	Fasting plasma glucose at baseline as follows 5.5 - 5.9 mmol/L 6.0 – 6.4 mmol/L 6.5 – 6.9 mmol/L HbA1c at baseline as follows: 42 – 44 mmol/mol [6.0 - 6.1%] 45 – 47 mmol/mol [6.2 - 6.4%] Ethnicity White BME BMI <25 kg/m2 25-29 kg/m2 30-34 kg/m2 35 kg/m2 and above Age <40 40-59 60-74 =>75 Previous history of gestational diabetes Socioeconomic status Grouping of data across doses and treatment durations will be carried out in discussion with the topic experts, as clinically appropriate

RQ2: Review Protocol	
Components	**Details**
Data extraction and quality assessment	**Sifting** Relevant studies will be identified through sifting the abstracts and excluding studies clearly not relevant to the PICO. In the case of relevant or potentially relevant studies, the full paper will be ordered and reviewed, whereupon studies considered being not relevant to the topic will be excluded. i) Selection based on titles and abstracts A 10% double-sift of titles and abstracts will be conducted. Included papers will either be systematic reviews of RCTs or RCTs, and we expect only a small number of papers to be included following the search. The review question is straight forward and therefore full double sifting is not warranted. In cases of uncertainty the following mechanisms will be in place: technical analyst will discuss with a support technical analyst comparison with included studies of other systematic reviews recourse to members of the committee ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted. However in cases of uncertainty the same mechanisms stated in i) above will be followed. **Data extraction** Relevant information from included studies will be extracted into standardised evidence tables adapted to suit this particular question. Baseline data on the following variables will be routinely extracted where reported Age Sex Body mass index (BMI) History of gestational diabetes Ethnicity Fasting plasma glucose/HbA1c at baseline Socioeconomic status **Critical appraisal** The risk of bias of each included study will be assessed using standardised checklists available in the NICE manual appropriate for the design of each included study. Quality assessment A modified GRADE methodology will be adopted for quality assessment for this question (for details on how GRADE was modified, see the section on methods and process). The quality of individual studies will be assessed using a checklist for observational studies. Risk of bias will be assessed using critical appraisal checklists Indirectness will be assessed after considering the population, intervention and outcomes of included studies, relative to the target population as specified in the review protocol; Inconsistency will only be assessed if data is pooled in a meta-analysis Imprecision will be assessed using 95% confidence intervals, where available

RQ2: Review Protocol	
Components	**Details**
	Quality Assurance: A 10% double-scoring quality assessment will not be conducted due to the nature of the review question (see above). Other quality assurance mechanisms will be in place as follows: Internal QA (10%) by CGUT technical adviser on the risk of bias and quality assessment that is being conducted. Any disagreement will be resolved through discussion. The Committee will be sent the evidence synthesis prior to the committee meeting and will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	A descriptive evidence summary outlining key issues such as volume, generalisability and quality of evidence and presenting the key findings from the evidence will be produced. Non-comparative data will be presented as proportions, and comparative data will be presented as risk ratios. Pooling using meta-analysis will be considered for comparative data. A random effects model will be used as it is expected that the studies will be heterogeneous in terms of population, which would make a fixed effects model inappropriate. Tau2 will be used to assess heterogeneity in this case. If substantial heterogeneity is identified, the source of this heterogeneity will be explored using subgroup analysis and consideration will be given to the appropriateness of pooling data.
Searches	**Sources to be searched** Clinical searches - Medline, Medline in Process, PubMed, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records) and HTA Economic searches - Medline, Medline in Process, PubMed, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. **Supplementary search techniques** None identified **Limits** Studies reported in English Prospective cohort studies and single arms of RCTs Animal studies will be excluded from the search results Conference abstracts will be excluded from the search results
Key papers	Barry E, Roberts S , Oke Jason, 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. Under review by BMJ.

Appendix B: Literature search strategies

B.1 Review question 1

B.1.1 Metformin

Sources searched to identify the clinical evidence:

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	26/08/16	Cochrane Central Register of Controlled Trials : Issue 7 of 12, July 2016	1663 (1747)*
Cochrane Database of Systematic Reviews (CDSR)	26/08/16	Cochrane Database of Systematic Reviews : Issue 8 of 12, August 2016	17 (19)*
Database of Abstracts of Reviews of Effect (DARE)	26/08/16	Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015	4 (9)*
Embase (Ovid)	26/08/16	Embase 1974 to 2016 Week 34	944 (1266)*
Health Technology Assessment (HTA Database)	26/06/16	Health Technology Assessment Database : Issue 3 of 4, July 2016	0
MEDLINE (Ovid)	25/08/16	Ovid MEDLINE(R) 1946 to August Week 3 2016	890 (1042)*
MEDLINE In-Process (Ovid)	26/08/16	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 25, 2016	58
PubMed	26/08/16		65

*Small adjustment made to search strategy October 2016 – figure in brackets shows number of studies after additional studies added (pre-de-dup)

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

The Pubmed translation was designed to capture references that had not yet appeared in the Medline in Process database.

Database: Medline
((prevent* or avoid* or delay* or decreas* or reduc* or stop*) adj5 (type II diabet* or type 2 diabet* or T2D or DM or diabet* or NIDDM)).ti,ab.
Diabetes Mellitus, Type 2/ and Preventive Medicine/
Diabetes Mellitus/pc

Database: Medline
Diabetes Mellitus, Type 2/pc
((Non-insulin* or Non insulin* or Noninsulin*) adj2 depend* adj2 (diabete* or diabetic*)).ti,ab.
(prevent* or avoid* or delay* or decreas* or reduc* or stop*).ti,ab.
5 and 6
or/1-4,7
prediabetic state/ or Glucose Intolerance/
(prediabet* or pre diabet* or rais* glucose intoleran* or high* glucose level* or high* glucose intoleran* or impair* glucose level* or impair* glucose toleran* or IGT or impair* fast* glucose or IFT or IFG or IGR or FPG or fast* plasma glucose or impair* glucose regulation or impair* glucose metabolism or rais* glycated haemoglobin or rais* glycated hemoglobin or high glycated Hb or hyperglycaemia or hyperglycemia or HBA1C).ti,ab.
Diabetes, Gestational/
Pregnancy in Diabetics/ or Pregnancy/
(gestational or pregnan* or postpartum or peripartum* or intrapartum*).ti,ab.
or/9-13
8 and 14
Metformin/
Hypoglycemic Agents/
(metformin or glucophage or bolamyn or glucient or metabet or sukkarto or diagemet xl).ti,ab.
or/16-18
15 and 19
Randomized Controlled Trial.pt.
Controlled Clinical Trial.pt.
Clinical Trial.pt.
exp Clinical Trials as Topic/
Placebos/
Random Allocation/
Double-Blind Method/
Single-Blind Method/
Cross-Over Studies/
((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
(random$ adj3 allocat$).tw.
placebo$.tw.
((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
(crossover$ or (cross adj over$)).tw.
or/21-34
Meta-Analysis.pt.
Meta-Analysis as Topic/
Review.pt.
exp Review Literature as Topic/
(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
(review$ or overview$).ti.
(systematic$ adj5 (review$ or overview$)).tw.
((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.

Database: Medline
((studies or trial$) adj2 (review$ or overview$)).tw.
(integrat$ adj3 (research or review$ or literature)).tw.
(pool$ adj2 (analy$ or data)).tw.
(handsearch$ or (hand adj3 search$)).tw.
(manual$ adj3 search$).tw.
or/36-48
35 or 49
20 and 50
animals/ not humans/
51 not 52
limit 53 to english language

B.1.2 Lifestyle interventions

Sources searched to identify the clinical evidence:

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	21/11/2016	Cochrane Central Register of Controlled Trials : Issue 10 of 12, October 2016	847
Cochrane Database of Systematic Reviews (CDSR)	21/11/2016	Cochrane Database of Systematic Reviews : Issue 11 of 12, November 2016	61
Database of Abstracts of Reviews of Effect (DARE)	21/11/2016	Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015	10
Embase (Ovid)	21/11/2016	Embase 1974 to 2016 Week 47	2698
(HTA Database) Health Technology Assessment	21/11/2016	Health Technology Assessment Database : Issue 4 of 4, October 2016	2
MEDLINE (Ovid)	21/11/2016	Ovid MEDLINE(R) 1946 to November Week 2 2016	1354
MEDLINE In-Process (Ovid)	21/11/2016	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 18, 2016	348
PubMed	21/11/2016		1389

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

The Pubmed translation was designed to capture references that had not yet appeared in the Medline in Process database.

#	Searches	Results
1	Diabetes Mellitus, Type 2/pc or Diabetes Mellitus/pc or *prediabetic state/	14521
2	(prediabetes or pre diabet*).tw.	4221
3	1 or 2	16505
4	exp Exercise/	160847
5	exp Diet/	250266
6	4 or 5	397878
7	3 and 6	3228
8	Diabetes Mellitus, Type 2/ or *prediabetic state/	115287
9	Secondary Prevention/ or Primary Prevention/ or Risk Reduction Behavior/	45589
10	8 and 9	1497
11	7 or 10	4510
12	((aerobic or yoga or pilates or tai chi or tai-chi or taichi or tai ji or tai-ji or taiji or qi gong or qigong or qi-gong or chi kung 8 or ch i-kung or chikung or ch-i-kung) adj1 (train or therap* or treat* or intervent* or medicin* or educat*)).tw.	1115
13	Behav* Modif*.tw.	4016
14	Behav* therap*.tw.	15439
15	((Cognitive* or cognition* or behaviour* or behavior* or individual*) adj1 (intervent* or therap* or stimulat* or aid* or techni* or train* or skill* or rehab* or treat* or counsel*)).tw.	60722
16	(counsel* or cbt).tw.	88769
17	Health* Educ*.tw.	26327
18	Health* Promot*.tw.	26512
19	Health* behav*.tw.	18246
20	Educat* program*.tw.	32733
21	Patient Educ*.tw.	13420
22	(Diet* adj2 Intervention*).tw.	7129
23	(Diet* adj2 Modif*).tw.	8410
24	Food habit*.tw.	1662
25	(Health* adj2 Eating).tw.	5323
26	(Nutrition* adj2 Counselling).tw.	303
27	(Nutrition* adj2 Therap*).tw.	3705
28	((Exercis* or kinesiotherap* or kinesiolo* or sport*) adj2 (intervention* or treat* or medicin* or educat*)).tw.	13095
29	Physical Exercise.tw.	11125
30	(Exercis* adj2 therap*).tw.	4824
31	Physical endurance.tw.	320
32	Physical education.tw.	3386
33	Physical Fitness.tw.	6657
34	Physical Activit*.tw.	76740
35	Physical Train*.tw.	4915
36	Resistance Train*.tw.	5413
37	Strength Train*.tw.	3812
38	(Lifestyle adj2 advice).tw.	647
39	(Lifestyle adj2 Guid*).tw.	168
40	(Lifestyle adj2 Modif*).tw.	5254

#	Searches	Results
41	(Lifestyle adj2 Chang*).tw.	7330
42	Lifestyle Program*.tw.	422
43	"diabetes prevention program*".tw.	825
44	Weight control*.tw.	5638
45	Weight Train*.tw.	1015
46	Weight reduc*.tw.	8786
47	weight loss.tw.	64783
48	(lifestyle adj2 intervention).tw.	3043
49	Sport*.tw.	48621
50	walk*.tw.	84068
51	jog*.tw.	1842
52	swim*.tw.	30509
53	cycle*.tw.	459738
54	Bicycle*.tw.	11303
55	exp Health Promotion/	70571
56	exp Program Evaluation/	68975
57	exp Patient Education as Topic/	82028
58	exp Diet Therapy/	50847
59	exp Nutrition Therapy/	94210
60	exp Exercise Therapy/	41833
61	exp Diet, Reducing/	11225
62	Physical fitness/ or Lifestyle/ or Sedentary Lifestyle/	84209
63	or/12-62	1328318
64	(diabet* adj4 (reduc* adj5 risk*)).tw.	2281
65	(diabet* adj4 (lower* adj5 incidence*)).tw.	331
66	(diabet* adj4 (decreas* adj5 risk*)).tw.	593
67	(diabet* adj4 (reduc* adj5 incidence*)).tw.	883
68	(diabet* adj4 (lower* adj5 risk*)).tw.	864
69	(diabet* adj4 (delay* adj5 onset*)).tw.	613
70	(diabet* adj4 (reduc* adj5 onset*)).tw.	228
71	(diabet* adj4 (reduc* adj5 progress*)).tw.	276
72	(diabet* adj4 (decreas* adj5 onset*)).tw.	105
73	(risk* adj4 develop* adj4 diabet*).tw.	4835
74	(reduc* adj4 develop* adj4 diabet*).tw.	441
75	(decreas* adj4 develop* adj4 diabet*).tw.	131
76	(diabet* adj4 prevent*).tw.	12954
77	(diabet* adj4 reduc*).tw.	11242
78	(diabet* adj4 decreas*).tw.	7142
79	(diabet* adj4 lower*).tw.	8576
80	(diabet* adj4 lessen*).tw.	62
81	(diabet* adj4 (reduc* adj5 prevalence)).tw.	170
82	(Diabet* adj4 (decreas* adj5 progress*)).tw.	123
83	(diabet* adj4 (lessen* adj5 prevalence)).tw.	2

#	Searches	Results
84	(diabet* adj4 (decreas* adj5 prevalence)).tw.	74
85	or/64-84	42178
86	63 and 85	7617
87	11 or 86	10883
88	exp Mobile Applications/ or Cell Phones/ or Social Networking/ or Electronic mail/	12550
89	Computer-Assisted Instruction/ or Internet/	75312
90	(device-based or mobile-based or web-based).tw.	21194
91	(smartphone* or smart phone* or iphone* or mobile* or cell phone* or tablet* or mhealth or m-health or online or video* or app or apps or email* or e-mail* or e mail* or podcast* or social media or ipad or twitter or skype* or facetime* or facebook).tw.	270091
92	((digital* or digiti* or electronic* or mobile or smart* or software) adj3 (technolog* or devic* or enabl* or app or apps or application* or educat*)).tw.	18867
93	(device* adj2 technolog*).tw.	1207
94	or/88-93	351232
95	87 and 94	274
96	Randomized Controlled Trial.pt.	469224
97	Controlled Clinical Trial.pt.	95041
98	Clinical Trial.pt.	527360
99	exp Clinical Trials as Topic/	322944
100	Placebos/	35346
101	Random Allocation/	95115
102	Double-Blind Method/	147658
103	Single-Blind Method/	24527
104	Cross-Over Studies/	42567
105	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.	937889
106	(random$ adj3 allocat$).tw.	25264
107	placebo$.tw.	182696
108	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.	144570
109	(crossover$ or (cross adj over$)).tw.	67807
110	or/96-109	1680664
111	Meta-Analysis.pt.	80986
112	Meta-Analysis as Topic/	16955
113	Review.pt.	2263546
114	exp Review Literature as Topic/	9961
115	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.	94675
116	(review$ or overview$).ti.	336090
117	(systematic$ adj5 (review$ or overview$)).tw.	88997
118	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.	6339
119	((studies or trial$) adj2 (review$ or overview$)).tw.	33105
120	(integrat$ adj3 (research or review$ or literature)).tw.	7695
121	(pool$ adj2 (analy$ or data)).tw.	20537
122	(handsearch$ or (hand adj3 search$)).tw.	7434
123	(manual$ adj3 search$).tw.	4221

#	Searches	Results
124	or/111-123	2462484
125	110 or 124	3840465
126	87 and 125	5113
127	(2014* or 2015* or 2016*).ed.	2788075
128	126 and 127	1343
129	95 and 125	150
130	128 or 129	1425
131	animals/ not humans/	4635009
132	130 not 131	1401
133	limit 132 to english language	1354

B.2 Review question 2

Sources searched to identify the clinical evidence:

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	15/12/2016	Cochrane Central Register of Controlled Trials : Issue 11 of 12, November 2016	1725
Cochrane Database of Systematic Reviews (CDSR)	15/12/2016	Cochrane Database of Systematic Reviews : Issue 12 of 12, December 2016	155
Database of Abstracts of Reviews of Effect (DARE)	15/12/2016	Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015	0
Embase (Ovid)	15/12/2016	Embase 1974 to 2016 Week 50	1770
(HTA Database) Health Technology Assessment	15/12/2016	Health Technology Assessment Database : Issue 4 of 4, October 2016	0
MEDLINE (Ovid)	15/12/2016	Ovid MEDLINE(R) 1946 to November Week 5 2016	1672
MEDLINE In-Process (Ovid)	15/12/2016	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 09, 2016	98
NHS Economic Evaluation Database (NHS EED)	15/12/2016	NHS Economic Evaluation Database : Issue 2 of 4, April 2015	8
PubMed	15/12/2016		238

The MEDLINE search strategy is presented below. This was translated for use in all of the other databases listed. The aim of the search was to identify evidence for the clinical question being asked.

The Pubmed translation was designed to capture references that had not yet appeared in the Medline in Process database.

Database: Medline

1 prediabetic state/ or Glucose Intolerance/ (13089)

2 Diabetes Mellitus/pc or Diabetes Mellitus, Type 2/pc (11344)

3 Diabetes, Gestational/ (8242)

4 (gestation* adj3 diabet*).tw. (9861)

5 (prediabet* or pre diabet* or rais* glucose intoleran* or high* glucose level* or high* glucose intoleran* or impair* glucose level* or impair* glucose toleran* or IGT or impair* fast* glucose or IFT or IFG or IGR or FPG or fast* plasma glucose or impair* glucose regulation or impair* glucose metabolism or rais* glycated haemoglobin or rais* glycated hemoglobin or high glycated Hb or hyperglycaemia or hyperglycemia or HBA1C).tw. (85223)

6 Diabetes Mellitus, Type 2/ (112888)

7 Secondary Prevention/ or Primary Prevention/ or Risk Reduction Behavior/ (45631)

8 6 and 7 (1467)

9 (diabet* adj3 (reduc* adj4 risk*)).tw. (1419)

10 (diabet* adj4 (decreas* adj5 risk*)).tw. (593)

11 (risk* adj3 develop* adj3 diabet*).tw. (3375)

12 (reduc* adj4 develop* adj4 diabet*).tw. (441)

13 (decreas* adj4 develop* adj4 diabet*).tw. (131)

14 (diabet* adj3 prevent*).tw. (9757)

15 (diabet* adj3 reduc*).tw. (7144)

16 or/1-5,8-15 (121475)

17 ((aerobic or yoga or pilates or tai chi or tai-chi or taichi or tai ji or tai-ji or taiji or qi gong or qigong or qi-gong or chi kung 8 or ch i-kung or chikung or ch-i-kung) adj1 (train or therap* or treat* or intervent* or medicin* or educat*)).tw. (1117)

18 Behav* Modif*.tw. (4017)

19 Behav* therap*.tw. (15466)

20 Health* Educ*.tw. (26351)

21 Health* Promot*.tw. (26543)

22 Health* behav*.tw. (18271)

23 Educat* program*.tw. (32749)

24 Patient Educ*.tw. (13430)

25 (Diet* adj2 Intervention*).tw. (7133)

26 (Diet* adj2 Modif*).tw. (8422)

27 Food habit*.tw. (1662)

28 (Health* adj2 Eating).tw. (5334)

29 (Nutrition* adj2 Counselling).tw. (303)

30 (Nutrition* adj2 Therap*).tw. (3707)

31 ((Exercis* or kinesiotherap* or kinesiolo* or sport*) adj2 (therap* or treat* or intervent* or medicin* or educat*)).tw. (17631)

32 Physical Exercise.tw. (11136)

33 (Exercis* adj2 therap*).tw. (4827)

34 Physical endurance.tw. (320)

35 Physical education.tw. (3390)

36 Physical Fitness.tw. (6663)

37 Physical Activit*.tw. (76841)

38 Physical Train*.tw. (4918)

39 Resistance Train*.tw. (5419)

40 Strength Train*.tw. (3814)

41 (Lifestyle adj2 advice).tw. (649)

42 (Lifestyle adj2 Guid*).tw. (169)

43 (Lifestyle adj2 Modif*).tw. (5258)

Database: Medline

44 (Lifestyle adj2 Chang*).tw. (7338)

45 Lifestyle Program*.tw. (422)

46 "diabetes prevention program*".tw. (826)

47 Weight control*.tw. (5643)

48 Weight Train*.tw. (1015)

49 Weight reduc*.tw. (8793)

50 (weight loss adj4 (therap* or treat* or intervent* or medicin* or educat*)).tw. (6117)

51 (lifestyle adj2 intervention).tw. (3049)

52 ((Sport* or walk* or jog* or swim* or cycle* or bicycle*) adj4 (therap* or treat* or intervent* or medicin* or educat*)).tw. (29463)

53 exp Health Promotion/ (70658)

54 exp Program Evaluation/ (69042)

55 exp Patient Education as Topic/ (82063)

56 exp Diet Therapy/ (50869)

57 exp Nutrition Therapy/ (94243)

58 exp Exercise Therapy/ (41867)

59 exp Diet, Reducing/ (11228)

60 Physical fitness/ or Lifestyle/ or Sedentary Lifestyle/ (84270)

61 Metformin/ (10378)

62 Hypoglycemic Agents/ (55560)

63 (metformin or glucophage or bolamyn or glucient or metabet or sukkarto or diagemet xl).tw. (12234)

64 or/17-63 (675274)

65 exp Mobile Applications/ or Cell Phones/ or Social Networking/ or Electronic mail/ (12579)

66 Computer-Assisted Instruction/ or Internet/ (75376)

67 (device-based or mobile-based or web-based).tw. (21224)

68 ((smartphone* or smart phone* or iphone* or mobile* or cell phone* or tablet* or mhealth or m-health or online or video* or app or apps or email* or e-mail* or e mail* or podcast* or social media or ipad or twitter or skype* or facetime* or facebook) adj2 (diabet* or prediabet* or pre diabet* or rais* glucose intoleran* or high* glucose level* or high* glucose intoleran* or impair* glucose level* or impair* glucose toleran*)).tw. (242)

69 ((digital* or digiti* or electronic* or mobile or smart* or software) adj3 (technolog* or devic* or enabl* or app or apps or application* or educat*)).tw. (18903)

70 (device* adj2 technolog*).tw. (1208)

71 or/65-70 (112404)

72 64 or 71 (773481)

73 16 and 72 (27793)

74 ((uptake or tak* up or took up or rate* or complian* or impact* or proportion* or attrition or engage* or effect* or disseminat* or distribut* or implement* or evaluat* or application* or use* or usage* or utiliti* or adherence* or influence* or measure*) adj4 (therap* or treat* or intervent* or medicin* or educat*)).tw. (1219470)

75 ("research into practice" or "evidence into practice").tw. (1287)

76 74 or 75 (1220419)

77 73 and 76 (5740)

78 Observational Studies as Topic/ (1999)

79 Observational Study/ (30202)

80 Epidemiologic Studies/ (7951)

81 exp Case-Control Studies/ (876998)

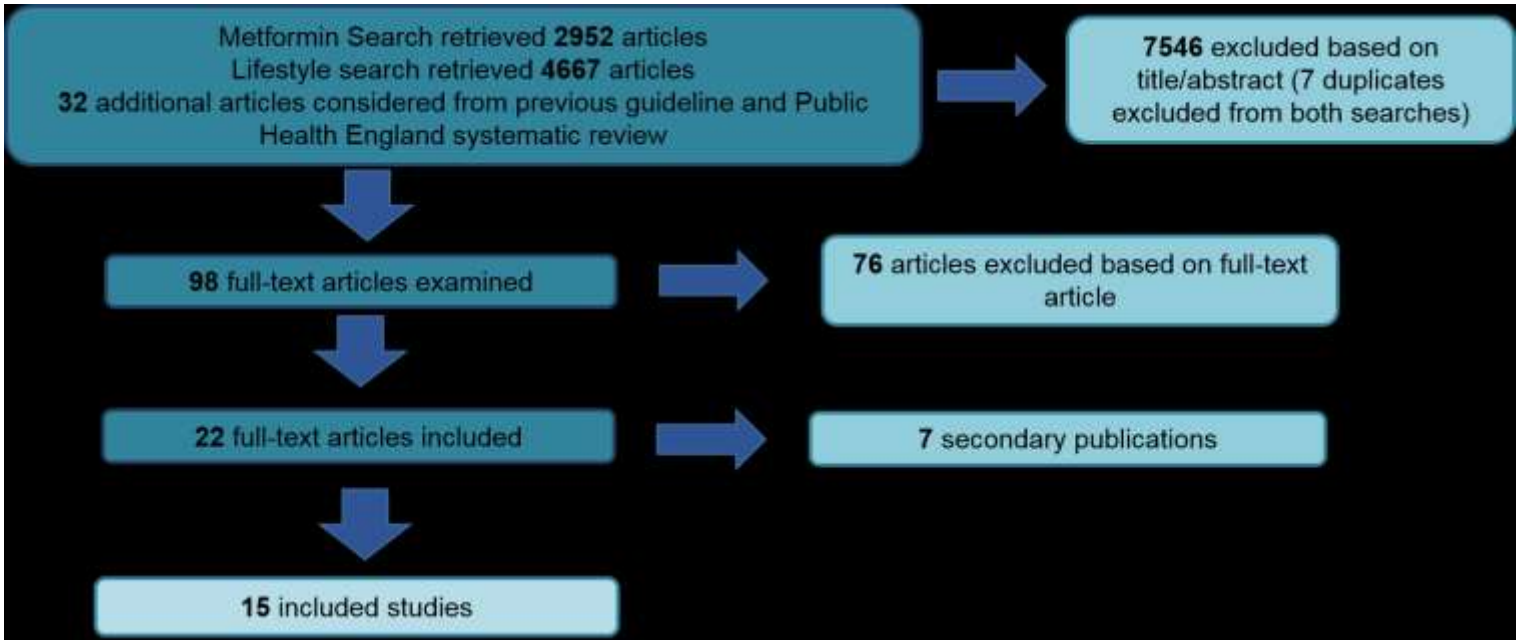
82 exp Cohort Studies/ (1714280)

83 Cross-Sectional Studies/ (255004)

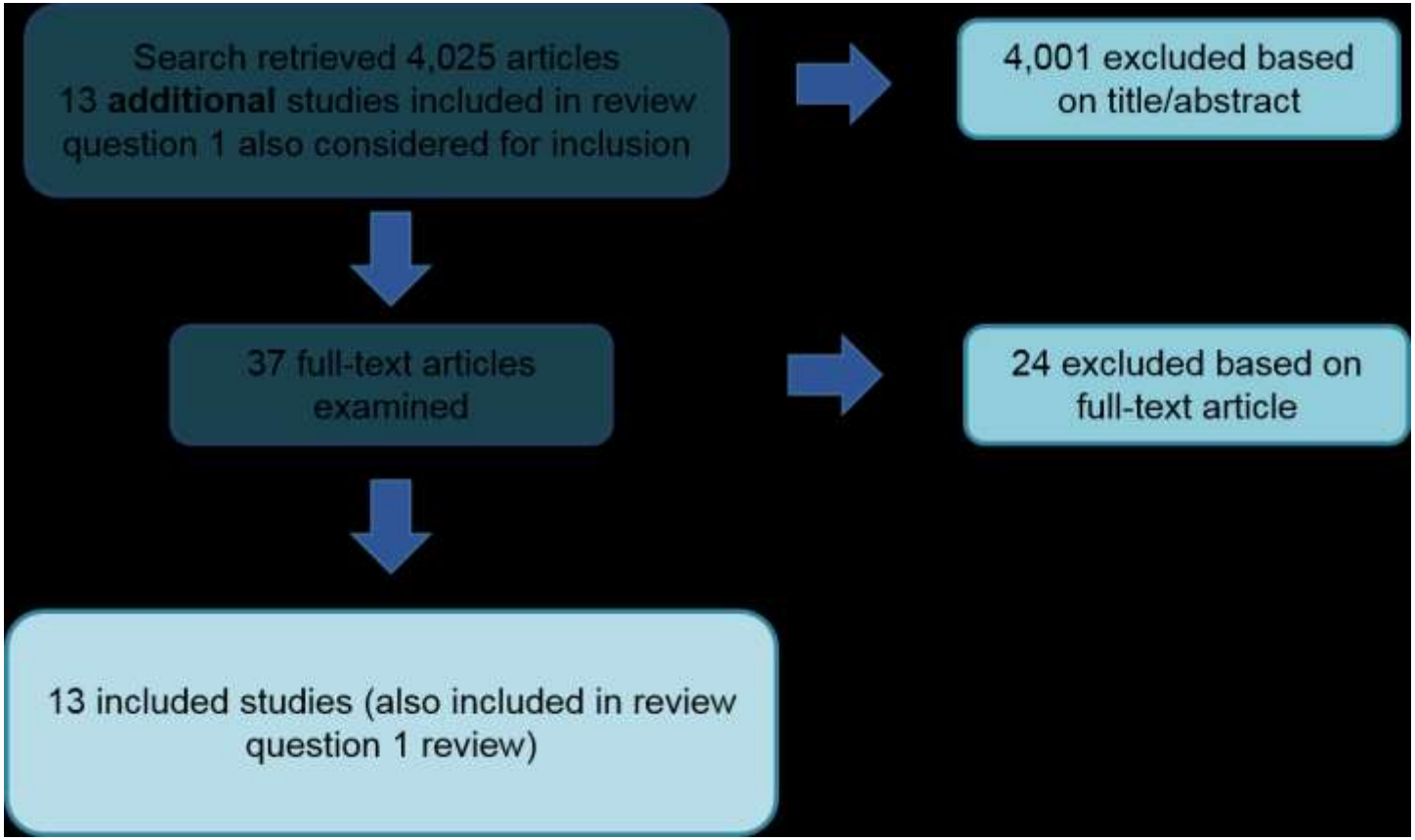
Database: Medline
84 Controlled Before-After Studies/ (208)
85 Historically Controlled Study/ (87)
86 Interrupted Time Series Analysis/ (261)
87 Comparative Study.pt. (1882149)
88 case control$.tw. (101251)
89 case series.tw. (44270)
90 (cohort adj (study or studies)).tw. (124994)
91 cohort analy$.tw. (5123)
92 (follow up adj (study or studies)).tw. (42366)
93 (observational adj (study or studies)).tw. (61168)
94 longitudinal.tw. (179020)
95 prospective.tw. (424951)
96 retrospective.tw. (336600)
97 cross sectional.tw. (220134)
98 or/78-97 (3970603)
99 77 and 98 (1874)
100 animals/ not humans/ (4636432)
101 99 not 100 (1800)
102 (letter or editorial or conference abstract or conference paper or "conference review" or historical article or news).pt. (2022642)
103 101 not 102 (1797)
104 limit 103 to english language (1672)

Appendix C: Clinical evidence study selection

C.1 Review question 1



C.21 Review question 2



*Two studies included in question 1 were identified in the search for review question 2, meaning that only 13 of 15 included studies needed to be considered in addition to those identified by the search.

1 Appendix D: Clinical evidence tables

2 **Table 5: Ackermann 2015**

Bibliographic reference	**Ackermann Rt, Liss Dt, Finch Ea, Schmidt Kk, Hays Lm, Marrero Dg, and Saha C (2015) A Randomized Comparative Effectiveness Trial for Preventing Type 2 Diabetes. American journal of public health 105(11), 2328-34**
Study type	Randomised controlled trial
Aim	To evaluate the weight loss effectiveness of a YMCA model for the Diabetes Prevention Program (DPP) lifestyle intervention.
Patient characteristics	**Inclusion criteria** - Aged 18 years or older - Body mass index of 24 or greater - no prior diagnosis of diabetes - at least 1 blood test indicating high risk for type 2 diabetes (fasting plasma glucose of 100---125 mg/dL; 2-hour post load plasma glucose of 140---199 mg/dL; or HbA1c of 5.7%---6.9%). **Exclusion criteria** - unable to provide informed consent - unable to read English - pregnant or planning pregnancy - actively taking a medication known to alter glucose metabolism (e.g., oral steroids or select antipsychotic medications) - blood pressure of 180/105 millimeters of mercury or greater - a comorbidity expected to limit life span to less than 3 years. **Recruitment** Clinical data managers at 9 urban primary care clinics used electronic databases to identify patients who met the inclusion criteria. **Baseline characteristics**

	Lifestyle (n=257)	**Usual care** (n=252)
Age (years,sd)	50.8 (12.2)	51.2 (12.0)

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Ackermann Rt, Liss Dt, Finch Ea, Schmidt Kk, Hays Lm, Marrero Dg, and Saha C (2015) A Randomized Comparative Effectiveness Trial for Preventing Type 2 Diabetes. American journal of public health 105(11), 2328-34</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><td>Sex (m/f)</td><td>70/187</td><td>79/173</td></tr>
<tr><td>Baseline body mass index (kg/m3, sd)*</td><td>37.1 (8.7)</td><td>36.5 (8.3)</td></tr>
<tr><td>Baseline fasting plasma glucose (mmol/l)</td><td>NR</td><td>NR</td></tr>
<tr><td>Baseline HbA1c (%)</td><td>6.1 (0.3)</td><td>6.0 (0.3)</td></tr>
<tr><td>History of gestational diabetes</td><td>NR</td><td>NR</td></tr>
<tr><td>Ethnicity</td><td>African American 147 (57.2)
Non-Hispanic White 91 (35.4)
Hispanic or Latino 12 (4.7)
Other or multirace 2 (0.8)
Don’t know or refuse to answer 5 (1.9)</td><td>African American 143 (56.7)
Non-Hispanic White 87 (34.5)
Hispanic or Latino 4 (1.6)
Other or multirace 9 (3.6)
Don’t know or refuse to answer 9 (3.6)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="3"><table>
<tr><td></td><td>Lifestyle</td><td>Usual care</td></tr>
<tr><td>Randomised</td><td>257</td><td>252</td></tr>
<tr><td>Dropouts (at 12 months)
- for primary outcome (weight loss)</td><td>44 (17%)*</td><td>35 (14%)*</td></tr>
</table>
* As indicated by study flow diagram

ITT analysis undertaken (estimated missing weight observations using the predictive mean matching imputation method).</td></tr>
<tr><td>Intervention</td><td colspan="3">Lifestyle intervention (n=257)
- Free of charge participation in YMCA-run DPP lifestyle intervention (active participation encouraged but not required)
- Interested participants met in groups of 8 to 12 at both YMCA and non-YMCA locations</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Ackermann Rt, Liss Dt, Finch Ea, Schmidt Kk, Hays Lm, Marrero Dg, and Saha C (2015) A Randomized Comparative Effectiveness Trial for Preventing Type 2 Diabetes. American journal of public health 105(11), 2328-34</td></tr>
<tr><td></td><td>- Involved goal setting, self-monitoring, and participant-centred problem solving to achieve modest weight loss (5%-7% reduction from baseline) through a combination of moderate physical activity (150 minutes/week, equivalent to walking) and lower dietary fat and calorie consumption
- Began with16 face-to-face, small-group lessons, each lasting 60 to 90 minutes, delivered over 16 to 24 weeks, followed by monthly support meetings, lasting about 60 minutes, for the duration of the trial
- Also offered tools such as step counter, measuring cups, food scales, fat and calorie tracking tools, and recipe guides.

Intervention delivered by trained instructors.</td></tr>
<tr><td>Comparison</td><td>Usual care (n=252)

Both groups received the following (standard practice for diagnosed pre-diabetes):
- information and encouragement to use local community resources and self-help materials from the National Diabetes Education Program at enrolment and each study visit
- Encouragement at enrolment to complete a visit with a registered dietitian at the clinic to develop an action plan for dietary changes and weight loss.</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Location</td><td>USA (recruitment from 9 urban primary care clinics in Indianapolis, Indiana)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Progression to type 2 diabetes
Not reported

Change in weight from baseline – kg (only relative data available)
<table>
<tr><th>Timepoint</th><th>Lifestyle vs usual care</th></tr>
<tr><td>12 months</td><td>mean difference=-2.3
95%CI=-3.4 to -1.1
se=0.59*</td></tr>
</table>
*calculated by reviewer

Change in HbA1c from baseline (%) (only relative data available)</td></tr>
</table>

Bibliographic reference	Ackermann Rt, Liss Dt, Finch Ea, Schmidt Kk, Hays Lm, Marrero Dg, and Saha C (2015) A Randomized Comparative Effectiveness Trial for Preventing Type 2 Diabetes. American journal of public health 105(11), 2328-34

Timepoint	Lifestyle vs usual care
12 months	mean difference=-0.04 95%CI=-0.1 to 0.0 se=0.03*

***calculated by reviewer**

Change in fasting plasma glucose from baseline (mmol/l)

Not reported

Adverse events / side effects

Not reported.

Change in systolic blood pressure from baseline- mmHg (only relative data available)

Timepoint	Lifestyle vs usual care
12 months	mean difference=-1.1 95%CI=-3.9 to 1.8 se=1.45*

***calculated by reviewer**

Change in total cholesterol from baseline – mmol/l (converted from mg/dl by reviewer - only relative data available)

Timepoint	Lifestyle vs usual care
12 months	mean difference=0.041 95%CI=-0.11 to 0.19 se=0.08*

***calculated by reviewer**

Uptake / adherence

Uptake: Not reported

Adherence: 103/257 (40.0%) completed 9 or more intervention lessons (assumed as a meaningful DPP dose, based on previous studies;

<table>
<tr><td>Bibliographic reference</td><td>Ackermann Rt, Liss Dt, Finch Ea, Schmidt Kk, Hays Lm, Marrero Dg, and Saha C (2015) A Randomized Comparative Effectiveness Trial for Preventing Type 2 Diabetes. American journal of public health 105(11), 2328-34</td></tr>
<tr><td></td><td>Dropout rate (indirect measure of adherence): 44/257 (17%)

-</td></tr>
<tr><td>Source of funding</td><td>Supported by the National Institute of Diabetes and Digestive and Kidney Diseases (grant R18 DK079855), the Robert Wood Johnson Foundation (grant 57398), and the Northwestern University Clinical and Translational Sciences Institute (grant UL1RR025741)</td></tr>
<tr><td>Comments</td><td>
<table>
<tr><th>Domain</th><th>Support for judgement</th><th>Review authors' judgment</th></tr>
<tr><td colspan="3">Selection bias</td></tr>
<tr><td>Random sequence generation</td><td>'individually randomized each participant (1:1)' 'computer generated randomization lists'</td><td>Low risk</td></tr>
<tr><td>Allocation concealment</td><td>'We blinded intervention assignment to research staff using individually sealed opaque envelopes.'</td><td>Low risk</td></tr>
<tr><td colspan="3">Performance bias</td></tr>
<tr><td>Blinding of participants and personnel</td><td>All reported outcomes considered low risk of bias due to lack of blinding</td><td>Low risk</td></tr>
<tr><td colspan="3">Detection bias</td></tr>
<tr><td>Blinding of outcome assessment</td><td>All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.</td><td>Low risk</td></tr>
<tr><td colspan="3">Attrition bias</td></tr>
<tr><td>Incomplete outcome data</td><td>Intention to treat analysis with imputation of missing data</td><td>Low risk</td></tr>
<tr><td colspan="3">Reporting bias</td></tr>
<tr><td>Selective reporting</td><td>Expected outcomes reported (for trial follow up duration)</td><td>Low risk</td></tr>
<tr><td colspan="3">Other bias</td></tr>
<tr><td>Other sources of bias</td><td>None</td><td>Low risk</td></tr>
</table>
</td></tr>
</table>

1 **Table 6: Davies 2016**

Bibliographic reference	**Davies M J; Gray L J; Troughton J; Gray A ; Tuomilehto J , et al. (2016) 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 84: 48-56.**
Study type	Cluster randomised controlled trial
Aim	To assess whether a structured education programme targeting lifestyle and behaviour change is effective at preventing progression to T2DM in people with pre-diabetes.
Patient characteristics	**Inclusion criteria** - aged 40 to 75 years if White European - aged 25–75 years if South Asian - presence of pre-diabetes (IFG and/or IGT according to WHO 1999 criteria) confirmed at screening visit via oral glucose tolerance test (OGTT) **Exclusion criteria** - pregnant or lactating - established diabetes - terminal illness - required an interpreter for a language other than one of the locally used South Asian languages accommodated by the study. **Recruitment** Practices in Leicestershire were recruited and randomised 1:1 using computer-generated list by independent researcher, using stratification by list size (<6000 or ≥6000) and ethnicity: % South Asian <21% or ≥21%). The Leicester Diabetes Practice Risk Score was used in each practice to identify people at high-risk of PDM/T2DM for invitation to screening. Top 10% of patients fulfilling study age inclusion criteria were invited for screening. Of all patients invited for screening, 19% attended. Screened patients found to have PDM progressed to cluster-randomised trial. Practices and participants were informed of allocation after baseline measurements were taken. Patients in practices allocated to the intervention arm were invited to participate in the Let's Prevent programme (intervention). **Baseline characteristics**

	Lifestyle (n=447)	**Usual care** (n=433)

Bibliographic reference	**Davies M J; Gray L J; Troughton J; Gray A ; Tuomilehto J , et al. (2016) 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 84: 48-56.**

Age (years,sd)	63.9 (7.6)	63.9 (7.9)
Sex (m/f)	282/195	278/155
Baseline body mass index (kg/m3, sd)*	32.0 (5.2)*	33.1 (5.8)*
Baseline fasting plasma glucose (mmol/l)	5.7 (0.7)	5.6 (0.7)
Baseline HbA1c (%)	6.1 (0.4)	6.1 (0.4)
History of gestational diabetes	NR	NR
Ethnicity - White European (n, %)	377 (84.5)	363 (84.3)

*Significant difference between the intervention and control groups ($p \leq 0.05$)

Number of Patients

	Lifestyle*	**Usual care**
Randomised	447	433
Dropouts (withdrew / died / lost to follow-up) - 1 year - 3 years	 69 (15%) 114 (25.5%)	 43 (10%) 91 (21.5%)

* Of participants in practices allocated to the lifestyle intervention, 101/447 (22.6%) did not attend first educational session and were excluded in per-protocol analyses.

Intervention

Lifestyle intervention (Let's Prevent programme) (n=447)

- Delivered by trained educators (and interpreters, where required) to groups of ten over 6 hours (one full day or two half-days), plus 3hr refresher sessions at 12 and 24 months and a 15 minute phone call every 3 months;
- Aim: to increase knowledge and realistic perceptions of PDM; reduce body weight by 5%; limit total saturated fat intake to 30% and 10% of total energy intake respectively; increase fibre intake; promote physical activity;
- Provided with pedometer and encouraged to form personalised step-per-day goals

<table>
<tr><td>Bibliographic reference</td><td>Davies M J; Gray L J; Troughton J; Gray A ; Tuomilehto J , et al. (2016) 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 84: 48-56.</td></tr>
<tr><td>Comparison</td><td>Usual care (n= 433)

Participants in both groups received an information booklet which included information on risk factors for T2DM, and how dietary and lifestyle changes and increased physical activity can prevent progression to T2DM.</td></tr>
<tr><td>Length of follow up</td><td>3 years</td></tr>
<tr><td>Location</td><td>UK (43 primary care practices in Leicestershire)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: Intention to treat analysis used using last value carried forward method.

Progression to type 2 diabetes
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Usual care</th></tr>
<tr><td>3 years, ITT</td><td>64/447

57.60 events per 1000 person years
95%CI=45.09 to 73.59</td><td>67/433

63.16 events per 1000 person years
95%CI=49.17 to 80.24</td></tr>
<tr><td>3 years, per protocol</td><td>51/347

53.04 events per 1000 person years
95%CI=40.31 to 69.80</td><td>67/433

63.16 events per 1000 person years
95%CI=47.71 to 80.24</td></tr>
</table>
Change in weight from baseline – kg
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Usual care</th><th>Relative effect (adj for clustering)</th></tr>
<tr><td>1 year</td><td>Mean=-0.19
sd=4.57
n=368</td><td>Mean=+0.02
sd=4.22
n=382</td><td>Mean difference=-0.27
95%CI=-1.17 to 0.63
se=0.46*</td></tr>
<tr><td>3 years</td><td>Mean=-0.59
sd=4.59</td><td>Mean=-0.46
sd=5.02</td><td>Mean difference=-0.26
95%CI=-1.17 to 0.65</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Davies M J; Gray L J; Troughton J; Gray A ; Tuomilehto J , et al. (2016) 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 84: 48-56.

	n=321	n=321	se=0.46*

***calculated by reviewer**

Change in HbA1c from baseline (%)

Timepoint	Lifestyle	Usual care	Relative effect (adj for clustering)
1 year	Mean=-0.03 % sd=0.26 n=361	Mean=+0.01 sd=0.32 n=379	Mean difference=-0.04 95%CI=-0.10 to 0.02 se=0.03*
3 years	Mean=-0.07 sd=0.39 n=322	Mean=+0.01 sd=0.44 n=328	Mean difference=-0.07 95%CI=-0.18 to 0.04 se=0.06*

***calculated by reviewer**

Change in fasting plasma glucose from baseline (mmol/l)

Timepoint	Lifestyle	Usual care	Relative effect (adj for clustering)
1 year	Mean=-0.02 sd=0.62 n=371	Mean=-0.02 sd=0.59 n=385	Mean difference=0.001 95%CI=-0.10 to 0.10 se=0.05*
3 years	Mean=+0.10 sd=0.76 n=329	Mean=+0.16 sd=0.64 n=327	Mean difference=-0.05 95%CI=-0.18 to 0.07 se=0.06*

***calculated by reviewer**

Adverse events / side effects

Not reported.

Change in systolic blood pressure from baseline- mmHg

Bibliographic reference	**Davies M J; Gray L J; Troughton J; Gray A ; Tuomilehto J , et al. (2016) 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 84: 48-56.**

Timepoint	Lifestyle	Usual care	Relative effect (adj for clustering)
1 year	Mean=-7.54 sd=17.00 n=370	Mean=-8.33 sd=15.65 n=382	Mean difference=1.22 95%CI=-0.85 to 3.30 se=1.06*
3 years	Mean=-7.57 sd=16.76 n=325	Mean=-8.00 Sd=17.36 n=322	Mean difference=0.55 95%CI=-2.09 to 3.19 se=1.35*

***calculated by reviewer**

Change in total cholesterol from baseline - mmol/l (SD)

Timepoint	Lifestyle	Usual care	Relative effect (adj for clustering)
1 year	Mean=-0.28 sd=0.73 n=367	Mean=-0.23 sd=0.74 n=381	Mean difference=-0.07 95%CI=-0.16 to 0.02 se=0.05*
3 years	Mean=-0.27 sd=0.84 n=331	Mean=-0.18 sd=0.90 n=330	Mean difference=-0.11 95%CI=-0.23 to 0.02 se=0.07*

***calculated by reviewer**

Uptake / adherence
Uptake: Not reported
Adherence: Lifestyle intervention: 346/447 (77.4%) attended first educational session.
Dropout rate (indirect measure of adherence): 114/447 (26%)

Source of funding	Funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Scheme (RP-PG-0606-1272).

Bibliographic reference	**Davies M J; Gray L J; Troughton J; Gray A ; Tuomilehto J , et al. (2016) 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 84: 48-56.**
Comments	

Domain	Support for judgement	Review authors' judgment
Selection bias		
Random sequence generation	'Practices in Leicestershire, UK, were recruited and randomised using a computer-generated list 1:1'	Low risk
Allocation concealment	'Practices and participants were informed of their allocation in the result letters after the screening/ baseline measurements were complete.' (participants not recruited after cluster randomisation)	Low risk
Performance bias		
Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding	Low risk
Detection bias		
Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
Attrition bias		
Incomplete outcome data	Intention to treat analysis with imputation of missing data	Low risk
Reporting bias		
Selective reporting	Expected outcomes reported (for trial follow up duration)	Low risk
Other bias		
Other sources of bias	Cluster RCT design: 'important differences at baseline were observed, with the intervention group having higher levels of social deprivation and smoking rates, but with lower	High risk

Bibliographic reference	**Davies M J; Gray L J; Troughton J; Gray A ; Tuomilehto J , et al. (2016) 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 84: 48-56.**		
		levels of BMI and waist circumference' Data were adjusted for clustering	

1 **Table 7: DPP 2002**

Bibliographic reference	**Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, and Nathan DM (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin.. The New England journal of medicine 346(6), 393-403** **Knowler W C, Fowler S E, Hamman R F, Christophi C A, Hoffman H J, Brenneman A T, Brown-Friday J O, Goldberg R, Venditti E, and Nathan D M (2009) 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet (London, and England) 374(9702), 1677-86** **Ratner R E, Christophi C A, Metzger B E, Dabelea D, Bennett P H, Pi-Sunyer X, Fowler S, and Kahn S E (2008) Prevention of diabetes in women with a history of gestational diabetes: Effects of metformin and lifestyle interventions. Journal of Clinical Endocrinology and Metabolism 93(12), 4774-4779** **Diabetes Prevention Program Research, and Group (2012) Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes care 35(4), 731-7** **Orchard T J, Temprosa M, Barrett-Connor E, Fowler S E, Goldberg R B, Mather K J, Marcovina S M, Montez M, Ratner R E, Saudek C D, Sherif H, and Watson K E (2013) Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: A report from the DPP Outcomes Study. Diabetic Medicine 30(1), 46-55**
Study type	Randomised controlled trial
Aim	To determine whether a lifestyle intervention or treatment with metformin prevents or delays progression to diabetes in people at high risk. Note that Knowler et al 2009 reports on a follow up study with data up to 10 years post treatment initiation. However these data are not included because an intensive lifestyle modification programme was offered to all intervention groups as part of this follow up study.
Patient characteristics	**Inclusion criteria**

- Age of at least 25 years
- BMI of 24 or higher (22 or higher in Asians)
- FPG 5.3 to 6.9 mmol/l
- Plasma glucose 7.8 to 11.0 mmol/l 2hr following 75g oral glucose

Exclusion criteria

- Taking medicines known to alter glucose tolerance
- Illnesses that could seriously reduce life expectancy or ability to participate in the trial
- Pregnancy (including 3-months post-partum or breastfeeding)
- Unable to walk 0.25 miles in 10 min

Recruitment

Used clinic-specific recruitment strategies appropriate for identified target populations, including mass media, mail, telephone contacts and recruitment through employment or social groups or health care systems.

Subjects initially assessed for eligibility by telephone, with FPG or casual glucose recorded in the field or at the clinic. Subsequent assessment of eligibility criteria undertaken (including lab tests), and a 3-week run-in / behavioural trial of compliance with pill taking and recordkeeping prior to confirmation of eligibility and randomisation to treatment group, stratified by clinical centre.

Baseline characteristics

	Placebo (n=1082)	**Metformin (n=1073)**	**Lifestyle (n=1079)**
Age (years,sd)	50.3 (10.4)	50.9 (10.3)	50.6 (11.3)
Sex (m/f)	335/747	363/710	345/734
Baseline body mass index (kg/m3, sd)	34.2 (6.7)	33.9 (6.6)	33.9 (6.8)
Baseline fasting plasma glucose (mmol/l)*	106.7 mg/dl sd 8.4 5.92 (0.47)	106.5 sd 8.5 5.91 (0.47)	mean 106.3 sd 8.1
Baseline HbA1c (%)	5.91% (0.5)	5.91% (0.5)	5.91% (0.5)
History of gestational diabetes	122 (16.3% women)	111 (15.7% women)	120 (16.3% women)
Ethnicity	White 586 African American 220 Hispanic 168	White 602 African American 221 Hispanic 162	White 580 African American 204 Hispanic 178

	American Indian 59 Asian 49	American Indian 52 Asian 36	American Indian 60 Asian 57

*converted from reported mg/dl

Number of Patients

	Placebo	Metformin	Lifestyle
Randomised	1082	1073	1079
Dropouts - not seen at year 3*	107 (9.9%)	106 (9.9%)	107 (9.9%)

* from study flow diagram (Knowler 2009)

Intervention

Metformin (n=1073)

- Initiated at 850-mg once per day and increased by 1 month to 850-mg twice daily unless gastrointestinal symptoms warranted a longer titration period
- Adherence assessed quarterly on basis of pill counts and structured interviews
- Standard lifestyle recommendations and written information on healthy eating, healthy weight, and physical activity provided annually

Lifestyle intervention (n=1079) (details extracted from US DPP manual, available online at http://www.diabetesprevention.pitt.edu/

- 16-lesson curriculum on diet, exercise and behaviour change.
- Included individual goal setting with regular review (7% reduction in body weight, 150 minutes of physical activity per week)
- Flexible, culturally sensitive and individualised.
- Goal setting and self-monitoring of weight, fat and calorie intake
- Stimulus control and problem solving
- Family members invited to attend any/all sessions
- Taught by case managers on a one-to-one basis during the first 24 weeks after enrolment; subsequent individual sessions (usually monthly) and group sessions with the case managers were designed to reinforce the behavioural changes.
- Unclear when the monthly sessions finished (presumed to continue throughout the follow up period).

Comparison

Placebo (n=1082)

- Initially given once a day then increased to twice daily, as per metformin intervention

<table>
<tr><td></td><td>- Adherence assessed quarterly on basis of pill counts and structured interviews
- Standard lifestyle recommendations and written information on healthy eating, healthy weight, and physical activity provided annually (written information plus 20-30 minute annual session)</td></tr>
<tr><td>Length of follow up</td><td>Up to 4 years with mean follow up of 2.8 years (data reported at longer time points was from the DPPOS follow-up study where all groups received a lifestyle intervention). These data are excluded from the review.</td></tr>
<tr><td>Location</td><td>USA, clinical centers (n=27)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: Reported to follow intention to treat principle, though details of how dropouts were dealt with is not provided. Orchard 2013: Analysis of quantitative changes over time used the normal errors longitudinal regression model with adjustment for DPP baseline levels.

Progression to type 2 diabetes *
<table>
<tr><th>Timepoint</th><th>Subgroup</th><th>Placebo</th><th>Metformin</th><th>Lifestyle</th><th>Metformin vs placebo (reduction in incidence)</th><th>Lifestyle vs placebo (reduction in incidence)</th></tr>
<tr><td>Mean 2.8 years follow up (Knowler et al 2002/2009)</td><td>Overall</td><td>incidence per 100 person years=11.0
95%CI=9.8 to 12.3
Person years: 3029.6
Events=333/1082</td><td>incidence per 100 person years=7.8
95%CI=6.8 to 8.8
n=1073
Person years: 3004.4
Events=234/1073</td><td>incidence per 100 person years=4.8
95%CI=4.1 to 5.7
Person years: 3021.2
Events=145/1079</td><td>31 (17 to 43)</td><td>58 (48 to 66)</td></tr>
<tr><td>Mean 2.8 years follow up (Knowler et al 2002)</td><td>Age 25-44</td><td>incidence per 100 person years=11.6
Person years=932.4
Events=108/333</td><td>incidence per 100 person years=6.7
Person years=932.4
Events=62/333</td><td>incidence per 100 person years=6.2
Person years=935.2
Events=58/334</td><td>44 (21 to 60)</td><td>48 (27 to 63)</td></tr>
<tr><td>Mean 2.8 years follow up</td><td>Age 45 -59</td><td>incidence per 100 person years=10.8</td><td>incidence per 100 person years=7.6</td><td>incidence per 100 person years=4.7</td><td>31 (10 to 46)</td><td>59 (44 to 70)</td></tr>
</table></td></tr>
</table>

(Knowler et al 2002)		Person years=1481.2 Events=160/529	Person years=1481.2 Events=113/529	Person years=1478.4 Events=69/528		
Mean 2.8 years follow up (Knowler et al 2002)	Age =>60	incidence per 100 person years=10.8 Person years=604.8 Events=65/216	incidence per 100 person years=9.6 Person years=604.8 Events=58/216	incidence per 100 person years=3.1 Person years=604.8 Events=19/216	11 (10 to 46)	71 (51 to 83)
Mean 2.8 years follow up (Knowler et al 2002)	Ethnicity: White	incidence per 100 person years=10.3 Person years:1640.8 Events=169/586	incidence per 100 person years=7.8 Person years:1685.6 Events=131/602	incidence per 100 person years=5.2 Person years: 1624 Events=84/580	24 (3 to 41)	51 (35 to 63)
Mean 2.8 years follow up (Knowler et al 2002)	Ethnicity: African American	incidence per 100 person years=12.4 Person years: 616 Events=76/220	incidence per 100 person years=7.1 Person years: 618.8 Events=44/221	incidence per 100 person years=5.1 Person years: 571.2 Events=29/204	44 (16 to 63)	61 (37 to 76)
Mean 2.8 years follow up (Knowler et al 2002)	Ethnicity: Hispanic	incidence per 100 person years=11.7 Person years: 470.4 Events=55/168	incidence per 100 person years=8.4 Person years: 453.6 Events=38/162	incidence per 100 person years=4.2 Person years: 498.4 Events=21/178	31 (9 to 56)	66 (41 to 80)
Mean 2.8 years follow up (Knowler et al 2002)	Ethnicity: American Indian	incidence per 100 person years=12.9 Person years: 165.2 Events=21/59	incidence per 100 person years=9.7 Person years: 145.6 Events=14/52	incidence per 100 person years=4.7 Person years: 168 Events=8/60	25 (72 to 68)	65 (7 to 87)

Mean 2.8 years follow up (Knowler et al 2002)	Ethnicity: Asian	incidence per 100 person years=12.1 Person years: 137.2 Events=17/49	incidence per 100 person years=7.5 Person years: 100.8 Events=8/36	incidence per 100 person years=3.8 Person years: 159.6 Events=6/57	38 (55 to 75)	71 (24 to 89)
Mean 2.8 years follow up (Knowler et al 2002)	BMI: 22 to<30	incidence per 100 person years=9.0 Person years:975.3 Events=88/349	incidence per 100 person years=8.8 Person years: 975.3 Events=86/348	incidence per 100 person years=3.3 Person years: 975.3 Events=32/348	3 (36 to 30)	65 (46 to 77)
Mean 2.8 years follow up (Knowler et al 2002)	BMI: 30 to <35	incidence per 100 person years=8.9 Person years: 928.7 Events=83/332	incidence per 100 person years=7.6 Person years: 928.7 Events=71/332	incidence per 100 person years=3.7 Person years: 928.7 Events=34/331	16 (19 to 41)	61 (40 to 75)
Mean 2.8 years follow up (Knowler et al 2002)	BMI:>=35	incidence per 100 person years=14.3 Person years: 1114.4 Events=159/398	incidence per 100 person years=7.0 Person years: 1114.4 Events=78/398	incidence per 100 person years=7.3 Person years: 1114.4 Events=81/398	53 (36 to 65)	51 (34 to 63)
Mean 2.8 years follow up (Knowler et al 2002)	FPG: 5.27 to 6.05 mmol/l	incidence per 100 person years=6.4 Person years: 2029.1 Events=130/724	incidence per 100 person years=5.5 Person years: 2029.1 Events=112/725	incidence per 100 person years=2.9 Person years: 2029.1 Events=59/725	15 (12 to 36)	55 (38 to 68)
Mean 2.8 years follow up (Knowler et al 2002)	FPG: 6.11 to 6.94 mmol/l	incidence per 100 person years=22.3 Person years: 989.3 Events=221/354	incidence per 100 person years=12.3 Person years: 989.3 Events=122/353	incidence per 100 person years=8.8 Person years: 989.3 Events=87/353	48 (33 to 60)	63 (51 to 72)

Mean 2.8 years follow up (Ratner et al 2008)	Gestational diabetes	incidence per 100 person years=15.2 Person years: 341.6 Events=52/122	incidence per 100 person years=7.8 Person years: 310.8 Events=24/111	incidence per 100 person years=7.4 Person years: 327.6 Events=24/117	-	-
Mean 2.8 years follow up (Ratner et al 2008)	Parous Women without gestational diabetes	incidence per 100 person years=8.9 Person years: 1363.6 Events=121/487	incidence per 100 person years=7.8 Person years: 1299.2 Events=101/464	incidence per 100 person years=4.7 Person years: 1302 Events=61/465	-	-

*Number of person years estimated by reviewer as N for reported outcome x mean follow up. When N was not reported for each intervention, participants were assumed to be distributed equally across interventions (random allocation with equal probability)

Change in Weight (kg)

Timepoint	Placebo	Metformin	Lifestyle
12 months (DPP 2012, Knowler 2002,2009)**	Mean=-0.43 Sd=4.7 n=1026	Mean=-2.7 Sd=4.7 n=1015	Mean=-6.7 Sd=4.7**** n=1023
3 years (Knowler 2009 web appendix)***	Mean=-0.2 Sd=4.7**** N=972	Mean=-1.9 Sd=4.7**** N=964	Mean=-4.3 Sd=4.7**** N=970

*Data available at later timepoints. 3 year follow up data reported because at later time points, all participants received additional intensive lifestyle intervention (DPPOS follow up study).

** Means and sd reported in DPP 2012 for placebo and metformin only, mean only reported on graph for lifestyle intervention in Knowler 2002, sd inferred by reviewer assuming same as other groups. Sample sizes extracted from Knowler 2009 web appendix

*** Data available at later timepoints. 3 year follow up data reported because at later time points, all participants received additional intensive lifestyle intervention (DPPOS follow up study).

****Standard deviations not reported. Inferred by reviewer as being the same as those reported at 12 months follow up for placebo and metformin groups. Mean changes estimated by reviewer from graph.

HbA1c (%) Not reported as change from baseline

Timepoint	Placebo	Metformin	Lifestyle
12 months (Knowler 2009 web appendix)	Mean=6.00 se=0.01 sd=0.32** n=1022	Mean=5.91 se=0.01 sd=0.32** n=1013	Mean=5.82 se=0.01 sd=0.32** n=1043
3 years (Knowler 2009 web appendix)*	Mean=6.04 se=0.01 sd=0.31** n=968	Mean=5.95 se=0.01 sd=0.31** n=960	Mean=5.87 se=0.01 sd=0.31** n=967

*Data available at later timepoints. 3 year follow up data reported because at later time points, all participants received additional intensive lifestyle intervention (DPPOS follow up study).

**calculated by reviewer from se and n

Fasting plasma glucose (mmol/l) Not reported as change from baseline

Timepoint	Group	Placebo	Metformin	Lifestyle
12 months (Knowler 2009 web appendix)	All	Mean=5.94 (mmol/l)** se=0.02 sd=0.64*** n=1028	Mean=5.68 (mmol/l)** se=0.02 sd=0.64*** n=1017	Mean=5.64 (mmol/l)** se=0.02 sd=0.64*** n=1026
3 years (Knowler 2009 web appendix)*	All	Mean=6.14 (mmol/l) se=0.02 sd=0.62*** n=959	Mean=5.89 (mmol/l) se=0.02 sd=0.62*** n=961	Mean=5.90 (mmol/l) se=0.02 sd=0.62*** n=966

*Data available at later timepoints. 3 year follow up data reported because at later time points, all participants received additional intensive lifestyle intervention DPPOS (follow up study).

**Reported as mg/dl. Converted by reviewer

*** Calculated by reviewer from se and n

Adverse events and side effects (GI symptoms, incidence per 100 person years)

Timepoint	Placebo	Metformin	Lifestyle	Metformin vs Placebo	Lifestyle vs Placebo (calculated	Metformin vs Lifestyle (calculated

				(calculated by reviewer)	**by reviewer)**	**by reviewer)**
Mean 2.8 years follow up (Knowler et al 2002)	incidence per 100 person years =30.7 Person years= 3029.6** Events=930** N=1082	incidence per 100 person years =77.8 Person years=3004.4** Events=2337** N=1073	incidence per 100 person years =12.9 Person years=3021.2** Events=390** N=1079	Rate ratio=2.53 ln(rate ratio)=0.93 ln(se)=0.039	Rate ratio=0.42 ln(rate ratio)=-0.87 ln(se)=0.06	Rate ratio=0.17 ln(rate ratio)=-1.8 ln(se)=0.06
1 year* (DPP 2012)	Incidence=17% (170**) N=1002	Incidence=34% (344**) N=1013	NR			

***Reported at other time points but not extracted as reported incidence for previous year or 3 months only, rather than across whole intervention period, and number of participants contributing to data not reported**

****Estimated by reviewer. Person years estimated as number randomised x mean follow up period**

Systolic blood pressure

Timepoint	Placebo	Metformin	Lifestyle
Mean 2.9 years follow up (Last DPP annual, Orchard 2013)*	Mean (mmHg)=123 95%CI=122 to 124 sd=16.8** N=1082**	Mean (mmHg)=123 95%CI=122 to 124 sd=16.7** N=1073**	Mean (mmHg)=120 95%CI=120 to 121 sd=8.4** N=1079**

*Data available at later timepoints. 3 year follow up data reported because at later time points, all participants received additional intensive lifestyle intervention DPPOS (follow up study).

**calculated by reviewer. N inferred from number randomised and reported intention to treat principle

Total cholesterol (mmol/l) Calculated by reviewer from HDL cholesterol and non-HDL cholesterol

Timepoint	Placebo	Metformin	Lifestyle
Mean 2.9 years follow up (Last DPP annual, Orchard 2013)*	Mean HDL =1.17 HDL 95%CI=1.17 to 1.19 HDL sd=0.17** Mean non-HDL=4.0 non-HDL 95%CI=4.0 to 4.1	Mean HDL =1.19 HDL 95%CI=1.19 to 1.22 HDL sd=0.25** Mean non-HDL=4.0 non-HDL 95%CI=3.9 to 4.0	Mean HDL =1.22 HDL 95%CI=1.22 to 1.22 HDL sd=0.00** Mean non-HDL=3.9 non-HDL 95%CI=3.9 to 4.0

	non-HDL sd=0.84** mean total=5.17** total sd=0.86** N=1082**	non-HDL sd=0.83** mean total=5.19** total sd=0.87** N=1073**	non-HDL sd=0.84** mean total=5.12** total sd=0.84** N=1079**

*Data available at later timepoints. 3 year follow up data reported because at later time points, all participants received additional intensive lifestyle intervention DPPOS (follow up study).

**calculated by reviewer. N inferred from number randomised and reported intention to treat principle

Uptake / adherence

Uptake: not reported

Adherence:

Lifestyle intervention: proportion who met the goal of at least 150 minutes of physical activity per week (assessed on the basis of logs kept by the participants) was 74% at 24 weeks and 58% at the most recent visit.

Metformin intervention: proportion who took ≥80% of prescribed dose of medication: 72%

Dropouts (indirect measure of adherence):

Metformin: 106/1073 (9.9%)

Lifestyle: 107/1079 (9.9%)

Source of funding

Lipha Pharmaceuticals provided metformin and placebo. LifeScan, Health-O-Meter, Hoechst Marion Roussel, Merck-Medco Managed Care, Merck, Nike, Slim-Fast Foods, and Quaker Oats provided materials, equipment, and medicines for concomitant conditions.

McKesson BioServices, Mathews Media Group, and the Henry M. Jackson Foundation provided support services provided under subcontract with the Coordinating Center.

Comments

Domain	Support for judgement	Review authors' judgment
Selection bias		
Random sequence generation	Allocation was randomised, but method of random sequence generation and allocation concealment not specified.	Unclear risk
Allocation concealment	Allocation was randomised, but method of random sequence generation and allocation concealment not specified.	Unclear risk
Performance bias		

	Blinding of participants and personnel	All reported outcomes except adverse events considered low risk of bias due to lack of blinding. Metformin vs placebo comparison described as 'double blinded'	Metformin vs placebo (all outcomes): Low risk Intensive exercise vs placebo (adverse events): High risk Intensive exercise vs placebo (other outcomes): Low risk
	Detection bias		
	Blinding of outcome assessment	All reported outcomes considered except adverse at low risk of bias due to lack of blinding of outcome assessment. Metformin vs placebo comparison described as 'double blinded'	Metformin vs placebo (all outcomes): Low risk Intensive exercise vs placebo (adverse events): High risk Intensive exercise vs placebo (other outcomes): Low risk
	Attrition bias		
	Incomplete outcome data	Drop-out rate similar across groups (9.9%) and analysis described as intention to treat.	Low risk
	Reporting bias		
	Selective reporting	Expected outcomes reported (across multiple publications)	Low risk
	Other bias		
	Other sources of bias	None	Low risk

1 **Table 8: Fontbonne 2009**

Bibliographic reference	**Fontbonne A, Diouf I, Baccara-Dinet M, Eschwege E, and Charles M A (2009) Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: A post-hoc analysis of the BIGPRO1 trial. Diabetes and Metabolism 35(5), 385-391**
Study type	Randomised controlled trial
Aim	The paper describes a post-hoc analysis of the BIGPRO1 trial for a subset of participants with impaired glucose tolerance. The main BIGPRO1 trial compared metformin with placebo in a population with a high waist to hip ratio (the main analysis for this trial did not meet the population inclusion criteria as the mean fasting plasma glucose fell below the range specified in the protocol). The trial also reports on an analysis of a subgroup of patients meeting

<table>
<tr><td>Bibliographic reference</td><td>Fontbonne A, Diouf I, Baccara-Dinet M, Eschwege E, and Charles M A (2009) Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: A post-hoc analysis of the BIGPRO1 trial. Diabetes and Metabolism 35(5), 385-391</td></tr>
<tr><td></td><td>criteria for entry into the US diabetes prevention programme. This group is a smaller (but overlapping) subset of the group with impaired glucose tolerance and so these data have not been extracted.</td></tr>
<tr><td>Patient characteristics</td><td>Inclusion criteria
Waist to hip ratio of =>0.95 (mean) or =>0.80 (women)
Non-diabetic according to 1985 WHO criteria (FPG<7.8mmol/l, 2hr post load glucose<11.1 mmol/l(
Age 35-60 years (men) or 40-65 years (women)

Exclusion criteria
Cardiovascular disease
Contraindications to use of metformin

Recruitment
Outpatient departments across France. Treatment allocation stratified by centre and gender.

Baseline characteristics
<table>
<tr><td></td><td>Metformin</td><td>Placebo</td></tr>
<tr><td>Age in years (sd)*</td><td>52.6 (6.2)</td><td>48.9 (6.7)</td></tr>
<tr><td>Sex (m/f)</td><td>12/37</td><td>22/30</td></tr>
<tr><td>Baseline body mass index (kg/m3, sd)</td><td>33.5 (5.9)</td><td>35.6 (7.5)</td></tr>
<tr><td>Baseline fasting plasma glucose (mmol/l)</td><td>5.8 (0.6)</td><td>5.6 (0.8)</td></tr>
<tr><td>Baseline HbA1c (%)</td><td>NR</td><td>NR</td></tr>
<tr><td>History of gestational diabetes</td><td>NR</td><td>NR</td></tr>
<tr><td>Ethnicity</td><td>NR</td><td>NR</td></tr>
</table>

* significant difference between treatment groups</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td>Metformin</td><td>Placebo</td></tr>
<tr><td>Randomised</td><td>49 with IFG / IGT</td><td>52 with IFG / IGT</td></tr>
<tr><td>Dropouts (at 12 months)</td><td>21 (43%)</td><td>16 (31%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Fontbonne A, Diouf I, Baccara-Dinet M, Eschwege E, and Charles M A (2009) Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: A post-hoc analysis of the BIGPRO1 trial. Diabetes and Metabolism 35(5), 385-391</td></tr>
<tr><td>Intervention</td><td>Metformin (n=49)
- 850mg tablet of metformin chlorhydrate twice daily for one year
- Given lifestyle advice on diet and exercise on each trial visit, but no lifestyle modification programme was undertaken.</td></tr>
<tr><td>Comparison</td><td>Placebo (n=52)
- One tablet twice daily for one year, as per intervention
- Given lifestyle advice on diet and exercise on each trial visit, but no lifestyle modification programme was undertaken.</td></tr>
<tr><td>Length of follow up</td><td>1 year</td></tr>
<tr><td>Location</td><td>France</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: Data reported below is for those completing the trial only.

Progression to type 2 diabetes
Not reported

Change in weight (kg relative to baseline, 95% CI)
<table>
<tr><th>Timepoint</th><th>Metformin</th><th>Placebo</th></tr>
<tr><td>12 months</td><td>Mean=-3.02
95% CI=-5.48 to -0.57
sd=6.33
n=28</td><td>Mean=-0.72
95%CI=-2.84 to 1.39
sd=6.25
n=36</td></tr>
</table>
*calculated by reviewer

Change in HbA1c levels from baseline
Not reported

Change in Fasting plasma glucose from baseline (mmol/l relative to baseline, 95%CI)
<table>
<tr><th>Timepoint</th><th>Metformin</th><th>Placebo</th></tr>
<tr><td>12 months</td><td>-0.33 (-1.08 to 0.42)
sd=1.93*</td><td>0.69 (0.03 to 1.36)
sd=1.97*</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Fontbonne A, Diouf I, Baccara-Dinet M, Eschwege E, and Charles M A (2009) Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: A post-hoc analysis of the BIGPRO1 trial. Diabetes and Metabolism 35(5), 385-391**

	n=28	n=36

***calculated by reviewer**

Adverse events and side effects (limited GI intolerance)
Not reported

Change in Systolic blood pressure from baseline (mmHg relative to baseline, 95%CI)

Timepoint	Metformin	Placebo
12 months	-14.1 (-20.6, -7.7) sd=16.63 n=28	-2.0 (-7.5 to 3.6) sd=16.4 n=36

Change in Total cholesterol from baseline (mmol/l relative to baseline, 95%CI)

Timepoint	Metformin	Placebo
12 months	-0.17 (-0.52, 0.18) sd=0.9 n=28	0.32 (0.02 to 0.63) sd=0.9 n=36

Uptake / adherence
Uptake: Not reported
Adherence: Not reported
Dropouts (indirect measure of adherence): Metformin: 21/49 (43%)

Funding	Merk Sante (manufacturers of metformin) provided funds for conference attendance and reported analysis. BIGPRO1 trial was supported by grants from INSERM and the 'Caisse nationale d'assurance maladie des travailleurs salaries' and Lipha Pharmaceuticals Ltd.
Comments	**Quality assessment**

Domain	Support for judgement	Review authors' judgment
Selection bias		

Bibliographic reference	Fontbonne A, Diouf I, Baccara-Dinet M, Eschwege E, and Charles M A (2009) Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: A post-hoc analysis of the BIGPRO1 trial. Diabetes and Metabolism 35(5), 385-391		
	Random sequence generation	Allocation was randomised, but method of random sequence generation not specified.	Unclear risk
	Allocation concealment	Allocation was randomised, but allocation concealment not specified.	Unclear risk
	Performance bias		
	Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
	Detection bias		
	Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
	Attrition bias		
	Incomplete outcome data	High rates of attrition which differed across treatment groups. Trial completers were significantly more likely to be taking medication for hypertension than dropouts. Analysis based on completers only.	High risk
	Reporting bias		
	Selective reporting	Expected outcome reported (given short term follow up period progression to type 2 diabetes not expected)	Low risk
	Other bias		
	Other sources of bias	None	Low risk

1

2 **Table 9: Katula 2011**

Bibliographic reference	**Katula JA ; Vitolins MZ ; Rosenberger EL ; Blackwell CS ; Morgan TM , et al. (2011). One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. Diabetes Care 34: 1451-7.**
Study type	Randomised controlled trial
Aim	To report the first-year results of a community-based translation of the DPP lifestyle weight loss (LWL) intervention on fasting glucose, insulin resistance, and adiposity.
Patient characteristics	**Inclusion criteria** - ≥21 years of age - evidence of prediabetes on two occasions, with a confirmatory fasting glucose between 95 and 125 mg/dL - BMI ≥25.0 kg/m2 and ≤39.9 kg/m2 **Exclusion criteria** - presence of comorbid conditions, including recent history of an acute CVD event, clinical history of type 2 diabetes, uncontrolled hypertension, cancer or other conditions limiting life expectancy - chronic use of medicines known to influence glucose metabolism - major psychiatric or cognitive problems, including moderate and severe depression - pregnancy, breastfeeding or planned pregnancy within 2 years - participation in a supervised program for weight loss or another research study Patients with contraindications to exercise were required to obtain a medical clearance from their physician prior to randomization. **Recruitment** Various strategies, including weekly mass mailings to selected zip codes (distributed through the marketing division of a local newspaper), referrals from primary care clinics, community and worksite screenings organized by the study team, and group presentations to community and civic groups. Interested participants undertook telephone screening; those who were potentially eligible were invited to information session where FPG and BP were measured and Physical Activity Readiness Questionnaire (PAR-Q) administered. Potentially eligible participants were screened for other eligibility criteria at a study clinic visit prior to randomisation. **Baseline characteristics**

Bibliographic reference	**Katula JA ; Vitolins MZ ; Rosenberger EL ; Blackwell CS ; Morgan TM , et al. (2011). One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. Diabetes Care 34: 1451-7.**

	Lifestyle (n=151)	**Enhanced usual care (n=150)**
Age (years,sd)	57.3 (10.1)	58.5 (9.0)
Sex (m/f)	64/87	64/86
Baseline body mass index (kg/m3, sd)	32.8 (3.9)	32.6 (4.1)
Baseline fasting plasma glucose (mmol/l)	5.85 (0.69)	
Baseline HbA1c (%)	NR	NR
History of gestational diabetes	NR	NR
Ethnicity (n, %) - White - African American - Other / refused	 111 (73.5) 39 (25.8) 1 (0.7)	 111 (74.0) 335 (23.3) 4 (2.7)

	Lifestyle	**Enhanced usual care**
Randomised	151	150
Dropouts at 12 months - Missed assessment visit / refused / withdrew	15 (9.9%)	10 (6.7%)

Intervention

Lifestyle intervention (n=151)

- Focused on weight loss for first 6 months; then maintenance of weight loss
- Delivered by trained community health workers (CHWs) who were financially compensated for the sessions they ran, had well-controlled type 2 diabetes and a history of healthy eating and physical activity; CHWs were overseen by registered dieticians

<table>
<tr><td>Bibliographic reference</td><td>Katula JA ; Vitolins MZ ; Rosenberger EL ; Blackwell CS ; Morgan TM , et al. (2011). One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. Diabetes Care 34: 1451-7.</td></tr>
<tr><td></td><td>- Weekly group sessions (8-12 participants) during the first 6 months, conducted at various community sites
- Three additional personalized consultations with a registered dietician (months 1, 3, and 6).
- During months 7–12, participants received one group session and one telephone contact with CHW
- Intervention content was supported by a DVD series covering nutrition and physical activity basics, energy balance, healthy eating, goal setting, and problem solving.</td></tr>
<tr><td>Comparison</td><td>Enhanced usual care (n=150)
- designed to exceed usual care for prediabetes to enhance retention
- consisted of two individual sessions with a nutritionist during the first 3 months covering healthy eating and physical activity education to support weight loss
- received monthly newsletter with information on healthy lifestyles and community resources.</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: Described as ‘intention to treat’ though details of how dropouts were accounted for are not provided. Least square means from a repeated-measures ANCOVA using the baseline value as a covariate

Progression to type 2 diabetes (data from supplementary table 1)
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Enhanced usual care</th></tr>
<tr><td>12 months</td><td>2/151</td><td>7/150</td></tr>
</table>

Weight – kg
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Enhanced usual care</th></tr>
<tr><td>Baseline</td><td>Mean=94.41
se=1.24
sd=15.24**
n=151</td><td>Mean=92.67
se=1.37
sd=16.78**
n=150</td></tr>
<tr><td>12 months</td><td>mean=87.44</td><td>mean=90.93</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Katula JA ; Vitolins MZ ; Rosenberger EL ; Blackwell CS ; Morgan TM , et al. (2011). One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. Diabetes Care 34: 1451-7.

	se=1.28 sd=15.73** n=151*	se=1.37 sd=16.78** n=150*

*inferred by reviewer from number randomised (intention to treat analysis)
**calculated by reviewer

Change in HbA1c (%)
Not reported.

Fasting plasma glucose - mmol/l

Timepoint	Lifestyle	Enhanced usual care
Baseline	Mean=5.86 se=0.06 sd=0.74** n=151*	Mean=5.88 se=0.05 sd=0.61** n=150*
12 months	mean=5.61 se=0.05 sd=0.61** n=151*	mean=5.78 se=0.05 sd=0.61** n=150*

*inferred by reviewer from number randomised (intention to treat analysis)
**calculated by reviewer

Adverse events / side effects (limited to gastrointestinal)
Not reported – only uncategorised adverse events reported.

Systolic blood pressure
Not reported

Total cholesterol
Not reported

Bibliographic reference	**Katula JA ; Vitolins MZ ; Rosenberger EL ; Blackwell CS ; Morgan TM , et al. (2011). One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. Diabetes Care 34: 1451-7.**
	Uptake / adherence **Uptake:** Not reported **Adherence:** Not reported **Dropouts (indirect measure of adherence):** 15/151 (10%)
Source of funding	Funded by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (R18-DK-69901).
Comments	

Domain	Support for judgement	Review authors' judgment
Selection bias		
Random sequence generation	Allocation was randomised, but method of random sequence generation not specified.	Unclear risk
Allocation concealment	Allocation was randomised, but allocation concealment not specified.	Unclear risk
Performance bias		
Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
Detection bias		
Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
Attrition bias		
Incomplete outcome data	Attrition similar across groups. Analysis described as intention to treat.	Low risk

Bibliographic reference	**Katula JA ; Vitolins MZ ; Rosenberger EL ; Blackwell CS ; Morgan TM , et al. (2011). One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. Diabetes Care 34: 1451-7.**

Reporting bias		
Selective reporting	Expected outcome reported	Low risk
Other bias		
Other sources of bias	None	Low risk

1 **Table 10: Kulzer 2009**

Bibliographic reference	**Kulzer B ; Hermanns N ; Gorges D ; Schwarz P ; Haak T (2009). Prevention of diabetes self-management program (PREDIAS): effects on weight, metabolic risk factors, and behavioral outcomes. Diabetes Care 32: 1143-6.**
Study type	Randomised controlled trial
Aim	To evaluate, in a 12 month follow-up, the efficacy of a group programme (PREDIAS) to modify weight and other lifestyle factors associated with an elevated diabetes risk.
Patient characteristics	**Inclusion criteria** - aged 20–70 years - BMI ≥26 kg/m2 - impaired glucose tolerance or impaired fasting glucose (not defined) - ability to read and understand German. **Exclusion criteria** - manifest diabetes or diagnosis of a serious illness (e.g., cancer). **Recruitment** Individuals with an elevated diabetes risk based on high score (>10) on the Diabetes Risk Score or according to assessment of a primary care physician were invited to a baseline examination. After a pool of 12–20 patients was created, a centrally performed block randomization (1:1) assigned subjects randomly to the PREDIAS lifestyle intervention or control group. **Baseline characteristics**

	Lifestyle (n=91)	**Control (n=91)**
Age (years, sd)*	56.3 (10.1)	

Bibliographic reference	**Kulzer B ; Hermanns N ; Gorges D ; Schwarz P ; Haak T (2009). Prevention of diabetes self-management program (PREDIAS): effects on weight, metabolic risk factors, and behavioral outcomes. Diabetes Care 32: 1143-6.**
	<table><tr><td>Sex (m/f)*</td><td colspan="2">104/78</td></tr><tr><td>Baseline body mass index (kg/m3, sd)</td><td>31.0 (4.7)</td><td>32.0 (5.7)</td></tr><tr><td>Baseline fasting plasma glucose (mmol/l)</td><td>5.87 (0.69)</td><td>5.86 (0.69)</td></tr><tr><td>Baseline HbA1c (%)</td><td>5.7 (0.5)</td><td>5.7 (0.6)</td></tr><tr><td>History of gestational diabetes</td><td>NR</td><td>NR</td></tr><tr><td>Ethnicity (n, %)</td><td>NR</td><td>NR</td></tr></table> *Not reported by treatment group. There were no significant baseline differences between the two groups on any characteristics.
Number of Patients	N=182 randomised; 17 participants (9.3%) lost to follow-up overall (does not report separately for each group). A dropout analysis showed no significant differences between participants study completers and those who dropped out.
Intervention	**Lifestyle** (n=91) - PREDIAS programme based on DPP. 12 lessons lasting 90 mins each; 8 core lessons (one per week for 8 weeks) followed by 4 bi-monthly booster sessions. - Conducted in small groups (median size seven people). - Delivered by either diabetes educators or psychologists
Comparison	**Control** (n=91) - Received PREDIAS written information and patient materials but did not attend group intervention programme.
Length of follow up	12 months
Location	Germany
Outcomes measures and effect size	**Analysis:** Intention to treat analysis (baseline value carried forward) **Progression to type 2 diabetes** Not reported

Bibliographic reference	Kulzer B ; Hermanns N ; Gorges D ; Schwarz P ; Haak T (2009). Prevention of diabetes self-management program (PREDIAS): effects on weight, metabolic risk factors, and behavioral outcomes. Diabetes Care 32: 1143-6.

Change in weight from baseline – kg

Timepoint	Lifestyle	Control
12 months	mean=-3.8 sd=5.2 n=61*	mean=-1.4 sd=4.0 n=61*

*inferred by reviewer from number randomised assuming equal distribution across groups and reported intention to treat analysis

Change in HbA1c from baseline - %

Timepoint	Lifestyle	Control
12 months	mean=+0.0 sd=0.3 n=61*	mean=+0.1 sd=0.4 n=61*

*inferred by reviewer from number randomised assuming equal distribution across groups and reported intention to treat analysis

Change in fasting plasma glucose from baseline - mmol/l (converted from mg/DL by reviewer)

Timepoint	Lifestyle	Control
12 months	mean=-0.2 sd=0.63 n=61*	mean=+0.1 sd=0.73 n=61*

*inferred by reviewer from number randomised assuming equal distribution across groups and reported intention to treat analysis

Adverse events / side effects

Not reported.

Change in systolic blood pressure from baseline – mmHg (SD)

Timepoint	Lifestyle	Control

Bibliographic reference	**Kulzer B ; Hermanns N ; Gorges D ; Schwarz P ; Haak T (2009). Prevention of diabetes self-management program (PREDIAS): effects on weight, metabolic risk factors, and behavioral outcomes. Diabetes Care 32: 1143-6.**

12 months	mean=-4.6 sd=19.1 n=61*	mean=-1.0 sd=16.7 n=61*

*inferred by reviewer from number randomised assuming equal distribution across groups and reported intention to treat analysis

Change in total cholesterol from baseline - mmol/l (converted from mg/DL by reviewer)

Timepoint	Lifestyle	Control
12 months	mean=-0.27 sd=0.93 n=61*	mean=-0.05 sd=0.91 n=61*

*inferred by reviewer from number randomised assuming equal distribution across groups and reported intention to treat analysis

Uptake / adherence
Uptake: Not reported
Adherence: Not reported
Dropouts (indirect measure of adherence): Not reported separately for each group

Source of funding	Supported by an unrestricted grant from Roche Diagnostics, Germany.
Comments	Selection bias: Unclear. Allocation was randomised, but method of random sequence generation and allocation concealment not specified Performance bias: Detection bias: Attrition bias: Reporting bias: Low. Expected outcomes reported. Other bias: Low.

Domain	Support for judgement	Review authors' judgment
Selection bias		

Bibliographic reference	**Kulzer B ; Hermanns N ; Gorges D ; Schwarz P ; Haak T (2009). Prevention of diabetes self-management program (PREDIAS): effects on weight, metabolic risk factors, and behavioral outcomes. Diabetes Care 32: 1143-6.**		
	Random sequence generation	Allocation was randomised, but method of random sequence generation not specified.	Unclear risk
	Allocation concealment	Allocation was randomised, but allocation concealment not specified.	Unclear risk
	Performance bias		
	Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
	Detection bias		
	Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
	Attrition bias		
	Incomplete outcome data	Analysis described as intention to treat. Analysis of completers only vs all participants showed similar results.	Low risk
	Reporting bias		
	Selective reporting	Expected outcome reported	Low risk
	Other bias		
	Other sources of bias	None	Low risk

1

1 **Table 11: Ma 2013**

Bibliographic reference	**Ma J ; Yank V ; Xiao L ; Lavori PW ; Wilson SR , et al. (2013) Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Internal Medicine 173: 113-21.**
Study type	Randomised controlled trial
Aim	To evaluate the effectiveness of 2 adapted DPP lifestyle interventions among overweight or obese adults with pre-DM, metabolic syndrome, or both: (1) a coach-led, face-to-face group intervention and (2) a self-directed DVD intervention.
Patient characteristics	**Inclusion criteria** - Age ≥18 years - BMI ≥25 - Presence of pre-DM (defined as impaired FPG level of 100-125 mg/dL) or metabolic syndrome (defined by joint 2005 criteria of AHA and National Heart, Lung and Blood Institute) **Exclusion criteria** - Serious medical or psychiatric condition (e.g. stroke, psychotic disorder) - Special life circumstances (e.g. pregnancy; planned move) **Recruitment** PCPs reviewed lists and approved potentially eligible patients deemed appropriate for contact. Approved patients were contacted for screening. 2 stage screening process: (i) Online self-directed screening / telephone screening to assess logistical constraints, known exclusionary medical conditions or treatments, and willingness to consider participation and undergo further screening. (ii) Medical screening (e.g., BMI measurements, laboratory testing) to confirm clinical eligibility (overweight/obesity and pre-diabetes or metabolic syndrome). Eligible patients were then invited for baseline evaluation & consent; those who met all eligibility criteria were randomized. **Baseline characteristics**

	Coach-led lifestyle (n=79)	**Usual care (n=81)**
Age (years,sd)	54.6 (11.0)	52.5 (10.9)

Bibliographic reference	**Ma J ; Yank V ; Xiao L ; Lavori PW ; Wilson SR , et al. (2013) Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Internal Medicine 173: 113-21.**

Sex (m/f)	41/38	44/37
Baseline body mass index (kg/m3, sd)	31.8 (5.1)	32.4 (6.3)
Baseline fasting plasma glucose (mmol/l)	5.58 (0.54)	5.51 (0.50)
Baseline HbA1c (%)	NR	NR
History of gestational diabetes	NR	NR
Ethnicity (%) - Non-Hispanic White - Asian / Pacific Islander - Latino/Hispanic	 77.2 16.5 5.1	 77.8 17.3 4.9

Number of Patients

	Coach-led lifestyle	**Usual care**
Randomised	79	81
Dropouts	Not reported	Not reported

Intervention

Coach-led group lifestyle intervention (n=79)

Intensive phase (months 1-3):

- 12 weekly group sessions (8-16 participants) of 90-120 mins duration, including 30-45 mins of guided physical activity
- Focused on weight loss; developing goals / action plans, sharing progress and discussing barriers
- Delivered by registered dietician and fitness instructor

Maintenance phase (months 4-15):

- Individual secure email (or phone) contacts every 2-4 weeks
- Personalised progress feedback and lifestyle coaching on weight and activity self-monitoring records; behaviour change maintenance, problem solving, and relapse prevention

Self-directed lifestyle intervention using DVD

<table>
<tr><td>Bibliographic reference</td><td>Ma J ; Yank V ; Xiao L ; Lavori PW ; Wilson SR , et al. (2013) Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Internal Medicine 173: 113-21.</td></tr>
<tr><td></td><td>Data not extracted for this study arm</td></tr>
<tr><td>Comparison</td><td>Usual care (n=81)
Standard medical care (no information about weight loss or weight-loss goals was provided by the study to usual care participants)</td></tr>
<tr><td>Length of follow up</td><td>15 months</td></tr>
<tr><td>Location</td><td>USA (single centre)</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: Intention to treat. All data for the 3 treatment groups are covariate-adjusted, mixed-model-based estimates for the ITT population. Unadjusted raw data not reported.

Progression to type 2 diabetes
<table>
<tr><th>Timepoint</th><th>Coach-led lifestyle</th><th>Usual care</th></tr>
<tr><td>15 months</td><td>1/79</td><td>1/81</td></tr>
</table>
Change in weight from baseline (kg)
<table>
<tr><th>Timepoint</th><th>Coach-led lifestyle</th><th>Usual care</th></tr>
<tr><td>15 months</td><td>mean=-6.3
se=0.9
sd=8.0**
n=79</td><td>mean=-2.4
se=0.9
sd=8.1**
n=81</td></tr>
</table>
**calculated by reviewer

Change in HbA1c from baseline (%)
Not reported.

Change in fasting plasma glucose from baseline (mmol/l)
<table>
<tr><th>Timepoint</th><th>Coach-led lifestyle</th><th>Usual care</th></tr>
<tr><td>15 months</td><td>mean=-0.23
se=0.09</td><td>mean=+0.01
se=0.09</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Ma J ; Yank V ; Xiao L ; Lavori PW ; Wilson SR , et al. (2013) Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Internal Medicine 173: 113-21.

	sd=0.75** n=69*	sd=0.75** n=70*

***inferred by reviewer (total n reported, assumed equal distribution across groups)**
****calculated by reviewer**

Adverse events / side effects (limited to GI intolerance)
No GI intolerance reported.

Change in systolic blood pressure from baseline (mmHg)

Timepoint	Coach-led lifestyle	Usual care
15 months -	mean=-1.2 se=1.5 sd=13.3** n=79*	mean=0.1 se=1.6 sd=14.2** n=79*

***inferred by reviewer (total n reported, assumed equal distribution across groups)**
****calculated by reviewer**

Change in total cholesterol from baseline (mmol/l) Converted from mg/dL by reviewer

Timepoint	Coach-led lifestyle	Usual care
15 months (n=218)	mean=0.101 se=0.145 sd=1.23** n=72*	mean=0.274 se=0.142 sd=1.21** n=73*

***inferred by reviewer (total n reported, assumed equal distribution across groups)**

Uptake / adherence
Uptake: Not reported.
Adherence: Not reported
Dropouts (indirect measure of adherence): Not reported

Bibliographic reference	**Ma J ; Yank V ; Xiao L ; Lavori PW ; Wilson SR , et al. (2013) Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Internal Medicine 173: 113-21.**
Source of funding	The E-LITE study was supported by grant R34DK080878 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a Scientist Development Grant award (0830362N) from the AHA, and internal funding from the Palo Alto Medical Foundation Research Institute. One author received support from the Clinical and Translational Science Award 1UL1 RR025744 for the Stanford Center for Clinical and Translational Education and Research (Spectrum) from the National Center for Research Resources.
Comments	

Domain	Support for judgement	Review authors' judgment
Selection bias		
Random sequence generation	Allocation was randomised, but method of random sequence generation not specified. (reported to be stratified by centre, sex and 2h plasma glucose value).	Unclear risk
Allocation concealment	Allocation was randomised, but allocation concealment not specified.	Unclear risk
Performance bias		
Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding. Participants and intervention personnel were not blinded.	Low risk
Detection bias		
Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment. Outcome assessment was however, blinded.	Low risk
Attrition bias		
Incomplete outcome data	Analysis was intention to treat, though number of dropouts, balance across groups and details	Unclear risk

Bibliographic reference	**Ma J ; Yank V ; Xiao L ; Lavori PW ; Wilson SR , et al. (2013) Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial. JAMA Internal Medicine 173: 113-21.**

	of imputation of missing data not reported.	
Reporting bias		
Selective reporting	Expected outcomes reported	Low risk
Other bias		
Other sources of bias	None	Low risk

1

2 **Table 12: Mensink 2003**

Bibliographic reference	**Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, and Feskens EJ (2003) Lifestyle intervention according to general recommendations improves glucose tolerance.. Obesity research 11(12), 1588-96** **Mensink M, Corpeleijn E, Feskens EJ, Kruijshoop M, Saris WH, de Bruin TW et al. (2003b) Study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Research and Clinical Practice 2003; 61: 49–58.** **Roumen C ; Corpeleijn E ; Feskens EJ ; Mensink M ; Saris WH ; Blaak EE (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine 25: 597-605.**
Study type	Randomised controlled trial
Aim	To investigate the impact of a 3-year combined dietary and physical activity intervention on glucose tolerance in IGT patients at increased risk for developing diabetes.
Patient characteristics	**Inclusion criteria** - Aged 40-70 years, with family history of diabetes or BMI ≥25m^2 - Caucasian - Mean of two 2-hr oral glucose tolerance tests between 7.8 and 12.5 mM, plus fasting glucose tolerance ≤7.8 mM **Exclusion criteria** - Previously diagnosed diabetes (other than gestational diabetes) - Medication known to interfere with glucose tolerance - Participation in regular vigorous exercise or intensive weight reduction programme in past 12 months

<table>
<tr><td>Bibliographic reference</td><td>Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, and Feskens EJ (2003) Lifestyle intervention according to general recommendations improves glucose tolerance.. Obesity research 11(12), 1588-96

Mensink M, Corpeleijn E, Feskens EJ, Kruijshoop M, Saris WH, de Bruin TW et al. (2003b) Study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Research and Clinical Practice 2003; 61: 49–58.

Roumen C ; Corpeleijn E ; Feskens EJ ; Mensink M ; Saris WH ; Blaak EE (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine 25: 597-605.</td></tr>
<tr><td></td><td>- Presence of any (chronic) disease hampering participation in lifestyle intervention
- Improbability of 5-year survival

Recruitment
Participants with high risk of glucose intolerance were selected from a known cohort and invited to undergo a glucose tolerance test to assess eligibility.

Baseline characteristics*
<table>
<tr><th></th><th>Lifestyle
(n=55)</th><th>Control
(n=59)</th></tr>
<tr><td>Age (years, SE)</td><td>55.6 (0.9)</td><td>57.8 (1.0)</td></tr>
<tr><td>Sex (m/f)*</td><td>30/25</td><td>34/25</td></tr>
<tr><td>Baseline body mass index (kg/m3, sd)</td><td>29.8 (0.5)</td><td>29.3 (0.4)</td></tr>
<tr><td>Baseline fasting plasma glucose (mmol/l)</td><td>5.9 (0.1)</td><td>5.8 (0.1)</td></tr>
<tr><td>Baseline HbA1c (%)</td><td>5.9 (0.1)</td><td>5.9 (0.1)</td></tr>
<tr><td>History of gestational diabetes</td><td>NR</td><td>NR</td></tr>
<tr><td>Ethnicity (n, %)
- Caucasian</td><td>
55 (100)</td><td>
59 (100)</td></tr>
</table>
*baseline characteristics as reported in Mensink 2003a. Data are mean ±SE</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Intensive lifestyle</th><th>Usual care</th></tr>
<tr><td>Randomised</td><td>55</td><td>59</td></tr>
<tr><td>Dropouts</td><td>14</td><td>8</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, and Feskens EJ (2003) Lifestyle intervention according to general recommendations improves glucose tolerance.. Obesity research 11(12), 1588-96

Mensink M, Corpeleijn E, Feskens EJ, Kruijshoop M, Saris WH, de Bruin TW et al. (2003b) Study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Research and Clinical Practice 2003; 61: 49–58.

Roumen C ; Corpeleijn E ; Feskens EJ ; Mensink M ; Saris WH ; Blaak EE (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine 25: 597-605.</td></tr>
<tr><td>Intervention</td><td>- Intervention was for the duration of the study (3 years)
- 14 sessions were scheduled (mixture of group and individual)
- First visit was 4 to 6 weeks after randomisation and then every 3 months.
- Dietary advice given by a dietician individually after considering a 3 day food record
- Weight loss target of 5-7% of bodyweight
- Mild energy restriction diet was prescribed if participants did not lose weight in first year.
- Participants encouraged to increase level of physical activity to at least 30 minutes per day for at least 5 days per week. Individual advice given on how to increase physical activity and individual goals were set.
- Encouraged to participate in 1hr weekly physical activity sessions that were provided free as part of the study.</td></tr>
<tr><td>Comparison</td><td>- Oral and written information provided about the beneficial effects of a healthy diet, weight loss and increased physical activity
- No individual advice</td></tr>
<tr><td>Length of follow up</td><td>2 years (reported in Mensink 2003a and 2003b)
3 years (reported in Roumen 2008)</td></tr>
<tr><td>Location</td><td>The Netherlands</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: Note: all the following data are from the ITT analysis reported in Roumen 2008 ; n=106 (n=52 Lifestyle; n=54 Control) unless otherwise stated

Progression to type 2 diabetes* – cumulative n/N, (%)
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Control</th></tr>
<tr><td>3 years
- Completers only
- ITT analysis</td><td>
8/44 (18%)
11/61 (18%)</td><td>
18/47 (38%)
19/60 (32%)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, and Feskens EJ (2003) Lifestyle intervention according to general recommendations improves glucose tolerance.. Obesity research 11(12), 1588-96** **Mensink M, Corpeleijn E, Feskens EJ, Kruijshoop M, Saris WH, de Bruin TW et al. (2003b) Study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Research and Clinical Practice 2003; 61: 49–58.** **Roumen C ; Corpeleijn E ; Feskens EJ ; Mensink M ; Saris WH ; Blaak EE (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine 25: 597-605.**

*reported in Roumen 2008

Change in weight from baseline – kg

Timepoint	Lifestyle	Usual care
1 year	mean=-2.77 sd=3.69 n=52	mean=-0.62 sd=3.92 n=54
2 years	mean=-1.76 sd=4.34 n=52	mean=-0.11 sd=3.26 n=54
3 years	mean=-1.08 sd=4.30 n=52	mean=+0.16 sd=4.91 n=54

Change in HbA1c from baseline %

Timepoint	Lifestyle	Usual care
1 year	mean=-0.24 sd=0.39 n=52	mean=-0.19 sd=0.32 n=54
2 years	mean=-0.09 sd= 0.62 n=52	mean=-0.11 sd= 0.38 n=54
3 years	mean=-0.09	mean=-0.10

Bibliographic reference	**Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, and Feskens EJ (2003) Lifestyle intervention according to general recommendations improves glucose tolerance.. Obesity research 11(12), 1588-96** **Mensink M, Corpeleijn E, Feskens EJ, Kruijshoop M, Saris WH, de Bruin TW et al. (2003b) Study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Research and Clinical Practice 2003; 61: 49–58.** **Roumen C ; Corpeleijn E ; Feskens EJ ; Mensink M ; Saris WH ; Blaak EE (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine 25: 597-605.**

	sd=0.43 n=52	sd=0.38 n=54

Change in fasting plasma glucose from baseline (mmol/l)

Timepoint	Lifestyle	Usual care
1 year	mean=--0.11 sd= 0.54 n=52	mean=-+0.02 sd= 0.63 n=54
2 years	mean=-+0.05 sd= 0.66 n=52*	mean=-+0.40 sd= 0.84 n=54
3 years	mean=-+0.32 sd= 0.83 n=52	mean=-+0.55 sd= 0.82 n=54

Adverse events / side effects

Not reported.

Change in systolic blood pressure from baseline – mmHg

Timepoint	Lifestyle	Usual care
1 year	mean=-4.7 sd= 15.4 n=52	mean=-4.2 sd= 13.6 n=54
2 years	mean=-5.7	mean=-5.9

Bibliographic reference	**Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, and Feskens EJ (2003) Lifestyle intervention according to general recommendations improves glucose tolerance.. Obesity research 11(12), 1588-96** **Mensink M, Corpeleijn E, Feskens EJ, Kruijshoop M, Saris WH, de Bruin TW et al. (2003b) Study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Research and Clinical Practice 2003; 61: 49–58.** **Roumen C ; Corpeleijn E ; Feskens EJ ; Mensink M ; Saris WH ; Blaak EE (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine 25: 597-605.**

	sd= 14.1 n=52	sd= 16.9 n=54
3 years	mean=-3.6 sd=15.8 n=52	mean=-3.5 sd= 15.6 n=54

Change in total cholesterol from baseline - mmol/l (SD)

Timepoint	Lifestyle	Usual care
1 year	mean=-0.00 sd= 0.69 n=52	mean=+0.10 sd= 0.57 n=54
2 years	mean=+0.22 sd= 0.81 n=52	mean=+0.32 sd= 0.75 n=54
3 years	mean=+0.41 sd= 0.86 n=52	mean=+0.26 sd= 0.94 n=54

Uptake/Adherence

Update: not reported

Adherence: 10/52 (19.2%). Adherence was defined as reaching two or three of the following three dietary goals: total fat intake < 35 energy%, saturated fatty acid intake < 10 energy%, and fiber intake more than 3 g/MJ and participation for at least 1 h/wk in the supervised exercise sessions during the 2 years of intervention.

Dropouts (indirect measure of adherence): 14/55 (25.5%)

Bibliographic reference	**Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, and Feskens EJ (2003) Lifestyle intervention according to general recommendations improves glucose tolerance.. Obesity research 11(12), 1588-96** **Mensink M, Corpeleijn E, Feskens EJ, Kruijshoop M, Saris WH, de Bruin TW et al. (2003b) Study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Research and Clinical Practice 2003; 61: 49–58.** **Roumen C ; Corpeleijn E ; Feskens EJ ; Mensink M ; Saris WH ; Blaak EE (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine 25: 597-605.**
Source of funding	Supported by grants from the Dutch Diabetes Research Foundation (DFN 98.901 and 2000.00.020), the Netherlands Organisation for Health Research and Development (ZonMW 940-35-034), and the Netherlands Organisation for Scientific Research (NOW 2200.0139)
Comments	

Domain	**Support for judgement**	**Review authors' judgment**
Selection bias		
Random sequence generation	Eligible subjects were randomly assigned of the staff members not involved in the intervention, with the use of a randomization list. Randomization was carried out with stratification for sex and mean 2-hour plasma glucose concentration.	Low risk
Allocation concealment	Allocation was by means of a randomisation list, so presumably unconcealed.	High risk
Performance bias		
Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
Detection bias		
Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk

Bibliographic reference	**Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, and Feskens EJ (2003) Lifestyle intervention according to general recommendations improves glucose tolerance.. Obesity research 11(12), 1588-96** **Mensink M, Corpeleijn E, Feskens EJ, Kruijshoop M, Saris WH, de Bruin TW et al. (2003b) Study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Research and Clinical Practice 2003; 61: 49–58.** **Roumen C ; Corpeleijn E ; Feskens EJ ; Mensink M ; Saris WH ; Blaak EE (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine 25: 597-605.**

Attrition bias		
Incomplete outcome data	Analysis based on intention to treatment principle, though how dropouts were dealt with is not described and dropouts were higher in the intervention group.	Unclear risk
Reporting bias		
Selective reporting	Expected outcomes reported	Low risk
Other bias		
Other sources of bias	None	Low risk

1

2

3 **Table 13: Nilsen 2011**

Bibliographic reference	**Nilsen V ; Bakke PS ; Gallefoss F (2011) Effects of lifestyle intervention in persons at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 11: 893**
Study type	Randomised controlled trial
Aim	
Patient characteristics	**Inclusion criteria** - Aged 18-64 years - Finnish Diabetes Risk Score (FINDRISC) ≥9

Bibliographic reference	**Nilsen V ; Bakke PS ; Gallefoss F (2011) Effects of lifestyle intervention in persons at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 11: 893**

Exclusion criteria

- Diagnosis of diabetes mellitus
- Presence of serious heart, lung, kidney or liver failure
- Serious psychiatric illness
- Substance abuse

Recruitment

General practitioners were asked to refer patients with a FINDRISC score of >9 to the hospital for possible participation in the study.

Baseline characteristics

	Individual + interdisciplinary group (n=109)	**Individual + usual care (n=104)**
Age (years, sd)	47.0 (11)	45.9 (11)
Sex (m/f)	51/58	55/49
Baseline body mass index (kg/m3, sd)*	37.6 (6)	35.9 (6)
	(n=93)**	**(n=89)****
Baseline fasting plasma glucose (mmol/l)	5.6 (0.8)	5.5 (0.8)
Baseline HbA1c (%)	5.6 (0.4)	5.6 (0.4)
History of gestational diabetes	NR	NR
Ethnicity (n, %)	NR	NR

*Significant difference in BMI

** Baseline values for following clinical and metabolic variables are only available for study completers at 18 months

Number of Patients		**Intensive lifestyle**	**Usual care**
	Randomised	109	104

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Nilsen V ; Bakke PS ; Gallefoss F (2011) Effects of lifestyle intervention in persons at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 11: 893</td></tr>
<tr><td></td><td>Dropouts</td><td>17</td><td>15</td></tr>
<tr><td>Intervention</td><td colspan="3">Low-intensity individual physician-delivered lifestyle counselling + interdisciplinary group (IIG)
In addition to the 3 visits to the study physician at 6, 12 and 18months post-randomisation (see description of comparator below), patients assigned to this group also participated in a group-based programme (≤10 participants) one day (5 hrs per day) each week for 6 weeks, plus an additional meeting after 12 weeks.

The topics for these group sessions were research findings and factual information about nutrition and physical activity, habit change, action plans, risk situations, coping strategies, etc. The group intervention also included a variety of physical training. The IIG programme was interdisciplinary (dietician, physiotherapist, ergonomist, nurse and physician). Motivational interviewing techniques were utilised. An individual 30-minute consultation with a nurse or ergonomist completed the intervention one month after the last group meeting.</td></tr>
<tr><td>Comparison</td><td colspan="3">Low-intensity individual physician-delivered lifestyle counselling + usual care (IG)
Patients consulted study physician three times following randomisation (at 6 months, 12 months and 18 months), otherwise receiving usual care from their GP. During the 3 visits, the study physician used elements of motivational interviewing, with emphasis on diet and exercise.</td></tr>
<tr><td>Length of follow up</td><td colspan="3">18 months</td></tr>
<tr><td>Location</td><td colspan="3">Norway</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Analysis: Outcome data reported for study completers only. No change scores and SDs reported so raw data for baseline and follow-up timepoints were extracted.

Progression to type 2 diabetes
Not reported.

Weight (kg)
<table>
<tr><th>Timepoint</th><th>Individual + interdisciplinary group (IIG)</th><th>Individual + usual care (IG) n=89</th></tr>
<tr><td>Baseline</td><td>mean=110.5
sd=22
n=93</td><td>mean=111.7
sd=22
n=89</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Nilsen V ; Bakke PS ; Gallefoss F (2011) Effects of lifestyle intervention in persons at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 11: 893

18 months	mean=108.0 sd=20 n=93	mean=108.7 sd=23 n=89

HbA1c (%)

Timepoint	Individual + interdisciplinary group (IIG)	Individual + usual care (IG)
Baseline	mean=5.6 sd=0.4 n=93	mean=5.6 sd=0.4 n=89
18 months	mean=5.6 sd=0.5 n=93	mean=5.6 sd=0.5 n=89

Fasting plasma glucose (mmol/l)

Timepoint	Individual + interdisciplinary group (IIG)	Individual + usual care (IG)
Baseline	mean=5.6 sd=0.8 n=93	mean=5.5 sd=0.8 n=89
18 months	mean=5.8 sd=1.2 n=93	mean=5.6 sd=0.7 n=89

Adverse events / side effects

Not reported.

Systolic blood pressure (mmHg)

<table>
<tr><td>Bibliographic reference</td><td>Nilsen V ; Bakke PS ; Gallefoss F (2011) Effects of lifestyle intervention in persons at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 11: 893</td></tr>
<tr><td></td><td>
<table>
<tr><th>Timepoint</th><th>Individual + interdisciplinary group (IIG)</th><th>Individual + usual care (IG) (n=89)</th></tr>
<tr><td>Baseline</td><td>mean=144
sd=20
n=93</td><td>mean=144
sd=18
n=89</td></tr>
<tr><td>18 months</td><td>mean=143
sd=19
n=93</td><td>mean=147
sd=19
n=89</td></tr>
</table>
Total cholesterol (mmol/l)
<table>
<tr><th>Timepoint</th><th>Individual + interdisciplinary group (IIG) (n=93)</th><th>Individual + usual care (IG) (n=89)</th></tr>
<tr><td>Baseline</td><td>mean=5.4
sd=1.1
n=93</td><td>mean=5.5
sd=1.1
n=89</td></tr>
<tr><td>18 months</td><td>mean=5.2
sd=1.1
n=93</td><td>mean=5.3
sd=1.0
n=89</td></tr>
</table>
Uptake/Adherence:
Update: Not reported
Adherence: Not reported
Dropout rate (indirect measure of adherence):17/109 (15.6%)
</td></tr>
<tr><td>Source of funding</td><td>Sørlandet kompetansefond, The Competence Development of Southern Norway and Department of Science, Sorlandet Hospital HF.</td></tr>
<tr><td>Comments</td><td>
<table>
<tr><th>Domain</th><th>Support for judgement</th><th>Review authors' judgment</th></tr>
<tr><td colspan="3">Selection bias</td></tr>
<tr><td>Random sequence generation</td><td>Random sequence generation not described.</td><td>Unclear risk</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Nilsen V ; Bakke PS ; Gallefoss F (2011) Effects of lifestyle intervention in persons at risk for type 2 diabetes mellitus - results from a randomised, controlled trial. BMC Public Health 11: 893		
	Allocation concealment	Allocation concealment incompletely described: 'They were randomly assigned…by use of closed envelope method with unknown block sizes'	Unclear risk
	Performance bias		
	Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
	Detection bias		
	Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
	Attrition bias		
	Incomplete outcome data	Analysis based on completers only. Report that 'dropouts differed from participants who completed testing by being younger and having poorer lifestyle parameters'	High risk
	Reporting bias		
	Selective reporting	Expected outcomes reported	Low risk
	Other bias		
	Other sources of bias	None	Low risk

1 **Table 14: Oldroyd 2006**

Bibliographic reference	Oldroyd JC, Unwin NC, White M, Mathers JC, and Alberti KG (2006) Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance.. Diabetes research and clinical practice 72(2), 117-27
Study type	Randomised controlled trial
Aim	To evaluate the effectiveness of lifestyle interventions in people with impaired glucose tolerance.

<table>
<tr><td>Bibliographic reference</td><td>Oldroyd JC, Unwin NC, White M, Mathers JC, and Alberti KG (2006) Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance.. Diabetes research and clinical practice 72(2), 117-27</td></tr>
<tr><td>Patient characteristics</td><td>
Inclusion criteria
- European origin
- Aged 24 to 75 years
- Impaired glucose tolerance on two consecutive tests, 2-12 weeks apart
Exclusion criteria
- Pregnant
- Already on therapeutic diet
- Unable to undertake moderate physical activity

Recruitment
Method of participant identification not reported.

Baseline characteristics
<table>
<tr><th></th><th>Lifestyle</th><th>Control</th></tr>
<tr><td>Age (years, range)</td><td>58.2 (range 41 to 75)</td><td>57.5 (41 to 73)</td></tr>
<tr><td>Sex (m/f)</td><td>17/20</td><td>22/10</td></tr>
<tr><td>Baseline body mass index (kg/m3, sd)*</td><td>NR</td><td>NR</td></tr>
<tr><td>Baseline fasting plasma glucose (mmol/l, sd)</td><td>6.05 (0.89)</td><td>6.16 (0.89)</td></tr>
<tr><td>Baseline HbA1c (%, sd)</td><td>NR</td><td>NR</td></tr>
<tr><td>History of gestational diabetes</td><td>NR</td><td>NR</td></tr>
<tr><td>Ethnicity (n, %)</td><td>All of European origin</td><td>All of European origin</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Intensive lifestyle</th><th>Usual care</th></tr>
<tr><td>Randomised</td><td>39</td><td>39</td></tr>
<tr><td>Dropouts</td><td>5</td><td>9</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>- 12 individual 15-30 minute review appointments over 24 months.</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Oldroyd JC, Unwin NC, White M, Mathers JC, and Alberti KG (2006) Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance.. Diabetes research and clinical practice 72(2), 117-27</td></tr>
<tr><td></td><td>- Motivational counselling from a National Health Service dietitian and physiotherapist based on the ‘stages of change’ model of behaviour change.
- Individual action plan for behaviour change with goal setting and written and oral information.
- Physiotherapist assessed level of physical activity and willingness to change and formed individual graded physical activity plan.
- Access to scheme offering 80% discount on use of public leisure facilities was offered.</td></tr>
<tr><td>Comparison</td><td>No dietary or physical activity advice was offered during the study.</td></tr>
<tr><td>Length of follow up</td><td>24 months</td></tr>
<tr><td>Location</td><td>UK</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: Described as intention to treat (further details of how dropouts account for are not provided).

Progression to type 2 diabetes
Not reported.

Change in Weight from baseline (kg)
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Control</th></tr>
<tr><td>12 months</td><td>mean=-1.1
sd=3.4
n=32</td><td>mean=1.5
sd=2.6
n=30</td></tr>
<tr><td>24 months</td><td>mean=-1.8
sd=5.9
n=30</td><td>mean=1.5
sd=2.6
n=24</td></tr>
</table>
Change in HbA1c (%)
Not reported

Change in Fasting plasma glucose from baseline (mmol/l)
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Control</th></tr>
</table></td></tr>
</table>

Bibliographic reference	**Oldroyd JC, Unwin NC, White M, Mathers JC, and Alberti KG (2006) Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance.. Diabetes research and clinical practice 72(2), 117-27**

12 months	mean=0.03 sd=0.60 n=32	mean=0.08 sd=0.97 n=30
24 months	mean=0.25 sd=0.77 n=30	mean=0.12 sd=1.0 n=24

Adverse events / side effects
Not reported.

Systolic blood pressure from baseline (mmHg)
Not reported

Change in total cholesterol from baseline (mmol/l)

Timepoint	Lifestyle	Control
12 months	mean=-0.12 sd=0.62 n=31	mean=-0.12 sd=0.62 n=29
24 months	mean=0.04 sd=0.79 n=29	mean=-0.06 sd=0.59 n=24

Uptake/Adherence:
Uptake: Not reported
Adherence: 12/39 participants (36%) attended all appointments for the lifestyle intervention.
Dropout rate (indirect measure of adherence):5/39 (12.8%)

Source of funding	The British Heart Foundation, Northern & Yorkshire NHS Research and Development and the Royal College of General Practitioners.

Comments	**Domain**	**Support for judgement**	**Review authors' judgment**

Bibliographic reference	Oldroyd JC, Unwin NC, White M, Mathers JC, and Alberti KG (2006) Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance.. Diabetes research and clinical practice 72(2), 117-27		
	Selection bias		
	Random sequence generation	Random sequence generation not described.	Unclear risk
	Allocation concealment	'Researchers performing the randomisation were blind to the group allocation.'	Low risk
	Performance bias		
	Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
	Detection bias		
	Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
	Attrition bias		
	Incomplete outcome data	Analysis described a 'intention to treat', though further details of how droupouts were dealt with was not provided.	Unclear risk
	Reporting bias		
	Selective reporting	Expected outcomes reported	Low risk
	Other bias		
	Other sources of bias	None	Low risk

1

2 **Table 15: Ramachandran 2006**

Bibliographic reference	**Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar A D, Vijay V, Indian Diabetes Prevention, and Programme (2006) 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 49(2), 289-97**
Study type	Randomised controlled trial
Aim	To determine the effectiveness of lifestyle modification and metformin, alone and in combination in a south Asian population. The study included 3 intervention groups: lifestyle modification, metformin and lifestyle modification plus metformin. However, the lifestyle modification programme did not meet the criteria in the review protocol (did not meet 9/12 NICE criteria specified in original NICE guidance) and so data for these groups were not extracted.
Patient characteristics	**Inclusion criteria** - Impaired glucose tolerance according to world health organisation criteria (fasting plasma glucose <7mmol/l and 2h glucose 7.8-11 mmol/l). Initial testing was done using a glucometer and eligibility was confirmed using venous plasma glucose within a week. - Aged 33-55 years **Exclusion criteria** - Diabetes - Major illness **Recruitment** Recruited from the middle-class population working in service organisations and their families. Identified by work-place announcements and circulars. **Baseline characteristics**

	Control	Metformin
Age (years,sd)	NR (age range 35-55)	NR (age range 35-55)
Sex (m/f)	104/32	107/26
Baseline body mass index (kg/m3, sd)	26.3 (3.7)	25.6 (3.7)
Baseline fasting plasma glucose (mmol/l)*	5.5 (0.8)	5.4 (0.8)
Baseline HbA1c (%)	6.2 (0.5)	6.2 (0.6)

<table>
<tr><td>Bibliographic reference</td><td colspan="3">Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar A D, Vijay V, Indian Diabetes Prevention, and Programme (2006) 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 49(2), 289-97</td></tr>
<tr><td></td><td colspan="3"><table>
<tr><td>History of gestational diabetes</td><td>NR</td><td>NR</td></tr>
<tr><td>Ethnicity</td><td>NR (however reported aim was to investigate prevention of type 2 diabetes in Asian Indians)</td><td>NR (however reported aim was to investigate prevention of type 2 diabetes in Asian Indians)</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td colspan="3"><table>
<tr><th></th><th>Metformin</th><th>Control</th></tr>
<tr><td>Randomised</td><td>133</td><td>136</td></tr>
<tr><td>Dropouts</td><td>5</td><td>3</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td colspan="3">Metformin. Subjects received metformin tablets and were given diaries to record their daily consumption of tablets, particularly whether any doses were missed. Three month’s supply was provided, and leftover tablets were counted to assess the compliance. The initial dose of 250 mg twice daily was increased to 500 mg twice daily in the first 50 patients after 2 weeks (26 patients in the metformin only group, reported here).</td></tr>
<tr><td>Comparison</td><td colspan="3">Standard healthcare advice (no placebo given)</td></tr>
<tr><td>Length of follow up</td><td colspan="3">3 years</td></tr>
<tr><td>Location</td><td colspan="3">India</td></tr>
<tr><td>Outcomes measures and effect size</td><td colspan="3">Analysis: Assumed analysis is based on intention to treat principle: adherent and non-adherent participants included in analysis. Not clear how dropouts were accounted for, but follow up rate was high (>95%) in both groups, so unlikely to have a large impact.

Progression to type 2 diabetes<table>
<tr><th>Timepoint</th><th>Control</th><th>Metformin</th></tr>
<tr><td>3 years</td><td>55.0% (46.0 to 63.5%)
73/133</td><td>40.5% (32.0 to 49.7%)
52/128</td></tr>
</table>
Change in waist circumference
Not extracted (no confidence intervals reported or calculable, so data not usable in analysis)

Change in weight (kg relative to baseline, 95% CI)</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar A D, Vijay V, Indian Diabetes Prevention, and Programme (2006) 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 49(2), 289-97</td></tr>
<tr><td></td><td>Not extracted (no confidence intervals reported or calculable, so data not usable in analysis)

Change in HbA1c levels from baseline
Not reported

Change in Fasting plasma glucose from baseline (mmol/l relative to baseline, 95%CI)
Not reported

Adverse events and side effects (limited GI intolerance)
Not extracted (reported for metformin group only, no data available for control group so not usable in analysis)

Change in Systolic blood pressure from baseline (mmHg relative to baseline, 95%CI)
Not reported

Total cholesterol from baseline
Not reported

Uptake/Adherence:
Uptake: Not reported
Adherence: Metformin: 90.9% of participants took >=50% of the prescribed medication.
Dropout rate (indirect measure of adherence): Metformin: 5/133 (3.8%)</td></tr>
<tr><td>Source of funding</td><td>M/S US Vitamins</td></tr>
<tr><td>Comments</td><td>
<table>
<tr><th>Domain</th><th>Support for judgement</th><th>Review authors' judgment</th></tr>
<tr><td colspan="3">Selection bias</td></tr>
<tr><td>Random sequence generation</td><td>Randomisation was described as 'consecutive'</td><td>High risk</td></tr>
<tr><td>Allocation concealment</td><td>Allocation concealment not described.</td><td>Unclear risk</td></tr>
<tr><td colspan="3">Performance bias</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar A D, Vijay V, Indian Diabetes Prevention, and Programme (2006) 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 49(2), 289-97**		
	Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
	Detection bias		
	Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
	Attrition bias		
	Incomplete outcome data	High follow up rate in both groups and analysis reported to be based on intention to treat principle.	Low risk
	Reporting bias		
	Selective reporting	Only progression to diabetes reported in sufficient detail for incorporation in the analysis.	High risk
	Other bias		
	Other sources of bias	None	Low risk

1 **Table 16: Ramachandran 2013**

Bibliographic reference	**Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, Shetty As, Godsland If, Chaturvedi N, Majeed A, Oliver N, Toumazou C, Alberti Kg, and Johnston Dg (2013) 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 1(3), 191-8**
Study type	Randomised controlled trial
Aim	To assess whether mobile phone messaging that encouraged lifestyle change could reduce incident type 2 diabetes in Indian Asian men with impaired glucose tolerance.
Patient characteristics	**Inclusion criteria**

Bibliographic reference	**Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, Shetty As, Godsland If, Chaturvedi N, Majeed A, Oliver N, Toumazou C, Alberti Kg, and Johnston Dg (2013) 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 1(3), 191-8**

- No diabetes (self-reported)or major illness, such as cancer, chronic liver or kidney disease
- Impaired glucose tolerance (defined as blood glucose of above 8.9 mmol/l 2h after 75g oral glucose) confirmed by second test within 1 week.
- no disorders with cognitive impairment, severe depression or mental imbalance
- no physical disability that would prevent regular physical activity
- no recruitment in another trial
- age 35–55 years
- ownership of a mobile phone and ability to read and understand mobile phone messages in English
- a positive family history of type 2 diabetes
- a BMI of 23 kg/m² or more

Exclusion criteria

None specified

Recruitment

Working Indian men were screened for eligibility by questionnaire. The men were employed in 10 public-sector and private-sector industrial units in southeast India.

Baseline characteristics

	Control	Text messaging lifestyle
Age (years,sd)	46.1 (4.6)	45.9 (4.8)
Sex (m/f)	266/0	271/0
Baseline body mass index (kg/m3, sd)	25.8 (3.0)	25.8 (3.3)
Baseline fasting plasma glucose (mmol/l)*	5.7 (0.55)	5.63 (0.53)
Baseline HbA1c (%)	NR	NR
History of gestational diabetes	NR	NR

<table>
<tr><td>Bibliographic reference</td><td>Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, Shetty As, Godsland If, Chaturvedi N, Majeed A, Oliver N, Toumazou C, Alberti Kg, and Johnston Dg (2013) 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 1(3), 191-8</td></tr>
<tr><td></td><td>
<table>
<tr><td>Ethnicity</td><td>NR, but trial population reported as ‘Indian Asian’</td><td>NR, but trial population reported as ‘Indian Asian’</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Text messaging lifestyle</th><th>Control</th></tr>
<tr><td>Randomised</td><td>271</td><td>266</td></tr>
<tr><td>Dropouts</td><td>10</td><td>10</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>
- At baseline, participants received personalised education and motivation about healthy lifestyle principles, and written information about diet and physical activity.
- Received frequent (2 to 4 messages per week mobile phone messages contained information about healthy lifestyle, the benefits of physical activity and diet, cues to start physical activity and healthy dietary practices, and strategies to avoid relapse and remain motivated to maintain physical activity and healthy dietary habits.
- The mobile phone message content at any time was based on the trans-theoretical model of behavioural change, with messages tailored according to the stage of behaviour change.
- Intervention continued throughout the study period.
</td></tr>
<tr><td>Comparison</td><td>At baseline, participants received the same personalised education and motivation about healthy lifestyle principles, and written information about diet and physical activity as the intervention group</td></tr>
<tr><td>Length of follow up</td><td>24 months</td></tr>
<tr><td>Location</td><td>India</td></tr>
<tr><td>Outcomes measures and effect size</td><td>
Analysis: Intention to treat analysis. Continuous data were analysed using mixed-linear regression with maximum likelihood parameter estimation.

Progression to type 2 diabetes
<table>
<tr><th>Timepoint</th><th>Control</th><th>Text messaging lifestyle</th></tr>
<tr><td>12 months</td><td>27/266</td><td>10/271</td></tr>
<tr><td>24 months</td><td>73/266</td><td>50/271</td></tr>
</table>
Weight (kg)
Reported as BMI rather than change in weight. Converted to weight by analyst using mean height for Indian men of 164.7cm reported by Mamidi, RS; Kulkarni, B; Singh, A (2011). "Secular trends in height in different states of India in relation to socioeconomic characteristics and dietary intakes". Food and nutrition bulletin. 32 (1): 23–34
</td></tr>
</table>

Bibliographic reference	Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, Shetty As, Godsland If, Chaturvedi N, Majeed A, Oliver N, Toumazou C, Alberti Kg, and Johnston Dg (2013) 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 1(3), 191-8

Timepoint	Control	Text messaging lifestyle
24 months	mean BMI=25.0 sd BMI=5.4 mean weight=67.82 sd weight=14.65 n=266	mean BMI=25.0 sd BMI=5.5 mean weight=67.82 sd weight=14.92 n=271

Change in HbA1c levels from baseline
Not reported

Change in Fasting plasma glucose from baseline (mmol/l relative to baseline, 95%CI)
Not reported

Adverse events and side effects (limited GI intolerance)
Not reported

Systolic blood pressure (mmHg)

Timepoint	Control	Text messaging lifestyle
24 months	mean=121.4 sd=13.0 n=266	mean=121.4 sd=13.0 n=271

Total cholesterol (mmol/L)

Timepoint	Control	Text messaging lifestyle
24 months	mean=4.9 sd=0.9	mean=4.9 sd=0.9

<table>
<tr><td>Bibliographic reference</td><td>Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, Shetty As, Godsland If, Chaturvedi N, Majeed A, Oliver N, Toumazou C, Alberti Kg, and Johnston Dg (2013) 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 1(3), 191-8</td></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>n=266</td><td>n=271</td></tr>
</table>

Uptake/Adherence:
Uptake: Not reported
Adherence: Not reported (only reported relative to control for diet and lifestyle separately)
Dropout rate (indirect measure of adherence): Text messaging lifestyle intervention: 10/271 (3.7%)
</td></tr>
<tr><td>Source of funding</td><td>UK India Education and Research Initiative (grant number IND/CONT/06-07/187E) and the World Diabetes Federation (WDF 08–406).</td></tr>
<tr><td>Comments</td><td>
<table>
<tr><th>Domain</th><th>Support for judgement</th><th>Review authors' judgment</th></tr>
<tr><td colspan="3">Selection bias</td></tr>
<tr><td>Random sequence generation</td><td>'A central investigator not involved in analysis of trial data used a computer-generated randomisation sequence to randomly allocate patients'</td><td>Low risk</td></tr>
<tr><td>Allocation concealment</td><td>Allocation concealment not described.</td><td>Unclear risk</td></tr>
<tr><td colspan="3">Performance bias</td></tr>
<tr><td>Blinding of participants and personnel</td><td>All reported outcomes considered low risk of bias due to lack of blinding.</td><td>Low risk</td></tr>
<tr><td colspan="3">Detection bias</td></tr>
<tr><td>Blinding of outcome assessment</td><td>All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.</td><td>Low risk</td></tr>
<tr><td colspan="3">Attrition bias</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, Shetty As, Godsland If, Chaturvedi N, Majeed A, Oliver N, Toumazou C, Alberti Kg, and Johnston Dg (2013) 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 1(3), 191-8**

Incomplete outcome data	High follow up rate in both groups and analysis reported to be based on intention to treat principle.	Low risk
Reporting bias		
Selective reporting	Expected outcomes reported	Low risk
Other bias		
Other sources of bias	None	Low risk

1 **Table 17: Tuomilehto 2001**

Bibliographic reference	**Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50** **Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6** **Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.**
Study type	Randomised controlled trial
Aim	To assess the effectiveness of an intensive lifestyle intervention for the prevention of diabetes in middle-aged, overweight participants with impaired glucose tolerance.
Patient characteristics	**Inclusion criteria** - Aged 40-64 years - BMI>25kg/m2 - Mean value of 2 oral glucose tolerance tests in impaired glucose tolerance range according to WHO criteria **Exclusion criteria** - None reported

Bibliographic reference	**Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50** **Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6** **Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.**
	-

Recruitment

Participants were recruited by screening high risk groups, such as those with a family history of diabetes who responded to local adverts, or who were identified by previous epidemiological surveys.

Baseline characteristics

	Lifestyle (n=265)	**Control (n=257)**
Age (years, sd)	55 (7)	55 (7)
Sex (m/f)	91/174	81/176
Baseline body mass index (kg/m3, sd)	31.4 (4.5)	31.1 (4.5)
Baseline fasting plasma glucose (mmol/l)	6.1 (0.8)	6.2 (0.7)
Baseline HbA1c (%)	5.7 (0.6)	5.6 (0.6)
History of gestational diabetes	NR	NR
Ethnicity (n, %)	NR	NR

Number of Patients	**Intensive Lifestyle**	**Control**

<table>
<tr><td>Bibliographic reference</td><td>Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50

Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6

Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.</td></tr>
<tr><td></td><td><table>
<tr><td>Randomised</td><td>265</td><td>257</td></tr>
<tr><td>Dropouts (end of intervention)</td><td>24</td><td>18</td></tr>
</table>*Note that trial was terminated early by data monitoring committee (see ‘other’ in quality assessment below).</td></tr>
<tr><td>Intervention</td><td>Intensive lifestyle intervention:
Intervention continued throughout the study (ranged from 1 to 6 years)
Face to face 30 min – 1hr sessions with a nutritionist at weeks 0,1-2, 5-6 months 3,4,6, and 9, then 3 per years for the rest of the intervention
First year sessions were on a pre-planned topic but were individualised and included individual problem solving
Printed material provided
Voluntary group sessions, expert lectures, low-fat cooking lessons, visits to local supermarkets and between visit phone calls and letters
Aim was to support permanent behavioural change, and used behaviour change techniques
Individual goal setting and review encouraged.
Monitoring of nutritional intake based on 3 day food records 4 times yearly. Weight was monitored at each visit and self-monitoring encouraged in addition.
Spouse invited to attend sessions.
Very low calorie diet offered after 6 months if preferred by participant to boost weight loss.
Individual guiding to increase overall physical activity by nutritionist during counselling sessions and by yearly visits to study physician.
Supervised progressive individually tailored circuit sessions offered free of charge.
Voluntary group walking/hiking offered.
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50

Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6

Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.</td></tr>
<tr><td>Comparison</td><td>- General information about lifestyle and diabetes risk provided at baseline individually or during a single group session (30min to 1 hour). Printed material provided. Advice was not individualised.</td></tr>
<tr><td>Length of follow up</td><td>1 to 6 years</td></tr>
<tr><td>Location</td><td>Finland</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: Analysis described as intention to treat.

Progression to type 2 diabetes (cumulative)– Data reported in Lindstrom 2003b
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Control</th></tr>
<tr><td>1 year</td><td>5/263* (1.9%)</td><td>16/262* (6.1%)</td></tr>
<tr><td>2 years</td><td>15 (6.3%), (3.2 to 9.2)</td><td>37 (14.4%), (9.9 to 18.6)</td></tr>
<tr><td>3 years</td><td>22/242* (9.1%), (5.4 to 12.6)</td><td>51/244* (20.9%), (15.5 to 25.9)</td></tr>
<tr><td>4 years</td><td>24 (10.9%), (6.4 to 15.2)</td><td>53 (23%), (16.9 to 28.6)</td></tr>
<tr><td>5 years</td><td>27 (20%), (8.8 to 29.8)</td><td>57 (34.4), (21.9 to 44.9)</td></tr>
<tr><td>6 years</td><td>27/135* (20%)</td><td>59/138* (42.6%)</td></tr>
</table>
*denominator calculated by reviewer from reported % and number of cases

Change in weight from baseline –kg Data reported from Lindstrom 2003 (slightly different data reported in Lindstom 2003b, but reason not apparent)
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Control</th></tr>
<tr><td>1 year</td><td>mean=-4.5
sd=5.0</td><td>mean=-1.0
sd=3.7</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50** **Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6** **Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.**

	n=256	n=250
3 years	mean=-3.5 sd=5.1 n=231	mean=-0.9 sd=5.4 n=203

Change in HbA1c from baseline – mean % (SD)

Timepoint	Lifestyle	Control
1 year	mean=-0.1 sd=0.7 n=256	mean=+0.1 sd=0.6 n=250
3 years	mean=-0.2 sd=0.6 n=231	mean=+0.0 sd=0.6 n=203

Change in fasting plasma glucose from baseline –mmol/l

Timepoint	Lifestyle	Control
1 year	mean=-0.2 sd=0.7 n=256	mean=+0.0 sd=0.7 n=250
3 years	mean=-0.0 sd=0.7 n=231	mean=+0.1 sd=0.7 n=203

Bibliographic reference	**Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50** **Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6** **Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.**

Adverse events / side effects
Not reported

Change in systolic blood pressure from baseline – mmHg

Timepoint	Lifestyle	Control
1 year	mean=-5 sd=14 n=256	mean=-1 sd=15 n=250
2 years	mean=-5 sd=14 n=231	mean=0 sd=15 n=203

Change in total cholesterol from baseline –mmol/l

Timepoint	Lifestyle	Control
1 year	mean=-0.1 sd=0.7 n=256	mean=-0.1 sd=0.7 n=250
3 years	mean=-0.1 sd=0.9 n=231	mean=0.1 sd=0.8 n=203

<table>
<tr><td>Bibliographic reference</td><td>Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50

Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6

Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.</td></tr>
<tr><td></td><td>Uptake / adherence
Uptake: Not reported
Adherence: Not reported
Dropouts (indirect measure of adherence): At end of intervention (lifestyle programme): 24/265 (9.1%) (data from Lindstrom 2006)</td></tr>
<tr><td>Source of funding</td><td>Finnish academy, Ministry of Education, Novo Nordisk Foundation, Yrjo Jahnsson Foundation, Juho Vainio Foundation, Finish diabetes foundation.</td></tr>
<tr><td>Comments</td><td>
<table>
<tr><th>Domain</th><th>Support for judgement</th><th>Review authors' judgment</th></tr>
<tr><td colspan="3">Selection bias</td></tr>
<tr><td>Random sequence generation</td><td>Allocation was randomised, but method of random sequence generation not specified. (reported to be stratified by centre, sex and 2h plasma glucose value).</td><td>Unclear risk</td></tr>
<tr><td>Allocation concealment</td><td>Allocation was randomised, but allocation concealment not specified.</td><td>Unclear risk</td></tr>
<tr><td colspan="3">Performance bias</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50** **Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6** **Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.**		
	Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
	Detection bias		
	Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
	Attrition bias		
	Incomplete outcome data	Attrition similar across groups. Analysis based on intention to treat principle.	Low risk
	Reporting bias		
	Selective reporting	Expected outcomes reported	Low risk
	Other bias		
	Other sources of bias	Study was prematurely terminated by independent endpoint committee as incidence of diabetes was significantly lower in the intervention group. Intervention continued until next yearly visit in the intervention group. However, unlikely to lead to substantial risk of bias.	Low risk

Bibliographic reference	**Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, and Uusitupa M (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.. The New England journal of medicine 344(18), 1343-50** **Lindstrom J ; Louheranta A ; Mannelin M ; Rastas M ; Salminen V, et al. (2003a) The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26: 3230-6** **Lindstrom J ; Eriksson JG ; Valle TT ; Aunola S ; Cepaitis Z , et al. (2003b). Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. Journal of the American Society of Nephrology 14: S108-13.**

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3 **Table 18: Van Name 2016**

Bibliographic reference	**Van Name MA, Camp AW, Magenheimer EA, Fanyong L, Dziura JD et al. (2016) Effective translation of an intensive lifestyle intervention for Hispanic women with prediabetes in a Community Health Center setting. Diabetes Care 39: 525-531.**
Study type	Randomised controlled trial
Aim	To investigate whether an intensive lifestyle intervention, based on the DPP, can be delivered in a Community Health Center setting to reduce the risk of diabetes in a disadvantaged female Hispanic population
Patient characteristics	**Inclusion criteria** - Female - Aged 18 to 65 years - At least one of the following risk factors for diabetes: BMI=>30kg/m2, family history of type 2 diabetes, history of gestational diabetes, child born > 4kg, diagnosis of hypertension, dyslipidaemia, cardiovascular disease - Fasting plasma glucose of 5.6mmol/L to 6.9 mmol/: or 2h plasma glucose of 7.8 mmol/L to 11 mmol/L **Exclusion criteria** - Pregnant or planning pregnancy

<table>
<tr><td>Bibliographic reference</td><td>Van Name MA, Camp AW, Magenheimer EA, Fanyong L, Dziura JD et al. (2016) Effective translation of an intensive lifestyle intervention for Hispanic women with prediabetes in a Community Health Center setting. Diabetes Care 39: 525-531.</td></tr>
<tr><td></td><td>- Taking medications that would affect weight or glucose metabolism
- Chronic medical or psychiatric disorders that would interfere with ability to participate in exercise or other programme component,

Recruitment
Women between 18 and 65 with at least one risk factor for diabetes were identified from a community health centre registry, and invited for screening.

Baseline characteristics
<table>
<tr><th></th><th>Lifestyle (n=61)</th><th>Usual care (n=61)</th></tr>
<tr><td>Age (years, sd)*</td><td>43.8 (10.8)</td><td>43.0 (9.7)</td></tr>
<tr><td>Sex (m/f)*</td><td>0/61</td><td>0/61</td></tr>
<tr><td>Baseline body mass index (kg/m3, sd)</td><td>35.4 (8.5)</td><td>35.2 (6.1)</td></tr>
<tr><td>Baseline fasting plasma glucose (mmol/l)</td><td>5.7 (0.5)</td><td>5.6 (0.6)</td></tr>
<tr><td>Baseline HbA1c (%)</td><td>5.8 (0.36)</td><td>6.0 (0.33)</td></tr>
<tr><td>History of gestational diabetes</td><td>NR</td><td>NR</td></tr>
<tr><td>Ethnicity (%)
- Hispanic
- African-American
- Non-Hispanic Caucasian</td><td colspan="2">90%
8%
2%</td></tr>
</table></td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Text messaging lifestyle</th><th>Control</th></tr>
<tr><td>Randomised</td><td>65</td><td>65</td></tr>
<tr><td>Dropouts</td><td>4</td><td>4</td></tr>
</table></td></tr>
<tr><td>Intervention</td><td>Modified version of the US Diabetes prevention programme (DPP) including:
- 14 week group program including 1 hour weekly lifestyle class focussing on healthy food choices, behaviour change and weight loss.
- Classes run by a bilingual nurse practitioner</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Van Name MA, Camp AW, Magenheimer EA, Fanyong L, Dziura JD et al. (2016) Effective translation of an intensive lifestyle intervention for Hispanic women with prediabetes in a Community Health Center setting. Diabetes Care 39: 525-531.</td></tr>
<tr><td></td><td>- 1 hour trainer-led exercise class 2-3 nights per week
- Followed the curriculum of the US DPP and was enhanced for a population with lower literacy with a hands on learning approach including weekly cooking demonstrations, group learning sessions in the local grocery store and encouragement to participate in the neighbourhood community farm
- Family based approach: participants encouraged to attend with family members including children and babies.</td></tr>
<tr><td>Comparison</td><td>Usual care, which included:
- One time diabetes prevention counselling recommending they lose 7% body weight and increase physical activity to 150 min/week.
- Follow up counselling by the health centre nutritionist</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: All data are reported as least squares mean (after adjustment for baseline). Data appears to be based on completers only.

Progression to type 2 diabetes
<table>
<tr><th>Timepoint</th><th>Lifestyle</th><th>Usual care</th></tr>
<tr><td>12 months</td><td>3/61 (4.9%)</td><td>4/61 (6.6%)</td></tr>
</table>

Change in weight from baseline – kg
<table>
<tr><th>Timepoint</th><th>Lifestyle
(n=61)</th><th>Usual care
(n=61)</th></tr>
<tr><td>12 months</td><td>mean=-3.8
95%CI=-4.6 to -3.0
sd=3.12*
n=61</td><td>mean=+1.4
95%CI=-+0.6 to 2.2
sd=3.12*
n=61</td></tr>
</table>
*calculated by reviewer

Change in HbA1c from baseline - % (95% CIs)</td></tr>
</table>

Bibliographic reference	Van Name MA, Camp AW, Magenheimer EA, Fanyong L, Dziura JD et al. (2016) Effective translation of an intensive lifestyle intervention for Hispanic women with prediabetes in a Community Health Center setting. Diabetes Care 39: 525-531.

Timepoint	Lifestyle	Usual care
12 months	mean=-0.1 95%CI=-0.1 to 0.0 sd=0.2* n=61	mean=0.0 95%CI=-0.1 to 0.1 sd=0.39* n=61

***calculated by reviewer**

Change in fasting plasma glucose from baseline (mmol/l)

Timepoint	Lifestyle	Usual care
12 months	mean=-0.19 95%CI=-0.34 to -0.04 sd=0.59* n=61	mean=-0.25 95%CI=-0.39 to -0.1 sd=0.57* n=61

***calculated by reviewer**

Adverse events / side effects

Not reported.

Change in systolic blood pressure from baseline (mmHg)

Timepoint	Lifestyle	Usual care
12 months	mean=-1.5 95%CI=-5.0 to +2.1 sd=13.86* n=61	mean=0 95%CI=-3.6 to 3.6 sd=14.06* n=61

***calculated by reviewer**

Bibliographic reference	**Van Name MA, Camp AW, Magenheimer EA, Fanyong L, Dziura JD et al. (2016) Effective translation of an intensive lifestyle intervention for Hispanic women with prediabetes in a Community Health Center setting. Diabetes Care 39: 525-531.**

Change in total cholesterol from baseline (mmol/l)

Timepoint	Lifestyle (n=61)	Usual care (n=61)
12 months	mean=-0.16 95%CI=-0.31 to -0.0 sd=0.61* n=61	mean=-0.06 95%CI=-0.22 to +0.1 sd=0.62* n=61

***calculated by reviewer**

Uptake/Adherence:
Uptake: Not reported
Adherence: Number of participants attending at least 14 classes: 42 (68%)**
Dropout rate (indirect measure of adherence): 4/65 (6.2%)

**denominator not reported and appears inconsistent with number randomised and reported %

Source of funding	Supported by the Donaghue Program for Research Leadership (DF08-313) and Fair Haven Community Health Center, along with grants from National Institutes of Health (UL1-TR-000142, P30-DK-045735, and K12-DK-094714).

Comments

Domain	Support for judgement	Review authors' judgment
Selection bias		
Random sequence generation	Random sequence generation not described.	Unclear risk
Allocation concealment	Allocation concealment not described.	Unclear risk
Performance bias		
Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk

Bibliographic reference	**Van Name MA, Camp AW, Magenheimer EA, Fanyong L, Dziura JD et al. (2016) Effective translation of an intensive lifestyle intervention for Hispanic women with prediabetes in a Community Health Center setting. Diabetes Care 39: 525-531.**

Detection bias		
Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
Attrition bias		
Incomplete outcome data	Analysis based on completers only.	High risk
Reporting bias		
Selective reporting	Expected outcomes reported	Low risk
Other bias		
Other sources of bias	None	Low risk

1 **Table 19: Yeh 2016**

Bibliographic reference	**Yeh M-C ; Heo M ; Suchday S ; Wong A ; Poon E , et al. (2016) Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City. Diabetic Medicine 33: 547-51.**
Study type	Randomised controlled trial
Aim	To evaluate the effectiveness and feasibility of implementing a linguistically and culturally tailored Diabetes Prevention Program among Chinese immigrants with prediabetes living in New Your City.
Patient characteristics	**Inclusion criteria** - Chinese speaker - Presence of prediabetes (defined as: HbA1c 5.7 – 6.4%) - BMI ≥23 kg/m^2 - No medical conditions for which the DPP lifestyle intervention would be contraindicated - Receiving care from a Chinese American Independent Practice Association (CAIPA) practice **Exclusion criteria** - No further criteria reported. **Recruitment**

<table>
<tr><td>Bibliographic reference</td><td>Yeh M-C ; Heo M ; Suchday S ; Wong A ; Poon E , et al. (2016) Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City. Diabetic Medicine 33: 547-51.</td></tr>
<tr><td></td><td>Recruited from medical practices within the Chinese American Medical practices association. Details of how participants were identified are not reported.

Baseline characteristics
<table>
<tr><th></th><th>Lifestyle (n=30)</th><th>Control (n=30)</th></tr>
<tr><td>Age (years, sd)*</td><td>56.8 (9.5)</td><td>60.9 (12.2)</td></tr>
<tr><td>Sex (m/f)*</td><td>11/19</td><td>15/15</td></tr>
<tr><td>Baseline body mass index (kg/m3, sd)</td><td>26.3 (2.4)</td><td>25.8 (2.3)</td></tr>
<tr><td>Baseline fasting plasma glucose (mmol/l)*</td><td>6.1 (0.5)</td><td>5.7 (0.7)</td></tr>
<tr><td>Baseline HbA1c (%)</td><td>6.2 (0.4)</td><td>6.0 (0.3)</td></tr>
<tr><td>History of gestational diabetes</td><td>NR</td><td>NR</td></tr>
<tr><td>Ethnicity**</td><td>NR</td><td>NR</td></tr>
</table>
*Significant difference in baseline FPG between treatment groups p<0.05
**All patients were Chinese-speaking</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Intensive lifestyle</th><th>Control</th></tr>
<tr><td>Randomised</td><td>30</td><td>30</td></tr>
<tr><td>Dropouts</td><td>0</td><td>2</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>- Based on the US DPP curriculum (see Knowler et al 2002 for a description of contents).
- Curriculum adapted based on feedback from 3 focus groups of Chinese participants with prediabetes. Adaptations included including more information on Asian diabetes risk and cultural and linguistic tailoring.
- 12 bi weekly core sessions and 6 monthly follow up sessions (sessions 1.5 to 2 hours) by trained lifestyle coaches.</td></tr>
<tr><td>Comparison</td><td>Details not reported</td></tr>
<tr><td>Length of follow up</td><td>12 months</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Analysis: All data presented are estimated percent changes (±SE) obtained based on application of mixed-effects linear models. Analysis was based on those who completed follow up (2 dropouts in control group only).</td></tr>
</table>

Bibliographic reference	Yeh M-C ; Heo M ; Suchday S ; Wong A ; Poon E , et al. (2016) Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City. Diabetic Medicine 33: 547-51.

Progression to type 2 diabetes
Not reported.

Change in weight from baseline – kg (converted from % change to absolute values by reviewer)

Timepoint	Lifestyle	Usual care
12 months	mean=-2.28 (-3.3%) se=0.48 (0.7%) sd=2.63* n=30	mean=0.19(+0.3%) se=0.39(0.6%) sd=2.06* n=28

***Calculated by reviewer**

Change in HbA1c from baseline –% (converted from % change to absolute values by reviewer)

Timepoint	Lifestyle	Usual care
12 months	mean=0.06 (+0.1%) se=0.062 (1%) sd=0.34* n=30	mean=0.228 (+3.8%) se=0.078 (1.3%) sd=0.41* n=28

***Calculated by reviewer**

Change in fasting plasma glucose from baseline - mmol/l (converted from % change to absolute values by reviewer)

Timepoint	Lifestyle	Usual care
12 months	mean=-0.29 (-4.8%) se=0.098 (1.6%)	mean=-0.09(-1.6%) se=0.091 (1.6%)

Bibliographic reference	Yeh M-C ; Heo M ; Suchday S ; Wong A ; Poon E , et al. (2016) Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City. Diabetic Medicine 33: 547-51.

	sd=0.54* n=30	sd=0.48* n=28

***Calculated by reviewer**

Adverse events / side effects

Not reported.

Change in systolic blood pressure from baseline – mmHg (converted from % change to absolute values by reviewer)

Timepoint	Lifestyle	Usual care
12 months	mean=-2.54 (-2.0%) se= 2.41 (1.9%) sd=13.2* n=30	mean=-1.90 (-1.5%) se=2.79 (2.2%) sd=14.76* n=28

***Calculated by reviewer**

Change in total cholesterol from baseline - mmol/l (converted from % change to absolute values by reviewer)

Timepoint	Lifestyle	Usual care
12 months	mean=-0.49 (-9.9%) se=0.14 (2.8%) sd=0.77* n=30	mean=-0.38 (-8.0%) se=0.12 (2.6%) sd=0.63* n=28

***Calculated by reviewer**

Uptake/Adherence:

Uptake: Not reported

Adherence: Not reported

Dropout rate (indirect measure of adherence): 0/30 (0%)

Bibliographic reference	**Yeh M-C ; Heo M ; Suchday S ; Wong A ; Poon E , et al. (2016) Translation of the Diabetes Prevention Program for diabetes risk reduction in Chinese immigrants in New York City. Diabetic Medicine 33: 547-51.**
Source of funding	Funded in part by National Institutes of Health grants from the National Institute of Diabetes, Digestive and Kidney Diseases (1 R34 DK090695 and 5P60DK20541) and the National Center for Advancing Translational Sciences Clinical Translational Science Award (UL1 TR001073, TL1 TR001072, KL2 TR001071).

Comments

Domain	Support for judgement	Review authors' judgment
Selection bias		
Random sequence generation	Random sequence generation not described.	Unclear risk
Allocation concealment	Allocation concealment not described.	Unclear risk
Performance bias		
Blinding of participants and personnel	All reported outcomes considered low risk of bias due to lack of blinding.	Low risk
Detection bias		
Blinding of outcome assessment	All reported outcomes considered at low risk of bias due to lack of blinding of outcome assessment.	Low risk
Attrition bias		
Incomplete outcome data	Analysis based on completers only, but drop-out rate was very low (2 in control group only).	Low risk
Reporting bias		
Selective reporting	Expected outcomes reported	Low risk
Other bias		
Other sources of bias	None	Low risk

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Appendix E: Forest plots

E.1 Review question 1

Studies that were included in the review, but excluded from the primary analysis are shown in forest plots for information, but assigned zero weight in the meta-analyses (see methods for details). Four studies (Fontbonne 2009, Nilsen 2011, Van Name 2016, Yeh 2016) were not included in the primary analysis because data were based on completers only. The committee agreed that these studies may overestimate treatment effects because they did not take into account attrition from interventions in the study. Ramachandran 2006 was not included in the primary analysis because the dose of metformin given in this trial was 500mg/d, which the committee agreed was too low to be representative of practice in the UK, and much lower than the other trials in the review. The US diabetes prevention programme trial was included in the primary analysis comparing metformin with control, but was not included in the analysis comparing intensive lifestyle intervention with control because the Committee considered that the lifestyle intervention that was used in this trial was substantially more intensive than other trials in the review, and current UK practice.

E.1.1 Metformin vs Control

Figure 1: Progression to type 2 diabetes (24 months+)

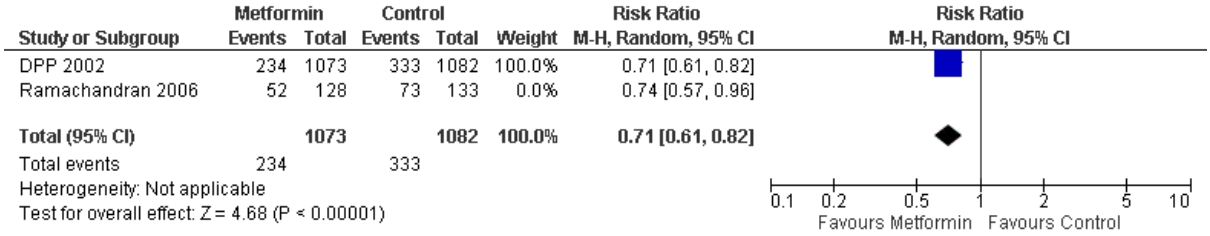


Figure 2: Change in weight (12 – 24 months)

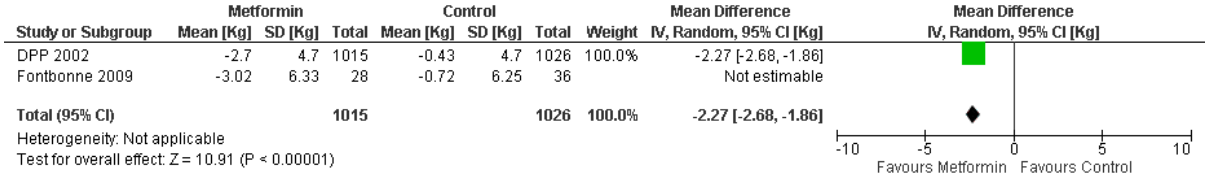


Figure 3: Change in weight (24 months+)

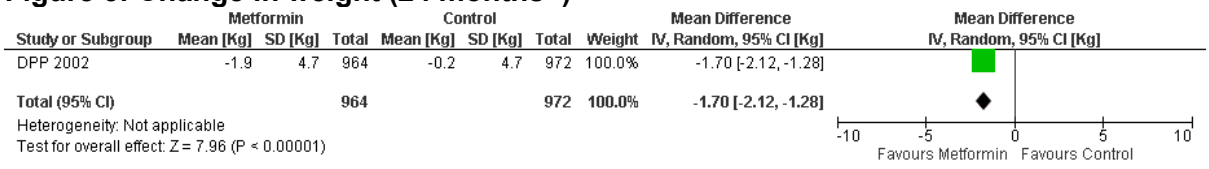


Figure 4: Change in HbA1c (12 – 24 months)

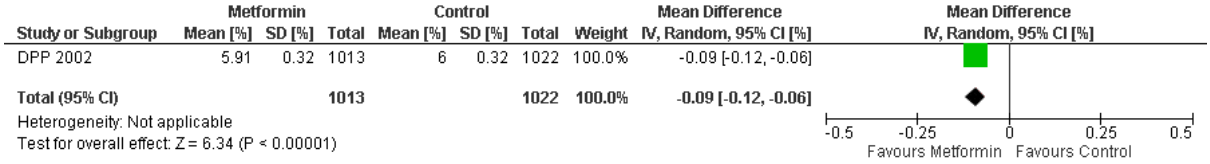


Figure 5: Change in HbA1c (24 months+)

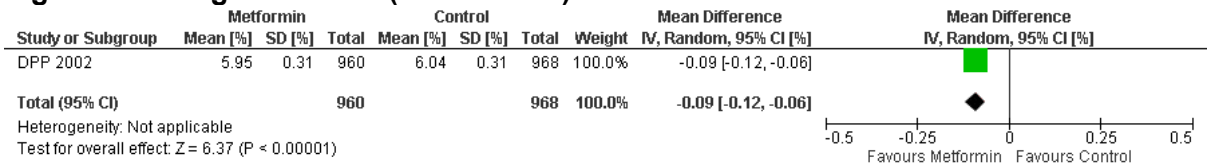


Figure 6: Change in FPG (12 – 24 months)

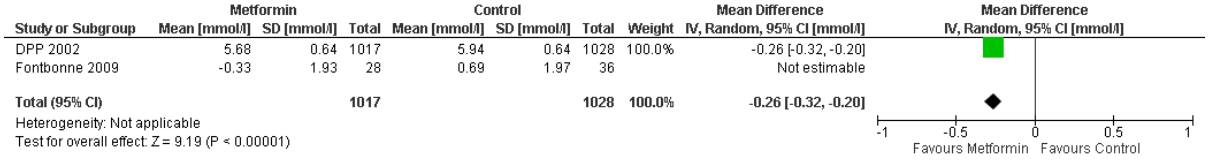


Figure 7: Change in FPG (24 months+)

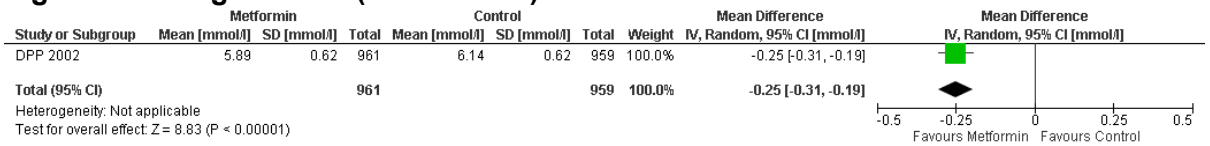


Figure 8: Adverse events – Gastrointestinal symptoms (12 – 24 months)

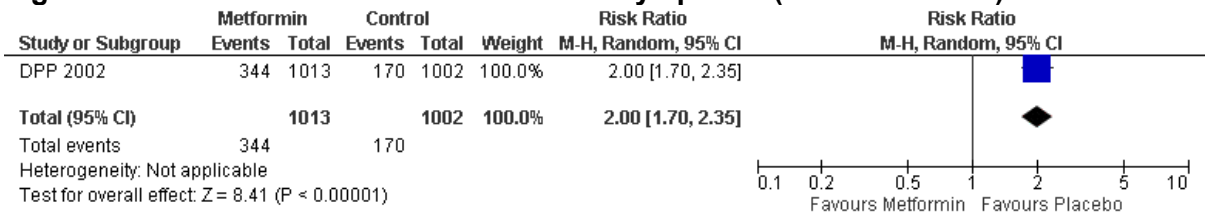


Figure 9: Adverse events – Gastrointestinal symptoms (24 months+)

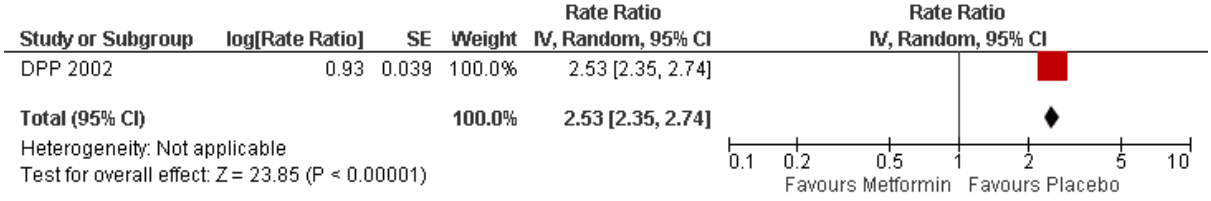


Figure 10: Systolic blood pressure (12 – 24 months)

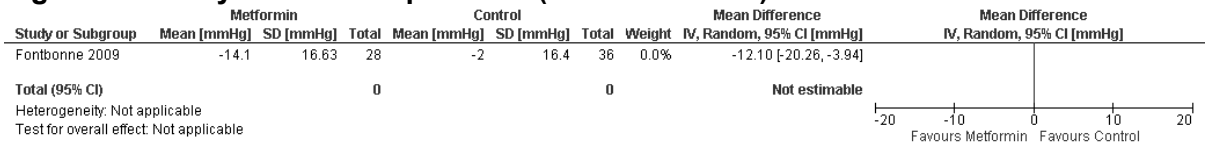


Figure 11: Systolic blood pressure (24 months+)

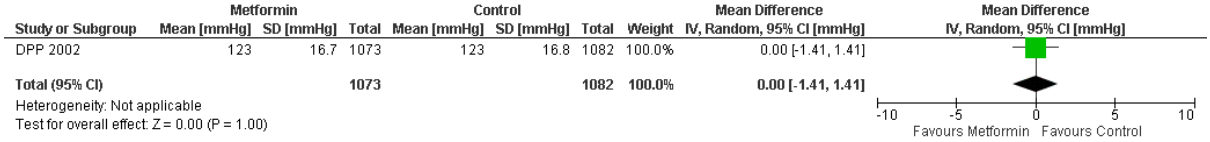


Figure 12: Total cholesterol (12 – 24 months)

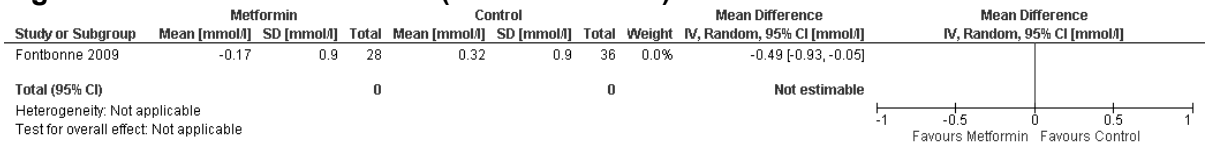
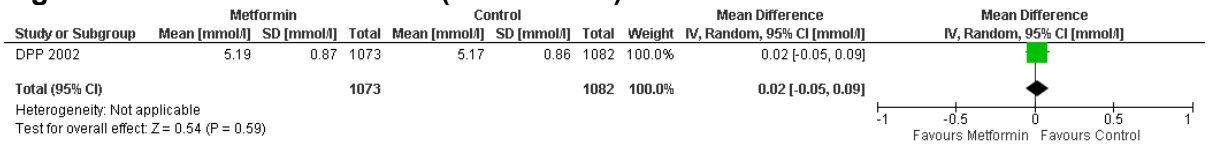


Figure 13: Total cholesterol (24 months+)



E.1.21 Metformin vs Control (Subgroups – within study)

Figure 14: Gestational diabetes subgroup: Progression to type 2 diabetes (24 months+)

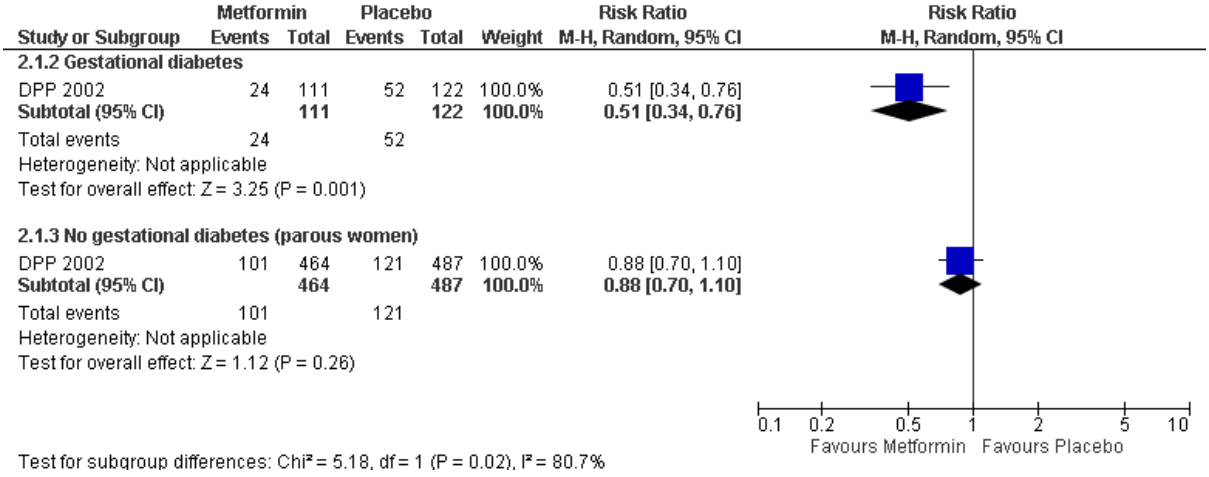


Figure 15: Age subgroups: : Progression to type 2 diabetes (24 months+)

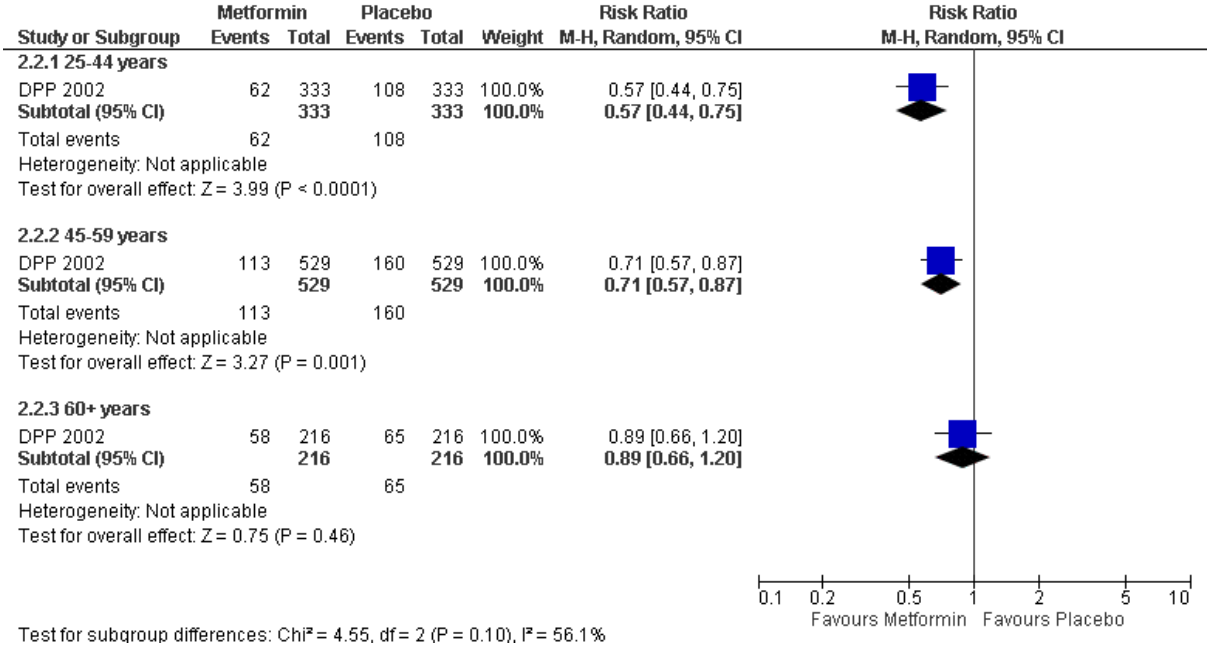


Figure 16: Ethnicity subgroups: : Progression to type 2 diabetes (24 months+)

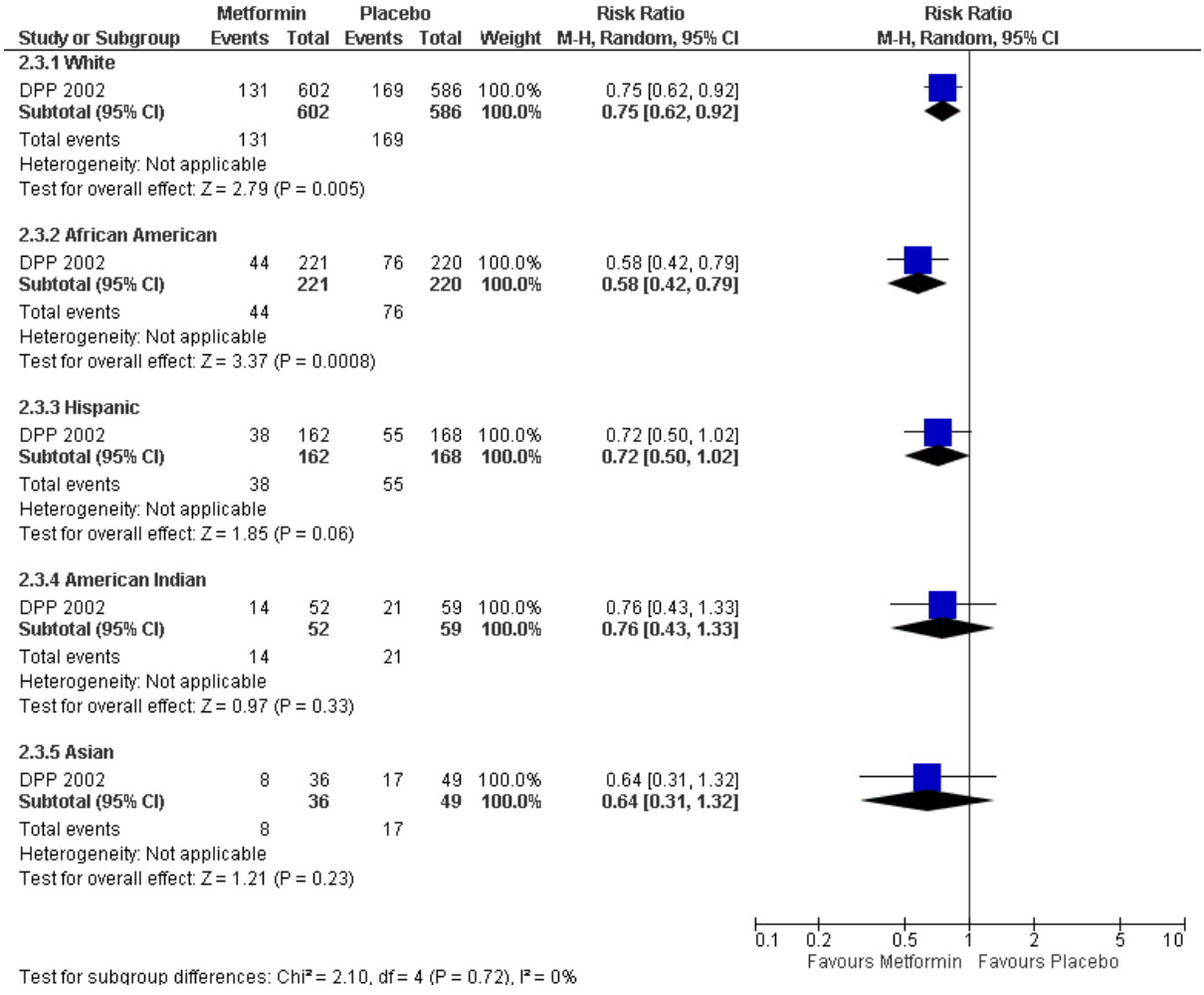


Figure 17: BMI subgroups: : Progression to type 2 diabetes (24 months+)

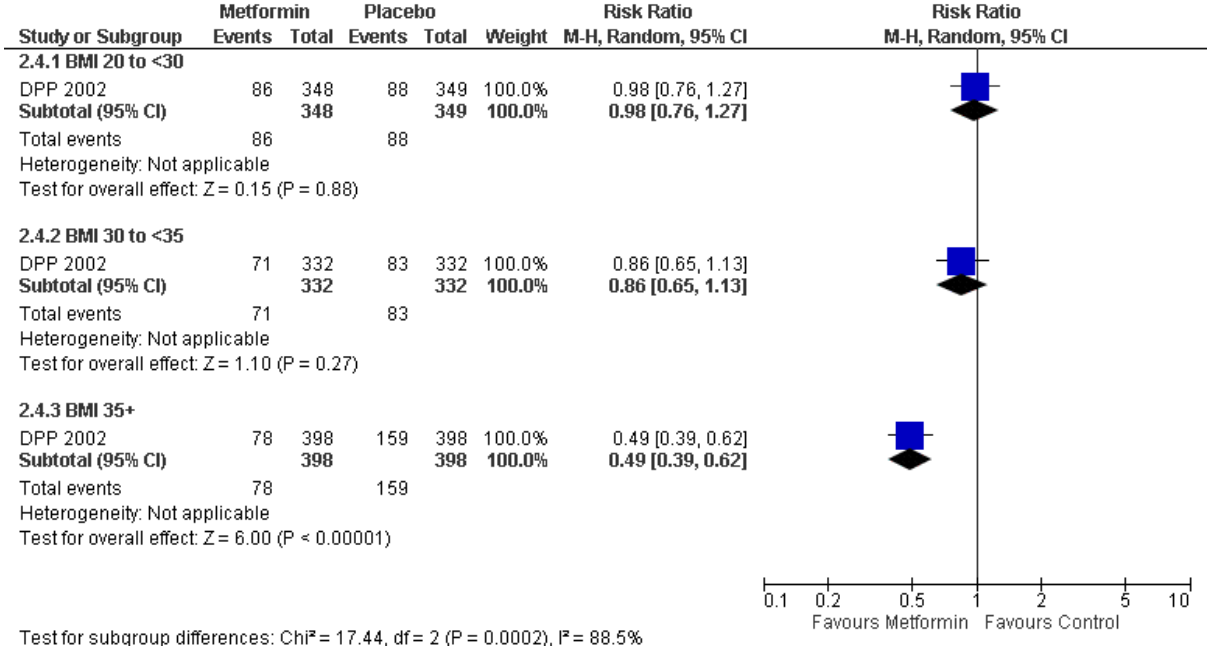
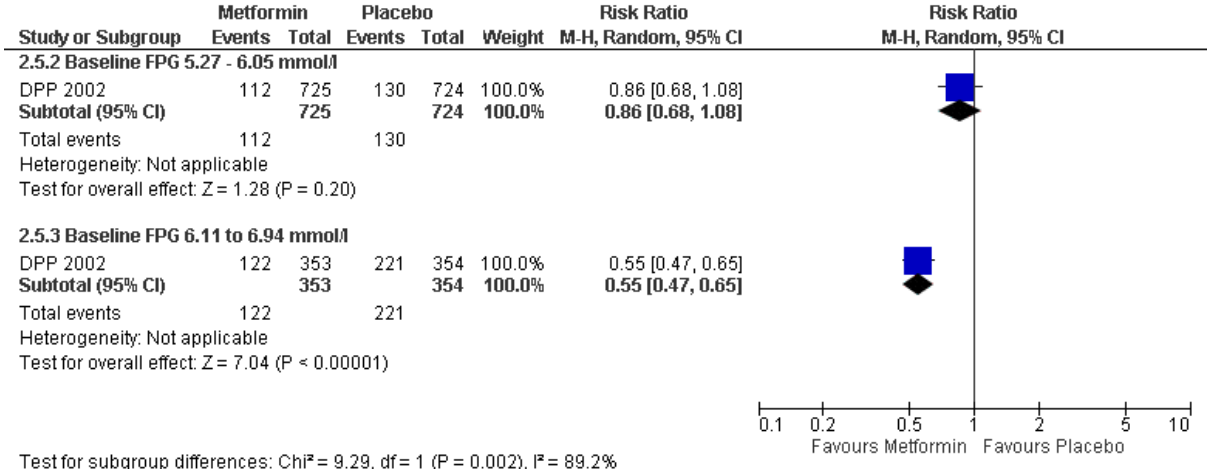


Figure 18: Baseline FPG subgroups: Progression to type 2 diabetes (24 months+)



E.1.31 Intensive lifestyle vs Control

Figure 19: Progression to type 2 diabetes (12 – 24 months)

Study or Subgroup	Intensive lifestyle Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Katula 2011	2	151	7	150	26.4%	0.28 [0.06, 1.34]
Ma 2013	1	79	1	81	8.4%	1.03 [0.07, 16.11]
Tuomilehto 2001	5	263	16	262	65.2%	0.31 [0.12, 0.84]
Van Name 2016	3	61	4	61	0.0%	0.75 [0.18, 3.21]
Total (95% CI)		**493**		**493**	**100.0%**	**0.34 [0.15, 0.75]**
Total events	8		24			

Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)

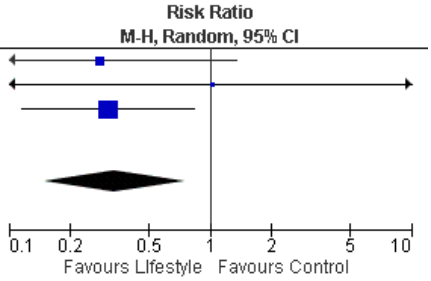


Figure 20: Progression to type 2 diabetes (24 months+)

Study or Subgroup	Intensive lifestyle Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Davies 2016	64	447	67	443	39.3%	0.95 [0.69, 1.30]
DPP 2002	145	1079	333	1082	0.0%	0.44 [0.37, 0.52]
Mensink 2003	11	61	19	60	27.0%	0.57 [0.30, 1.09]
Tuomilehto 2001	22	242	51	244	33.7%	0.43 [0.27, 0.69]
Total (95% CI)		**750**		**747**	**100.0%**	**0.63 [0.37, 1.08]**
Total events	97		137			

Heterogeneity: Tau² = 0.16; Chi² = 7.85, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 1.68 (P = 0.09)

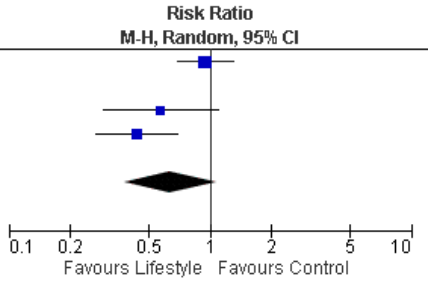


Figure 21: Change in weight (12 - 24 months)

Study or Subgroup	Mean difference (Kg)	SE	Intensive Lifestyle Total	Control Total	Weight	Mean difference (Kg) IV, Random, 95% CI
Ackermann 2015	-2.3	0.59	257	252	14.7%	-2.30 [-3.46, -1.14]
Davies 2016	-0.27	0.46	368	382	15.9%	-0.27 [-1.17, 0.63]
DPP 2002	-6.27	0.2077	1023	1026	0.0%	-6.27 [-6.68, -5.86]
Katula 2011	-3.49	1.875	151	150	5.5%	-3.49 [-7.16, 0.18]
Kulzer 2009	-2.4	0.84	61	61	12.4%	-2.40 [-4.05, -0.75]
Ma 2013	-3.9	1.2728	79	81	8.8%	-3.90 [-6.39, -1.41]
Mensink 2003	-2.15	0.7392	52	54	13.3%	-2.15 [-3.60, -0.70]
Nilsen 2011	-0.7	3.2008	93	89	0.0%	-0.70 [-6.97, 5.57]
Oldroyd 2006	-2.6	0.7659	32	30	13.1%	-2.60 [-4.10, -1.10]
Tuomilehto 2001	-3.5	0.3904	256	250	16.5%	-3.50 [-4.27, -2.73]
Van Name 2016	-5.2	0.5649	61	61	0.0%	-5.20 [-6.31, -4.09]
Yeh 2016	-2.47	0.6182	30	28	0.0%	-2.47 [-3.68, -1.26]
Total (95% CI)			**1256**	**1260**	**100.0%**	**-2.41 [-3.44, -1.38]**

Heterogeneity: Tau² = 1.52; Chi² = 31.11, df = 7 (P < 0.0001); I² = 78%
Test for overall effect: Z = 4.60 (P < 0.00001)

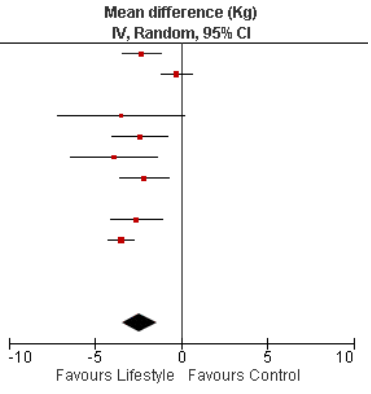


Figure 22: Change in weight (24 months+)

Study or Subgroup	Mean difference (Kg)	SE	Favours Lifestyle Total	Control Total	Weight	Mean difference (Kg) IV, Random, 95% CI
Davies 2016	-0.26	0.46	321	321	29.9%	-0.26 [-1.16, 0.64]
DPP 2002	-4.1	0.213	970	972	0.0%	-4.10 [-4.52, -3.68]
Mensink 2003	-1.2	0.896	52	54	22.7%	-1.20 [-2.96, 0.56]
Oldroyd 2006	-3.3	1.201	30	24	18.1%	-3.30 [-5.65, -0.95]
Tuomilehto 2001	-2.6	0.506	231	203	29.3%	-2.60 [-3.59, -1.61]
Total (95% CI)			**634**	**602**	**100.0%**	**-1.71 [-3.17, -0.24]**

Heterogeneity: Tau² = 1.66; Chi² = 14.31, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 2.28 (P = 0.02)

Figure 23: Change in HbA1c (12 – 24 months)

Study or Subgroup	Mean difference (%)	SE	Intensive lifestyle Total	Control Total	Weight	Mean difference (%) IV, Random, 95% CI
Ackermann 2015	-0.04	0.03	257	252	28.5%	-0.04 [-0.10, 0.02]
Davies 2016	-0.04	0.0214	361	379	35.3%	-0.04 [-0.08, 0.00]
DPP 2002	-0.18	0.0141	1043	1022	0.0%	-0.18 [-0.21, -0.15]
Kulzer 2009	-0.1	0.064	61	61	11.9%	-0.10 [-0.23, 0.03]
Mensink 2003	-0.05	0.0694	52	54	10.5%	-0.05 [-0.19, 0.09]
Nilsen 2011	0	0.0741	93	89	0.0%	0.00 [-0.15, 0.15]
Tuomilehto 2001	-0.2	0.0579	256	250	13.8%	-0.20 [-0.31, -0.09]
Van Name 2016	-0.1	0.0561	61	61	0.0%	-0.10 [-0.21, 0.01]
Yeh 2016	-0.168	0.0993	30	28	0.0%	-0.17 [-0.36, 0.03]
Total (95% CI)			**987**	**996**	**100.0%**	**-0.07 [-0.12, -0.02]**

Heterogeneity: Tau² = 0.00; Chi² = 7.51, df = 4 (P = 0.11); I² = 47%
Test for overall effect: Z = 2.75 (P = 0.006)

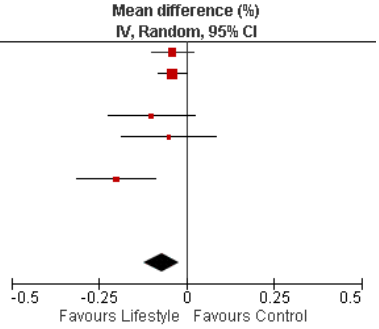


Figure 24: Change in HbA1c (24 months+)

Study or Subgroup	Mean difference (%)	SE	Intevesive lifestyle Total	Control Total	Weight	Mean difference (%) IV, Random, 95% CI
Davies 2016	-0.07	0.06	322	328	36.0%	-0.07 [-0.19, 0.05]
DPP 2002	-0.17	0.014	967	968	0.0%	-0.17 [-0.20, -0.14]
Mensink 2003	0.01	0.079	52	54	28.4%	0.01 [-0.14, 0.16]
Tuomilehto 2001	-0.2	0.061	256	203	35.6%	-0.20 [-0.32, -0.08]
Total (95% CI)			**630**	**585**	**100.0%**	**-0.09 [-0.21, 0.02]**

Heterogeneity: Tau² = 0.01; Chi² = 4.88, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 1.57 (P = 0.12)

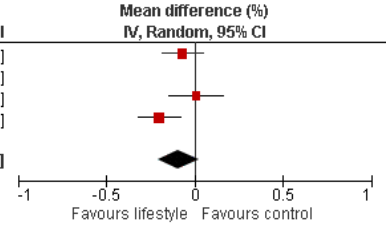


Figure 25: Change in FPG (12 – 24 months)

Study or Subgroup	Mean difference (mmol/l)	SE	Intensive lifestyle Total	Control Total	Weight	Mean difference (mmol/l) IV, Random, 95% CI
Davies 2016	0.001	0.05	371	385	24.5%	0.00 [-0.10, 0.10]
DPP 2002	-0.3	0.028	1028	1028	0.0%	-0.30 [-0.35, -0.25]
Katula 2011	-0.17	0.07	151	150	19.2%	-0.17 [-0.31, -0.03]
Kulzer 2009	-0.3	0.123	61	61	10.0%	-0.30 [-0.54, -0.06]
Ma 2013	-0.24	0.127	69	70	9.6%	-0.24 [-0.49, 0.01]
Mensink 2003	-0.13	0.114	52	54	11.1%	-0.13 [-0.35, 0.09]
Nilsen 2011	0.2	0.145	93	89	0.0%	0.20 [-0.08, 0.48]
Oldroyd 2006	-0.05	0.206	32	30	4.4%	-0.05 [-0.45, 0.35]
Tuomilehto 2001	-0.2	0.062	256	250	21.2%	-0.20 [-0.32, -0.08]
Van Name 2016	0.06	0.105	61	61	0.0%	0.06 [-0.15, 0.27]
Yeh 2016	-0.2	0.134	30	28	0.0%	-0.20 [-0.46, 0.06]
Total (95% CI)			**992**	**1000**	**100.0%**	**-0.14 [-0.24, -0.05]**

Heterogeneity: Tau² = 0.01; Chi² = 11.19, df = 6 (P = 0.08); I² = 46%
Test for overall effect: Z = 3.12 (P = 0.002)

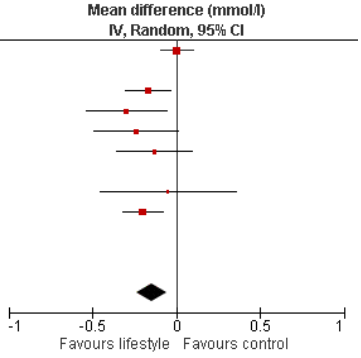


Figure 26: Change in FPG (24 months+)

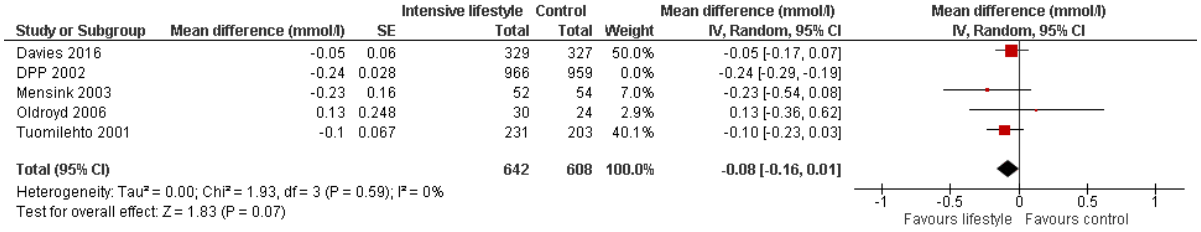


Figure 27: Adverse events – Gastrointestinal symptoms (24 months+)

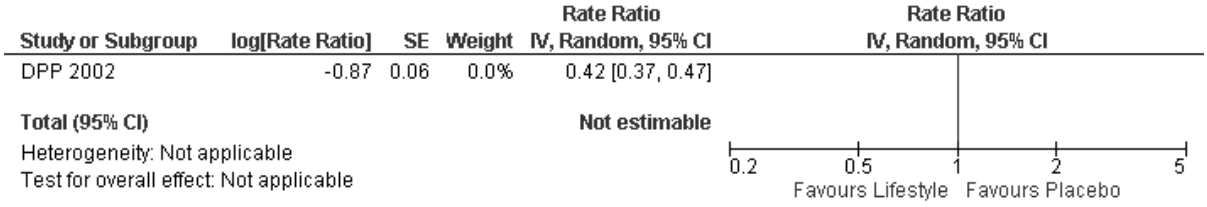


Figure 28: Systolic blood pressure (12 – 24 months)

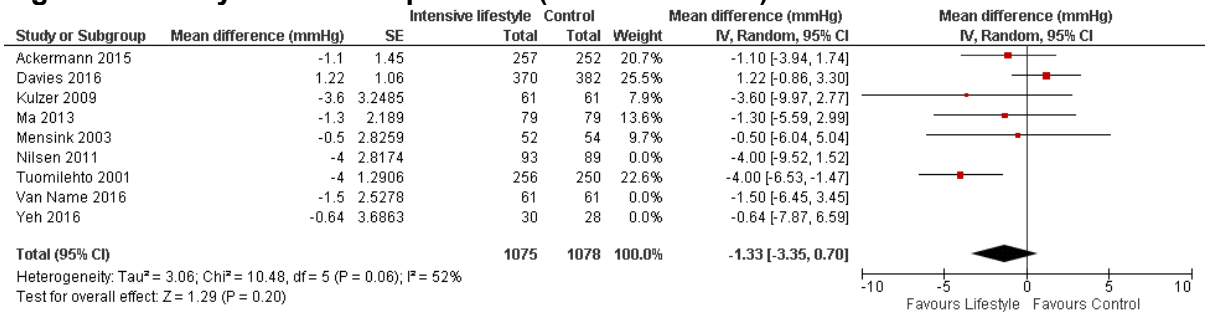


Figure 29: Systolic blood pressure (24 months+)

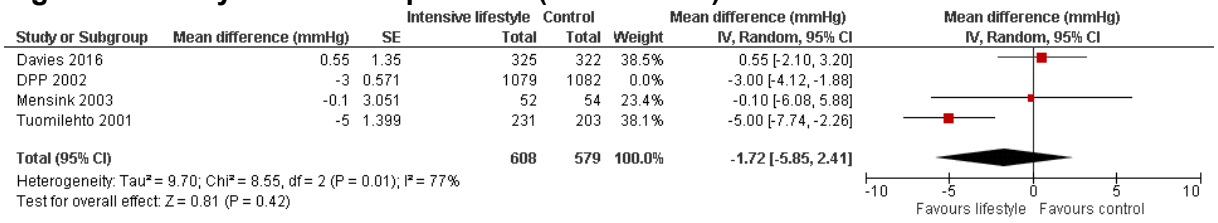


Figure 30: Total cholesterol (12 – 24 months)

Study or Subgroup	Mean difference (mmol/L)	SE	Intensive Lifestyle Total	Control Total	Weight	Mean difference (mmol/L) IV, Random, 95% CI
Ackermann 2015	0.041	0.08	257	252	15.9%	0.04 [-0.12, 0.20]
Davies 2016	-0.07	0.05	367	381	40.8%	-0.07 [-0.17, 0.03]
Kulzer 2009	-0.22	0.1666	61	61	3.7%	-0.22 [-0.55, 0.11]
Ma 2013	-0.173	0.2027	72	73	2.5%	-0.17 [-0.57, 0.22]
Mensink 2003	-0.1	0.1232	52	54	6.7%	-0.10 [-0.34, 0.14]
Nilsen 2011	-0.1	0.1557	93	89	0.0%	-0.10 [-0.41, 0.21]
Oldroyd 2006	0	0.1602	31	29	4.0%	0.00 [-0.31, 0.31]
Tuomilehto 2001	0	0.0622	256	250	26.4%	0.00 [-0.12, 0.12]
Van Name 2016	-0.1	0.1114	61	61	0.0%	-0.10 [-0.32, 0.12]
Yeh 2016	-0.11	0.1842	30	28	0.0%	-0.11 [-0.47, 0.25]
Total (95% CI)			**1096**	**1100**	**100.0%**	**-0.04 [-0.10, 0.02]**

Heterogeneity: Tau² = 0.00; Chi² = 3.69, df = 6 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)

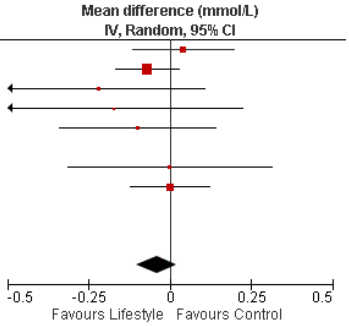
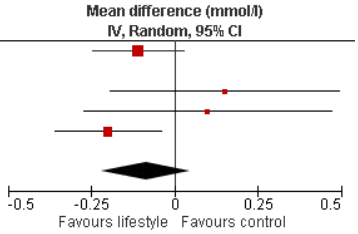


Figure 31: Total cholesterol (24 months+)

Study or Subgroup	Mean difference (mmol/l)	SE	Intensive lifestyle Total	Control Total	Weight	Mean difference (mmol/l) IV, Random, 95% CI
Davies 2016	-0.11	0.07	331	330	41.1%	-0.11 [-0.25, 0.03]
DPP 2002	-0.05	0.037	1079	1082	0.0%	-0.05 [-0.12, 0.02]
Mensink 2003	0.15	0.175	52	54	12.6%	0.15 [-0.19, 0.49]
Oldroyd 2006	0.1	0.19	29	24	10.9%	0.10 [-0.27, 0.47]
Tuomilehto 2001	-0.2	0.082	231	203	35.4%	-0.20 [-0.36, -0.04]
Total (95% CI)			**643**	**611**	**100.0%**	**-0.09 [-0.22, 0.05]**

Heterogeneity: Tau² = 0.01; Chi² = 4.63, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 1.26 (P = 0.21)



E.1.41 Intensive lifestyle vs Control (Subgroups – across studies)

Figure 32: Age subgroups: Change in weight (12 – 24 months)

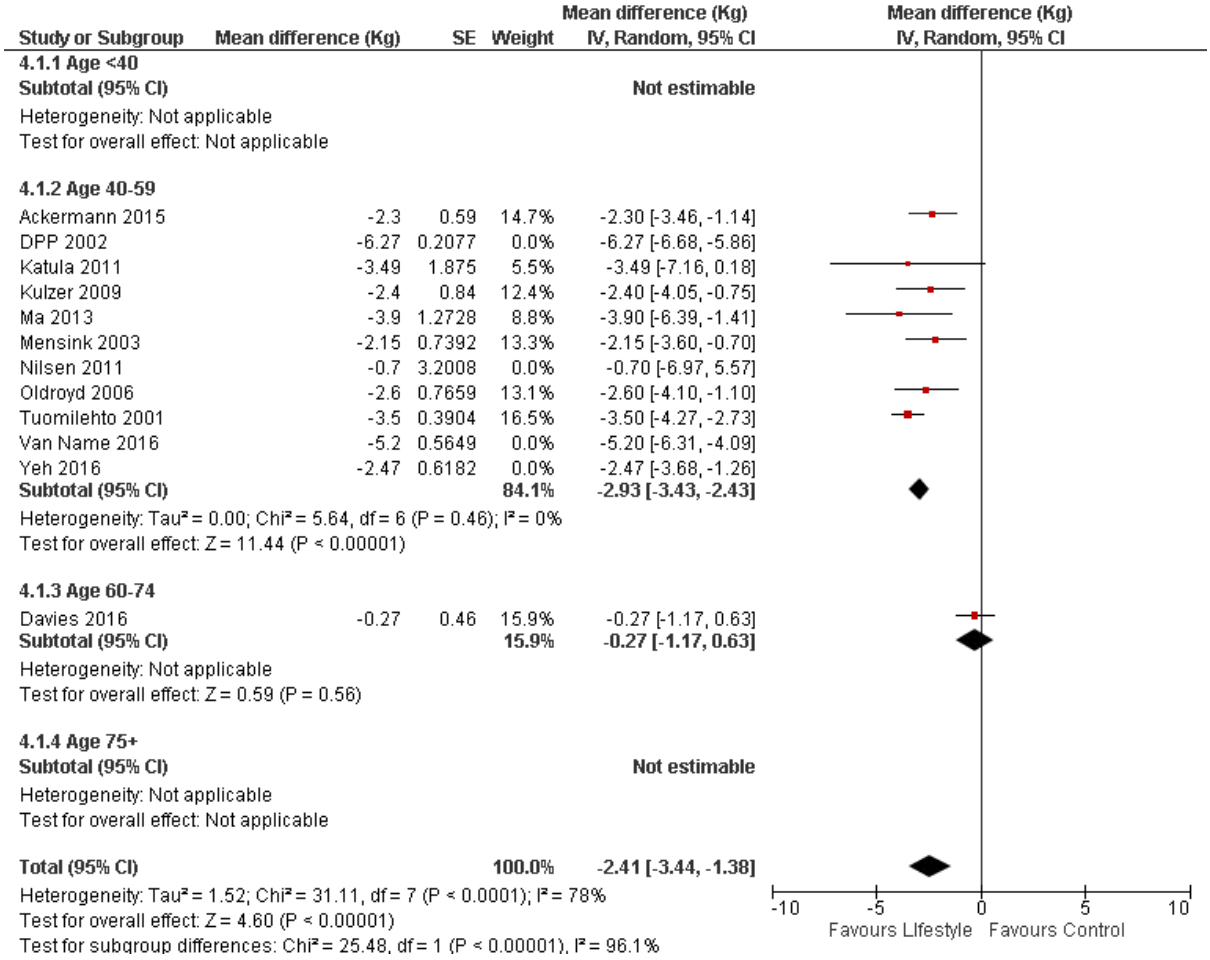


Figure 33: BMI subgroups: Change in weight (12 – 24 months)

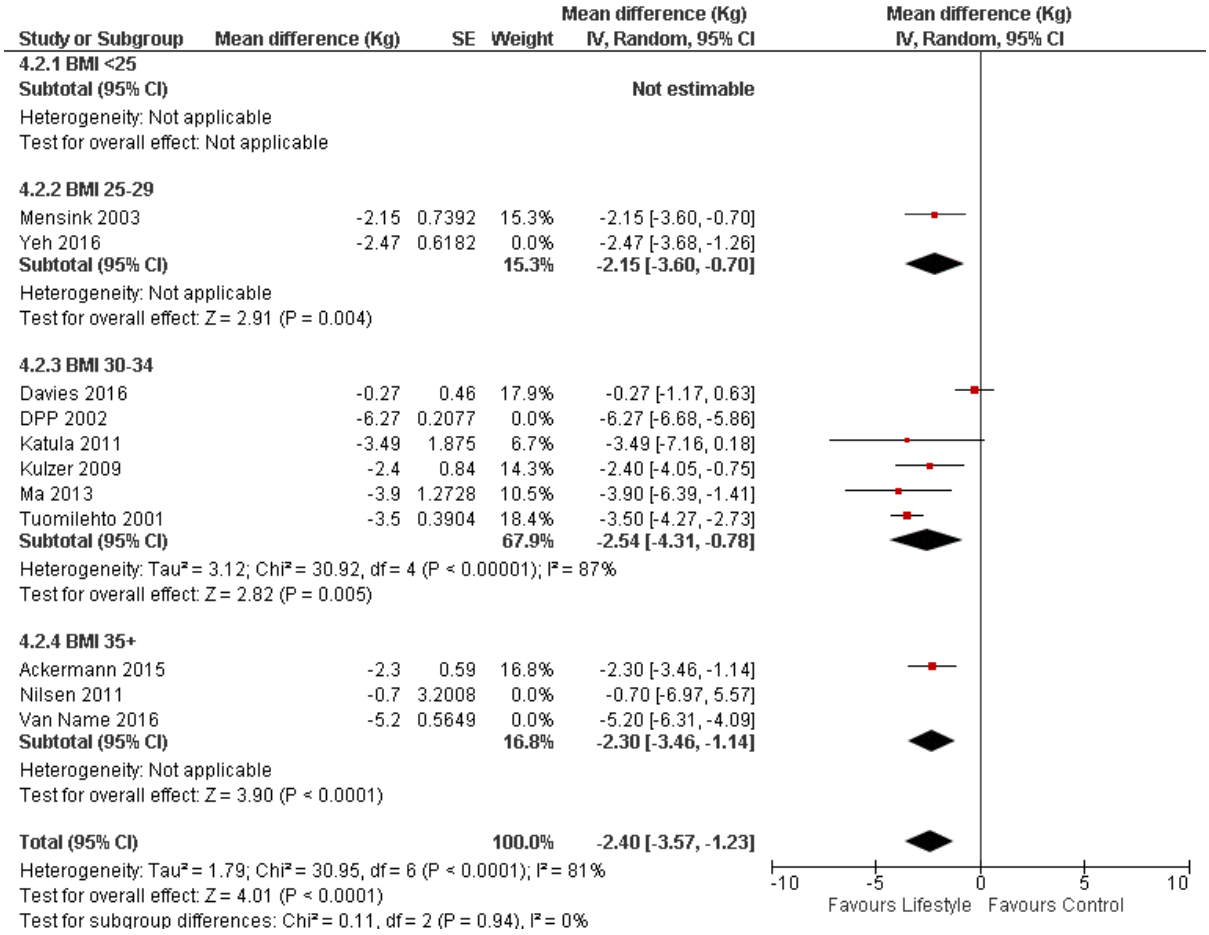


Figure 34: FPG subgroups: Change in weight (12 – 24 months)

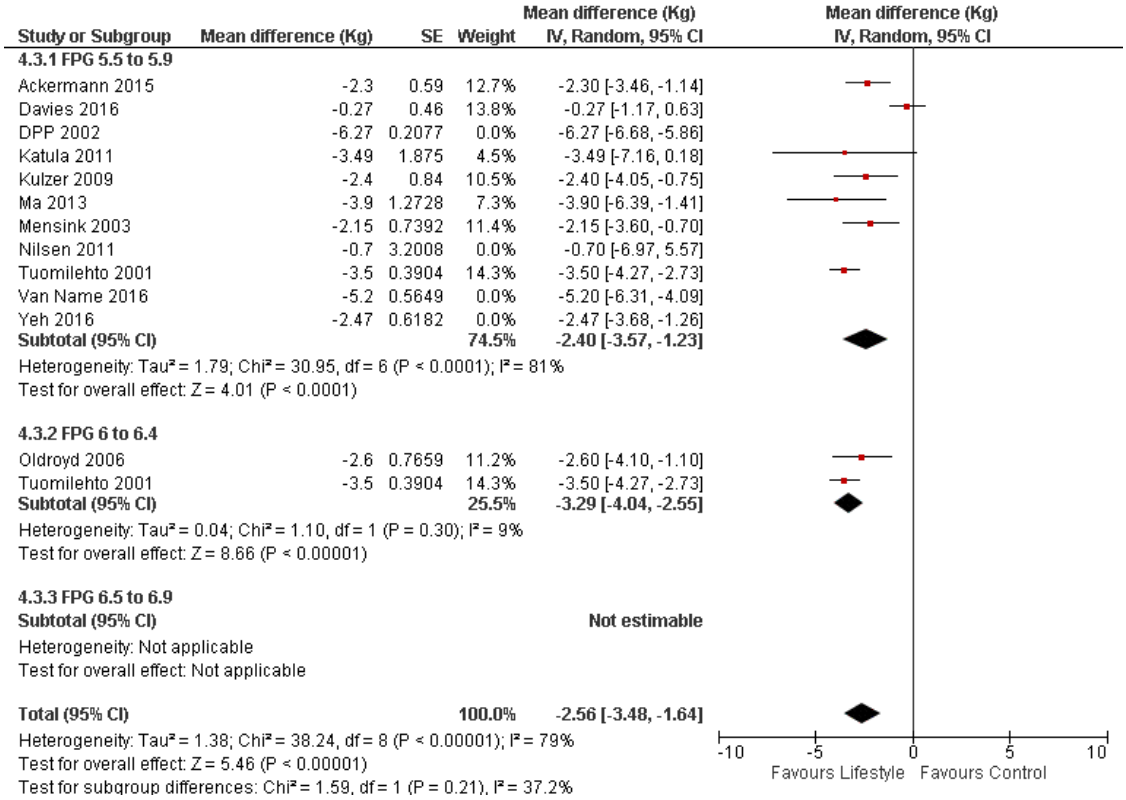


Figure 35: HbA1c subgroups: Change in weight (12 – 24 months)

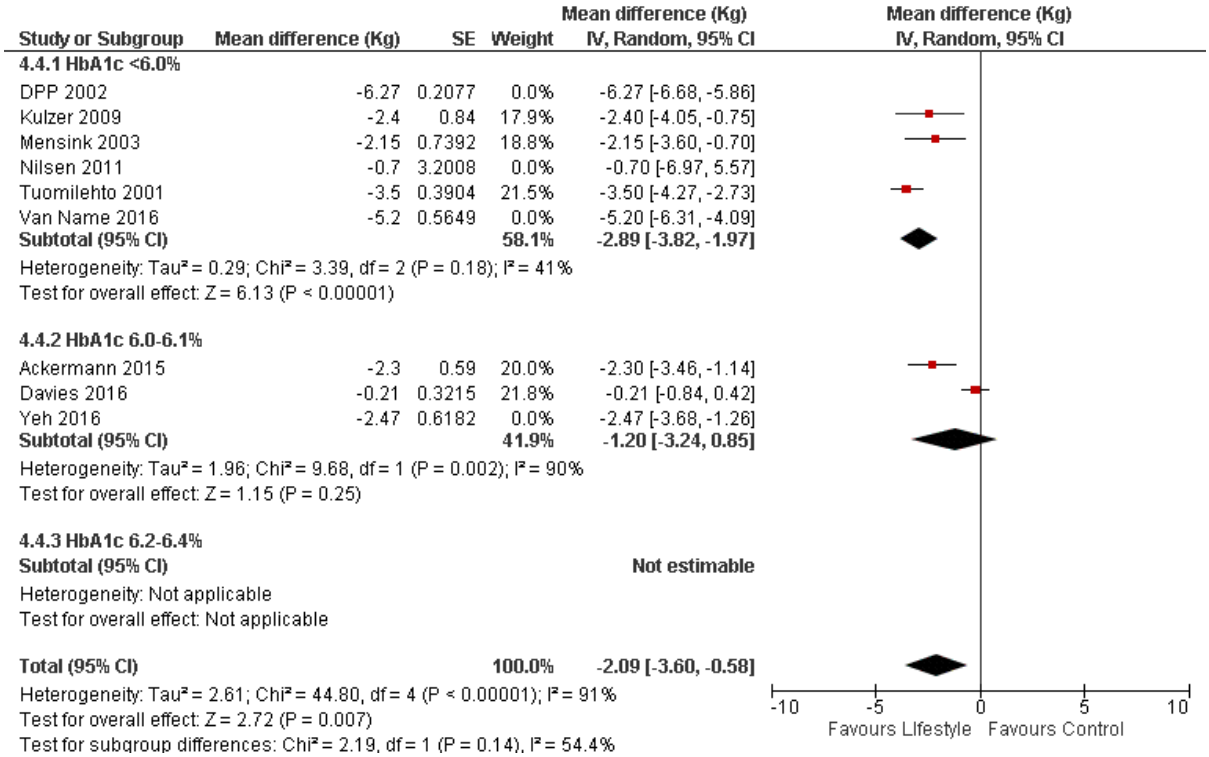


Figure 36: Age subgroups: Change in HbA1c (12 – 24 months)

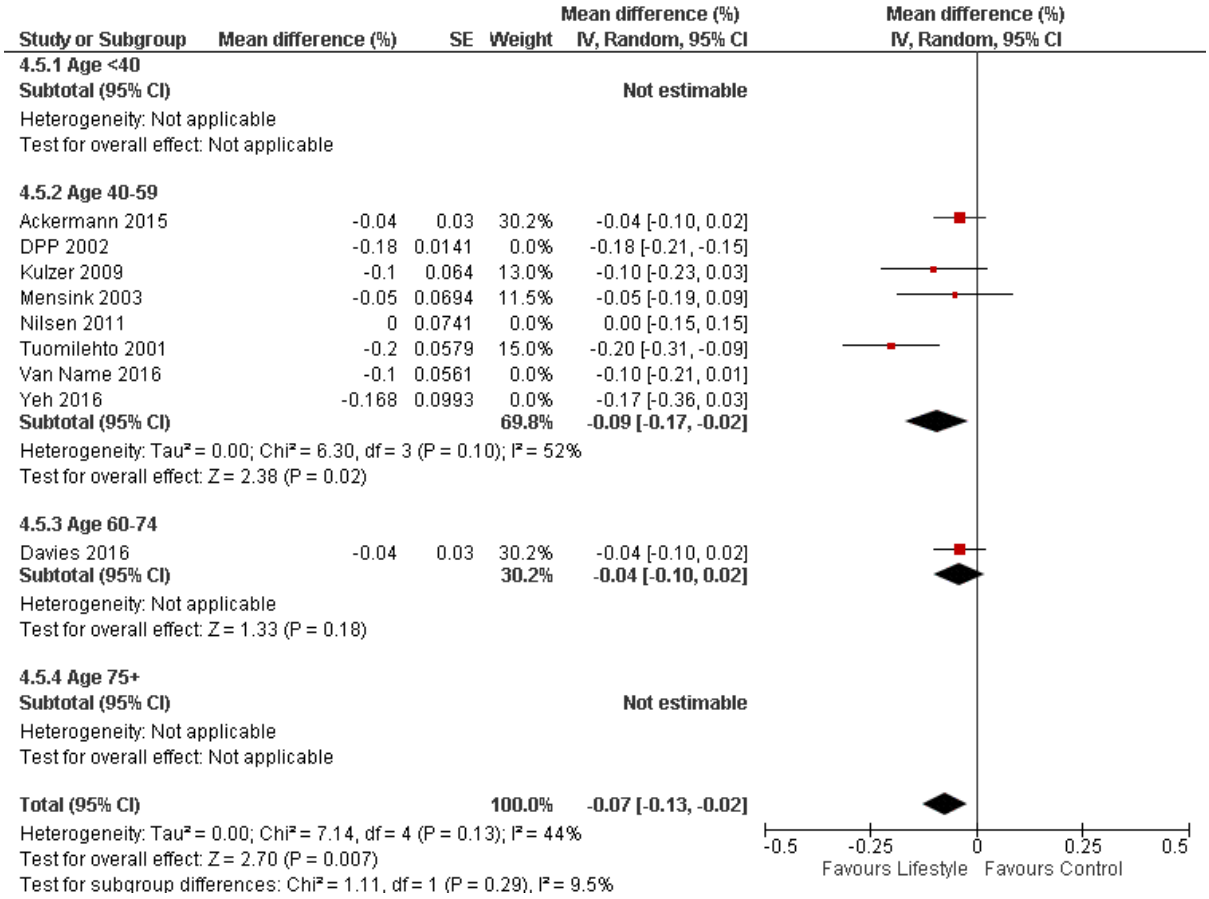


Figure 37: BMI subgroups: Change in HbA1c (12 – 24 months)

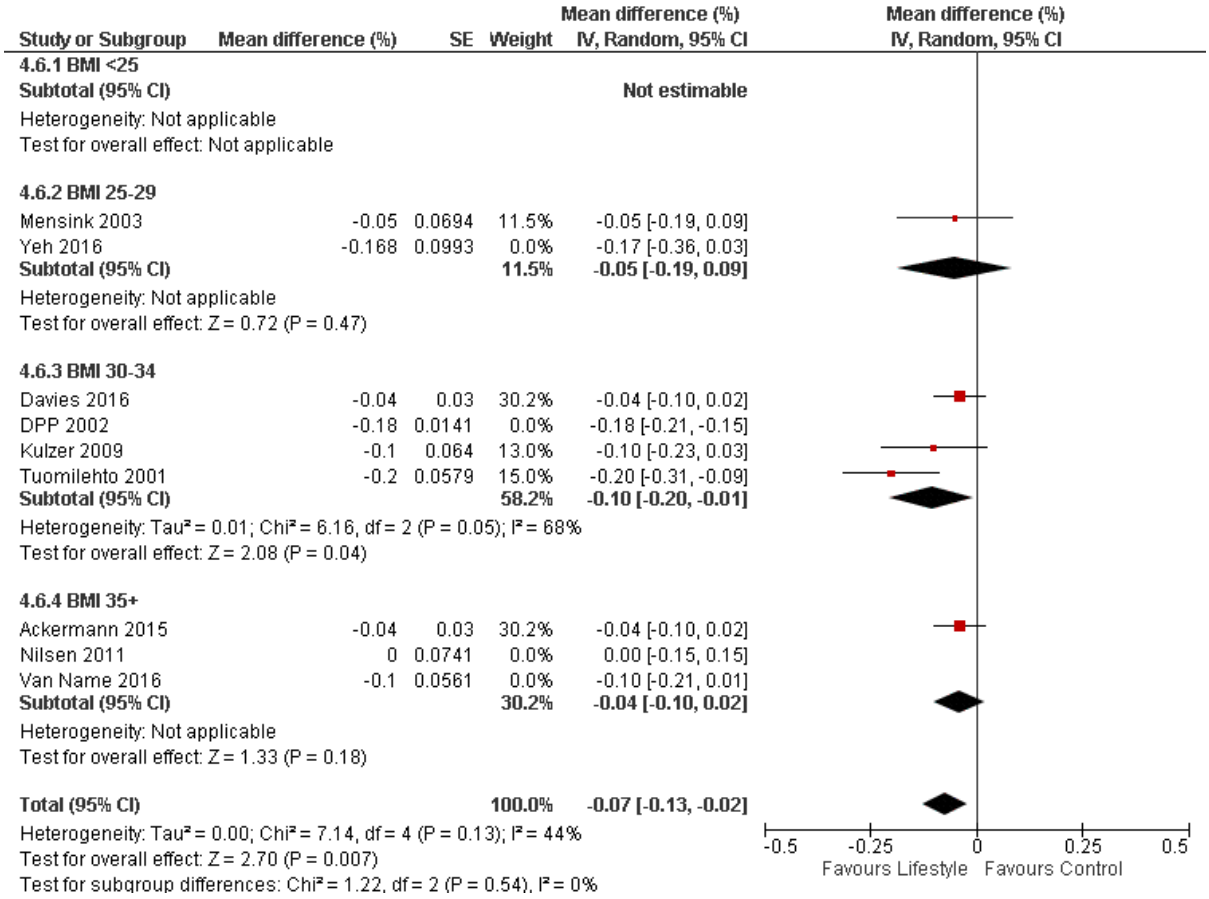


Figure 38: FPG subgroups: Change in HbA1c (12 – 24 months)

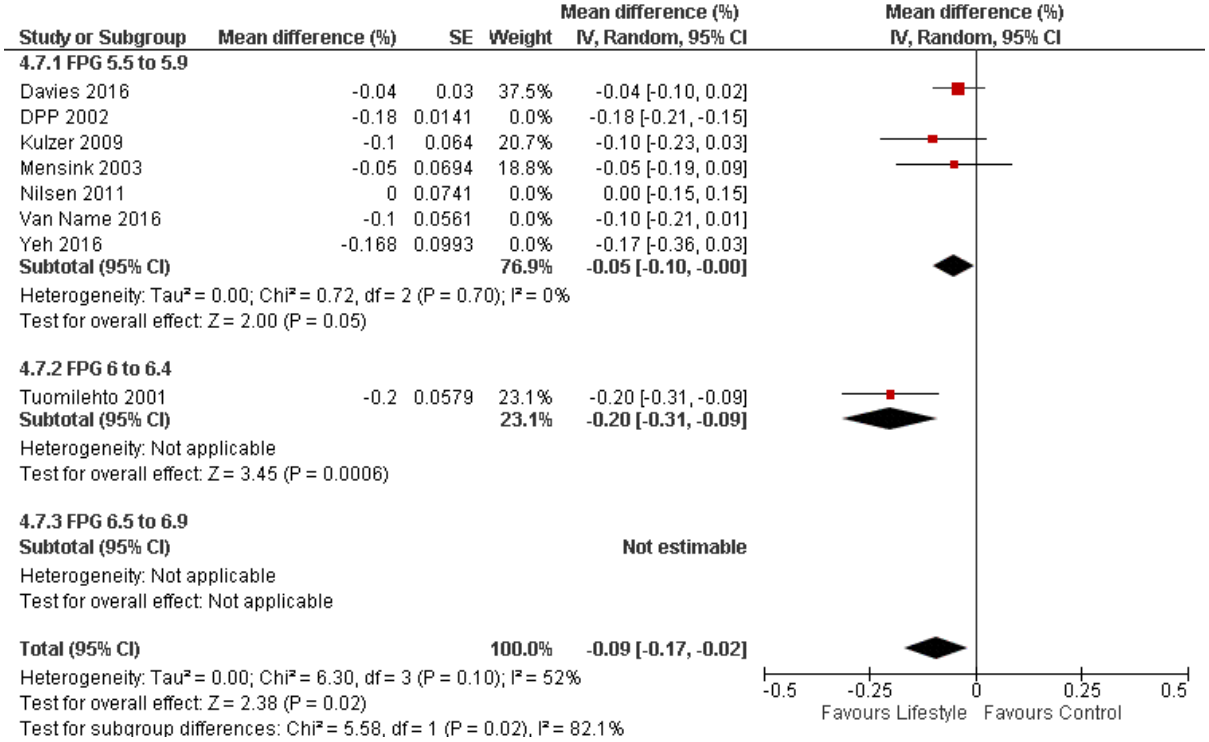
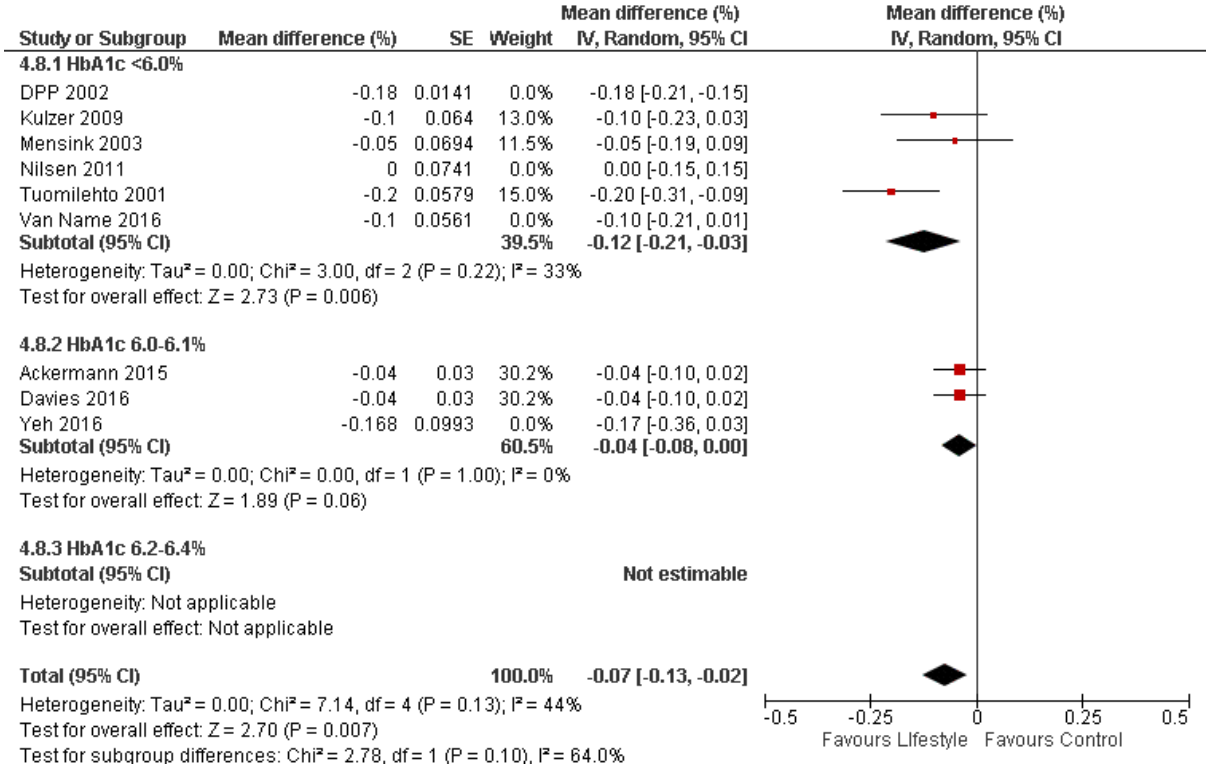


Figure 39: HbA1c subgroups: Change in HbA1c (12 – 24 months)



E.1.51 Digital lifestyle programme vs Control

Figure 40: Progression to type 2 diabetes (12 – 24 months)

Study or Subgroup	Digital lifestyle Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramachandran 2013	10	271	27	266	100.0%	0.36 [0.18, 0.74]
Total (95% CI)		**271**		**266**	**100.0%**	**0.36 [0.18, 0.74]**
Total events	10		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.81 (P = 0.005)

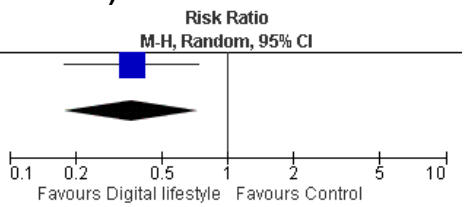


Figure 41: Progression to type 2 diabetes (24 months+)

Study or Subgroup	Digital lifestyle Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramachandran 2013	50	271	73	266	100.0%	0.67 [0.49, 0.92]
Total (95% CI)		**271**		**266**	**100.0%**	**0.67 [0.49, 0.92]**
Total events	50		73			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.45 (P = 0.01)

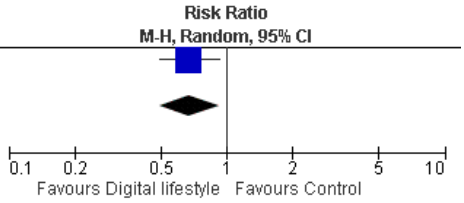


Figure 42: Change in weight (24 months+)

Study or Subgroup	Digital lifestyle Mean [Kg]	SD [Kg]	Total	Control Mean [Kg]	SD [Kg]	Total	Weight	Mean Difference IV, Random, 95% CI [Kg]
Ramachandran 2013	67.82	14.65	266	67.82	14.92	271	100.0%	0.00 [-2.50, 2.50]
Total (95% CI)			**266**			**271**	**100.0%**	**0.00 [-2.50, 2.50]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

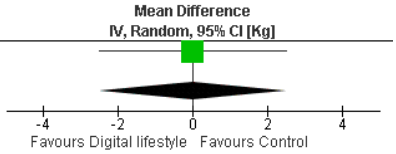


Figure 43: Systolic blood pressure (24 months+)

Study or Subgroup	Digital lifestyle Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ramachandran 2013	121.4	13	271	121.4	13	266	100.0%	0.00 [-2.20, 2.20]
Total (95% CI)			**271**			**266**	**100.0%**	**0.00 [-2.20, 2.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

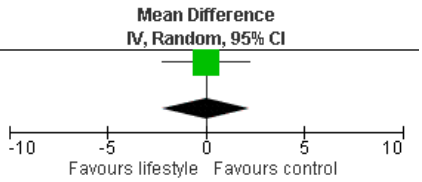
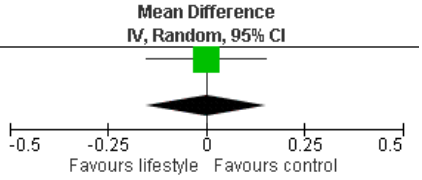


Figure 44: Total cholesterol (24 months+)

Study or Subgroup	Digital lifestyle Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ramachandran 2013	4.9	0.9	271	4.9	0.9	266	100.0%	0.00 [-0.15, 0.15]
Total (95% CI)			**271**			**266**	**100.0%**	**0.00 [-0.15, 0.15]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



2

1 Appendix F:GRADE tables

F.12 Review question 1

F.1.13 Metformin vs Control

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin	Control	Relative (95% CI)	Absolute	Quality
Progression to type 2 diabetes (24 months+)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	234/1073 (21.8%)	333/1082 (30.8%)	RR 0.71 (0.61 to 0.82)	89 fewer per 1000 (from 55 fewer to 120 fewer)	MODERATE
Change in weight (12-24 months) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	1015	1026	-	MD 2.27 lower (2.68 to 1.86 lower)	MODERATE
Change in weight (24 months+) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	964	972	-	MD 1.7 lower (2.12 to 1.28 lower)	MODERATE
Change in HbA1c (12-24 months) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	1013	1022	-	MD 0.09 lower (0.12 to 0.06 lower)	MODERATE
Change in HbA1c (24 months+) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	960	968	-	MD 0.09 lower (0.12 to 0.06 lower)	MODERATE
Change in FPG (12-24 months) (Better indicated by lower values)											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin	Control	Relative (95% CI)	Absolute	Quality
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	1017	1028	-	MD 0.26 lower (0.32 to 0.2 lower)	MODERATE
Change in FPG (24 months+) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	961	959	-	MD 0.25 lower (0.31 to 0.19 lower)	MODERATE
Adverse events - Gastrointestinal symptoms (12-24 months)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	no serious imprecision	none	344/1013 (34%)	170/1002 (17%)	RR 2 (1.7 to 2.35)	170 more per 1000 (from 119 more to 229 more)	MODERATE
Adverse events - Gastrointestinal symptoms (24 months+)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	no serious imprecision	none	2237/1073 (208.5%)	930/1082 (86%)	Rate ratio 2.53 (2.35 to 2.74)	1000 more per 1000 (from 1000 more to 1000 more)	MODERATE
Systolic blood pressure (24 months+) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	1073	1082	-	MD 0 higher (1.41 lower to 1.41 higher)	MODERATE
Total Cholesterol (24 months+) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	serious[4]	n/a[3]	none	1073	1082	-	MD 0.02 higher (0.05 lower to 0.09 higher)	MODERATE

1 [1] US DPP (2002)
2 [2] Single study
3 [3] Outcome (with associated imprecision) feeds directly into decision model
4 [4] Adherence rates in study higher than those expected in clinical practice (as judged by the expert opinion of the committee)

F.1.21 Intensive lifestyle vs control

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intensive lifestyle	Control	Relative (95% CI)	Absolute	Quality
Progression to type 2 diabetes (12-24 months)											
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	n/a[2]	none	8/493 (1.6%)	24/493 (4.9%)	RR 0.34 (0.15 to 0.75)	32 fewer per 1000 (from 12 fewer to 41 fewer)	HIGH
Progression to type 2 diabetes (24 months+)											
3[3]	randomised trials	no serious risk of bias	very serious[4]	no serious indirectness	n/a[2]	none	97/750 (12.9%)	137/747 (18.3%)	RR 0.63 (0.37 to 1.08)	68 fewer per 1000 (from 116 fewer to 15 more)	LOW
Change in weight (12-24 months) (Better indicated by lower values)*											
8[5]	randomised trials	no serious risk of bias	very serious[4]	no serious indirectness	n/a[2]	none	1256	1260	-	MD 2.41 lower (3.44 to 1.38 lower)	LOW
Change in weight (24 months+) (Better indicated by lower values)											
4[6]	randomised trials	no serious risk of bias	very serious[4]	no serious indirectness	n/a[2]	none	634	602	-	MD 1.71 lower (3.17 to 0.24 lower)	LOW
Change in HbA1c (12-24 months) (Better indicated by lower values)*											
5[7]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	n/a[2]	none	987	744	-	MD 0.07 lower (0.12 to 0.02 lower)	MODERATE
Change in HbA1c (24 months+) (Better indicated by lower values)											
3[9]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	n/a[2]	none	630	585	-	MD 0.09 lower (0.21 lower to 0.02 higher)	MODERATE
Change in FPG (12-24 months) (Better indicated by lower values)											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intensive lifestyle	Control	Relative (95% CI)	Absolute	Quality
7[10]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	n/a[2]	none	992	1000	-	MD 0.14 lower (0.24 to 0.05 lower)	MODERATE
Change in FPG (24 months+) (Better indicated by lower values)											
4[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	n/a[2]	none	642	608	-	MD 0.08 lower (0.16 lower to 0.01 higher)	HIGH
Change in systolic blood pressure (12-24 months) (Better indicated by lower values)											
6[11]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	n/a[2]	none	1075	1078	-	MD 1.33 lower (3.35 lower to 0.70 higher)	MODERATE
Change in systolic blood pressure (24 months+) (Better indicated by lower values)											
3[8]	randomised trials	no serious risk of bias	very serious[4]	no serious indirectness	n/a[2]	none	608	579	-	MD 1.72 lower (5.85 lower to 2.41 higher)	LOW
Change in total cholesterol (12-24 months) (Better indicated by lower values)											
7[12]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	n/a[2]	none	1096	1100	-	MD 0.04 lower (0.10 lower to 0.02 higher)	HIGH
Change in total cholesterol (24 months+) (Better indicated by lower values)											
4[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	n/a[2]	none	643	611	-	MD 0.09 lower (0.22 lower to 0.05 higher)	HIGH

*Subgroup results were considered not to be robust due to the level of additional between trial heterogeneity, and therefore pooled results are reported

[1] Katula 2011, Ma 2013, Tuomilehto 2001

[2] Outcome (with associated imprecision) feeds directly into decision model

[3] Davies 2016, Mensink 2003, Tuomilehto 2001

[4] $I^2 > 75\%$.

[5] Ackermann 2015, Davies 2016, Katula 2011, Kulzer 2009, Ma 2013, Mensink 2003, Oldroyd 2006, Tuomilehto 2001

[6] Davies 2016, Mensink 2003, Oldroyd 2006, Tuomilehto 2001

[7] Ackermann 2015, Davies 2016, Kulzer 2009, Mensink 2003, Tuomilehto 2001

[8] $I^2 > 40\%$

[9] Davies 2016, Mensink 2003, Tuomilehto 2001
[10] Davies 2016, Katula 2011, Kulzer 2009, Ma 2013, Mensink 2003, Oldroyd 2006, Tuomilehto 2001
[11] Ackermann 2015, Davies 2016, Kulzer 2009, Ma 2013, Mensink 2003, Tuomilehto 2001
[12] Ackermann 2015, Davies 2016, Kulzer 2009, Ma 2013, Mensink 2003, Oldroyd 2006, Tuomilehto 2001

F.1.35 Digital lifestyle vs control

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digital lifestyle	Control	Relative (95% CI)	Absolute	Quality
Progression to type 2 diabetes (12-24 months)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	very serious[3]	no serious imprecision	none	10/271 (3.7%)	27/266 (10.2%)	RR 0.36 (0.18 to 0.74)	65 fewer per 1000 (from 26 fewer to 83 fewer)	LOW
Progression to type 2 diabetes (24 months+)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	very serious[3]	serious[4]	none	50/271 (18.5%)	73/266 (27.4%)	RR 0.67 (0.49 to 0.92)	91 fewer per 1000 (from 22 fewer to 140 fewer)	VERY LOW
Change in weight (24 months+) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	very serious[3]	no serious imprecision	none	266	271	-	MD 0 higher (2.5 lower to 2.5 higher)	LOW
Systolic blood pressure (24 months+) (Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	n/a[2]	very serious[3]	no serious imprecision	none	271	266	-	MD 0 higher (2.2 lower to 2.2 higher)	LOW
Total Cholesterol (24 months+) (Better indicated by lower values)											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digital lifestyle	Control	Relative (95% CI)	Absolute	Quality
1[1]	randomised trials	no serious risk of bias	n/a[2]	very serious[3]	no serious imprecision	none	271	266	-	MD 0 higher (0.15 lower to 0.15 higher)	LOW

[1] Ramachandran 2013
[2] Single study
[3] Important differences between study population and UK population at risk of diabetes (study population was Indian men with relatively low BMI). Text messaging intervention also has limited applicability to mobile 'app' interventions currently implemented.
[4] Confidence intervals cross one minimally important difference.

F.26 Review question 2

F.2.17 Metformin

Quality assessment							No of patients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin	Effect	Quality
Uptake									
0	-	-	-	-	-	-	-	-	-
Adherence									
1[1]	randomised trials (non-comparative data from single arms)	no serious risk of bias	n/a[2]	serious[3]	no serious	none	1073	See Table 4 for adherence definitions and rates	VERY LOW
Dropout rate (indirect measure of adherence)									
3[4]	randomised trials (non-comparative data from single arms)	no serious risk of bias	very serious[5]	very serious[6]	no serious	none	1255	range=3.8% to 43%	VERY LOW

1 US DPP 2002

2 Data from single study
3 Adherence data from single arm of a randomised controlled trial of limited applicability to the real world, as trial population likely to be more motivated than general population.
4 Fontbonne 2009, Ramachandran 2006, Fontbonne 2009
5 Larger range of trial dropout rates greater than expected due to chance.
6 Dropout rates in a randomised controlled trial very indirect measure of adherence in the real world.

F.2.26 Intensive lifestyle intervention

Quality assessment							No of patients		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intensive lifestyle**	**Effect**	**Quality**
Uptake									
0	-	-	-	-	-	-	-	-	-
Adherence									
6[1]	randomised trials (non-comparative data from single arms)	no serious risk of bias	very serious[2]	serious[3]	no serious	none	1943	See Table 4 for adherence definitions and rates	VERY LOW
Dropout rate (indirect measure of adherence)									
10[4]	randomised trials (non-comparative data from single arms)	no serious risk of bias	very serious[5]	very serious[6]	no serious	none	2498	range=0% to 26%	VERY LOW

1 Ackermann 2015, Davies 2016, Mensink 2003, Oldroyd 2006, US DPP 2002, Van Name 2016
2 Large range of trial adherence rates and greater than expected due to chance (as judged by the reviewer).
3 Adherence data from single arm of a randomised controlled trial of limited applicability to the real world, as trial population likely to be more motivated than general population.
4 Ackermann 2015, Davies 2016, Katula 2011, Mensink 2003, Nielsen 2011, Oldroyd 2006, Tuomilehto 2001, US DPP 2002, Van Name 2016, Yeh 2016
5 Large range of trial dropout rates greater than expected due to chance (as judged by the reviewer).
6 Dropout rates in a randomised controlled trial very indirect measure of adherence in the real world.

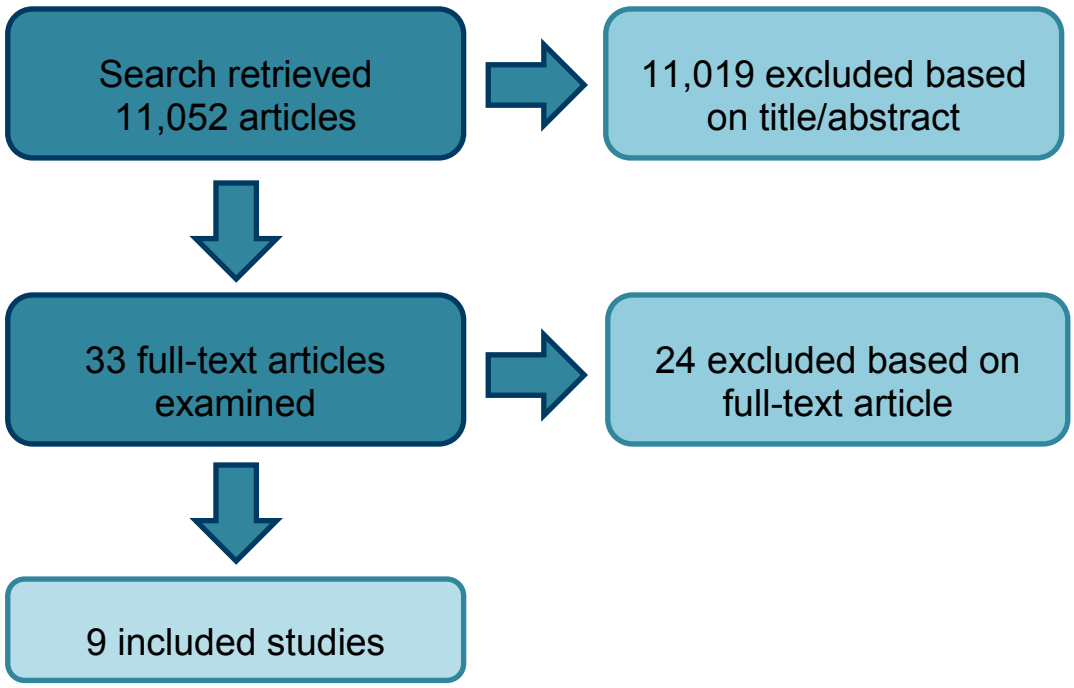
F.2.33 Digital lifestyle intervention

Quality assessment							No of patients		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Digital lifestyle**	**Effect**	**Quality**
Uptake									

Quality assessment							No of patients		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digital lifestyle	Effect	Quality
0	-	-	-	-	-	-	-	-	-
Adherence									
0	-	-	-	-	-	-	-	-	-
Dropout rate (indirect measure of adherence)									
1[1]	randomised trials (non-comparative data from single arms)	no serious risk of bias	n/a[2]	very serious[3]	no serious	none	271	10/271 (3.7%)	VERY LOW

1 *1 Ramachandran 2013*
2 *2 Single study*
3 *3 Dropout rates in a randomised controlled trial very indirect measure of adherence in the real world.*

Appendix G: Economic evidence study selection



Appendix H: Economic evidence tables

Bibliographic reference	**Diabetes Prevention Program Research Group. "Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes." Diabetes care 26.9 (2003): 2518-2523.**

Evaluation design

Interventions	Lifestyle intervention, metformin
Comparators	Placebo
Base-line cohort characteristics	Patients in the DPP trial – adults of at least 25 years of age with a BMI of 24 or higher and fasting plasma glucose concentration of 95 to 125mg/dL
Type of Analysis	Cost-utility
Structure	In-trial
Cycle length	N/A
Time horizon	3 years
Perspective	US health care system/societal perspective
Country	USA
Currency unit	USD
Cost year	2000
Discounting	None in base case, 3% in sensitivity analysis
Other comments	Analysis of DPP outcomes

Results

Outcomes from healthcare system perspective analysis:

Strategy	Cost	QALYs	Incremental cost (versus placebo)	Incremental QALYs (versus placebo)	ICER (versus placebo)
Placebo	$5,229	2.02	-	-	-
Metformin	$7,420	2.04	$2,191	0.022	$99,171
Lifestyle intervention	$7,498	2.09	$2,269	0.072	$31,512

<table>
<tr><td>Bibliographic reference</td><td colspan="2">Diabetes Prevention Program Research Group. "Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes." Diabetes care 26.9 (2003): 2518-2523.</td></tr>
<tr><td>Data sources</td><td colspan="2"><table>
<tr><td>Base-line data</td><td>N/A – costs and utilities taken directly from RCT</td></tr>
<tr><td>Effectiveness data</td><td>N/A – costs and utilities taken directly from RCT</td></tr>
<tr><td>Cost data</td><td>Medical costs associated with the DPP trial over 3 years</td></tr>
<tr><td>Utility data</td><td>Utilities were elicited using the Self-Administered Quality of Well-Being Index (QWB-SA) at yearly intervals during the DPP trial</td></tr>
</table></td></tr>
<tr><td>Uncertainty</td><td colspan="2"><table>
<tr><td>One-way sensitivity analysis</td><td><table>
<tr><th>Scenario</th><th>ICER – Lifestyle intervention versus placebo</th><th>ICER – Metformin versus placebo</th></tr>
<tr><td>‘No intervention’ used as comparator rather than placebo</td><td>$34,543</td><td>$109,531</td></tr>
<tr><td>50% reduction in personnel cost</td><td>$15,811</td><td>$56,814</td></tr>
<tr><td>20% reduction in intervention effectiveness</td><td>$39,389</td><td>$124,514</td></tr>
<tr><td>Lifestyle intervention delivered as group (assuming same effectiveness)</td><td>$8,982</td><td>-</td></tr>
<tr><td>3% discount rate used for costs and outcomes</td><td>$32,029</td><td>$102,164</td></tr>
</table></td></tr>
<tr><td>Probabilistic sensitivity analysis</td><td>N/A</td></tr>
</table></td></tr>
<tr><td>Applicability</td><td colspan="2">Partially Applicable

This study compares the relevant outcomes, but is only partially applicable due to the non-UK setting and lack of outcomes stratified by patient subgroups</td></tr>
<tr><td>Limitations</td><td colspan="2">Potentially serious limitations

This study suffers from the limitation of a short time horizon (3 years).</td></tr>
</table>

Bibliographic reference	**Diabetes Prevention Program Research Group. "Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes." Diabetes care 26.9 (2003): 2518-2523.**
Conflicts	**None listed**

1

Bibliographic reference	**Diabetes Prevention Program Research Group. "The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention." Diabetes care 35.4 (2012): 723-730.**
Evaluation design	

Interventions	Lifestyle intervention, metformin
Comparators	Placebo
Base-line cohort characteristics	Patients in the DPP/DPPOS trial – adults of at least 25 years of age with a BMI of 24 or higher and fasting plasma glucose concentration of 95 to 125mg/dL
Type of Analysis	Cost-utility
Structure	In-trial
Cycle length	N/A
Time horizon	10 years
Perspective	US health care system/societal perspective
Country	USA
Currency unit	USD
Cost year	2010
Discounting	None in base case, 3% in sensitivity analysis
Other comments	Analysis of DPP and DPPOS outcomes

<table>
<tr><td>Bibliographic reference</td><td>Diabetes Prevention Program Research Group. "The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention." Diabetes care 35.4 (2012): 723-730.</td></tr>
<tr><td>Results</td><td>Outcomes from healthcare system perspective analysis, discounted at 3%:
<table>
<tr><th>Strategy</th><th>Incremental cost</th><th>Incremental QALYs</th><th>ICER</th></tr>
<tr><td>Lifestyle intervention versus placebo</td><td>$1,226</td><td>0.12</td><td>$10,037</td></tr>
<tr><td>Metformin versus placebo</td><td>-$159</td><td>0.02</td><td>Dominates</td></tr>
<tr><td>Lifestyle intervention versus metformin</td><td>$1,384</td><td>0.10</td><td>$13,420</td></tr>
</table></td></tr>
<tr><td>Data sources</td><td>
<table>
<tr><td>Base-line data</td><td>N/A – costs and utilities taken directly from RCT</td></tr>
<tr><td>Effectiveness data</td><td>N/A – costs and utilities taken directly from RCT</td></tr>
<tr><td>Cost data</td><td>Medical costs associated with the DPP trial over first 3 years and DPPOS trial over remaining years</td></tr>
<tr><td>Utility data</td><td>Utilities were elicited using the Self-Administered Quality of Well-Being Index (QWB-SA) at yearly intervals during the DPP and DPPOS trials</td></tr>
</table></td></tr>
<tr><td>Uncertainty</td><td>
<table>
<tr><td>One-way sensitivity analysis</td><td>ICERs with no discounting:
Lifestyle versus placebo: $6,651
Metformin versus placebo: Dominates
Lifestyle intervention versus metformin: $10,555</td></tr>
<tr><td>Probabilistic sensitivity analysis</td><td>N/A</td></tr>
</table></td></tr>
<tr><td>Applicability</td><td>Partially Applicable

This study compares the relevant outcomes, but is only partially applicable due to the non-UK setting and lack of outcomes stratified by patient subgroups</td></tr>
</table>

Bibliographic reference	**Diabetes Prevention Program Research Group. "The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention." Diabetes care 35.4 (2012): 723-730.**
Limitations	**Minor limitations** This study is categorised as having only minor limitations as, although the time horizon does not extend to patients' entire lifetimes, results demonstrate that lifestyle intervention is clearly cost effective, and extending the time horizon would only result in lower ICERs.
Conflicts	**None listed**

1

Bibliographic reference	**Eddy, David M., Leonard Schlessinger, and Richard Kahn. "Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes." Annals of Internal medicine 143.4 (2005): 251-264.**
Evaluation design	

Interventions	Lifestyle intervention as per DPP, lifestyle intervention in patients whose fasting plasma glucose exceeds 125mg/dL, metformin
Comparators	Control
Base-line cohort characteristics	Patients equivalent to those in the DPP trial – adults of at least 25 years of age with a BMI of 24 or higher and fasting plasma glucose concentration of 95 to 125mg/dL
Type of Analysis	Cost-utility
Structure	Individual patient simulation (Archimedes model)
Cycle length	N/A
Time horizon	30 years
Perspective	Societal perspective
Country	USA
Currency unit	USD
Cost year	2010
Discounting	3%
Other comments	-

Bibliographic reference	**Eddy, David M., Leonard Schlessinger, and Richard Kahn. "Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes." Annals of Internal medicine 143.4 (2005): 251-264.**

Results

Outcomes from societal perspective, discounted at 3%:

Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Baseline	$37,171	11.319	-	-	-
Only initiate lifestyle intervention when FPG level >125mg/dL	$40,237	11.444	$3,066	0.125	$24,523
DPP lifestyle	$47,140	11.478	$6,903	0.034	$201,818
Metformin	$41,189	11.432	Dominated	Dominated	Dominated

Data sources

Base-line data	Data used to populate the Archimedes model were derived from a variety of empirical sources identified via literature review
Effectiveness data	Data on the effectiveness of interventions in reducing weight and blood pressure, improving LDL cholesterol, HDL cholesterol, and total cholesterol levels, and decreasing fasting plasma glucose levels were taken from a range of sources and used to simulate the effectiveness of interventions
Cost data	Cost data were sourced from the DPP trial
Utility data	Utilities were elicited using the Self-Administered Quality of Well-Being Index (QWB-SA) at yearly intervals during the DPP and DPPOS trials

Uncertainty

One-way sensitivity analysis	The analysis provides a healthcare system perspective ICER of around $143,000/QALY for the DPP lifestyle intervention compared to control. In addition, a number of one-way sensitivity analyses were conducted on this ICER. Of these, the only analysis which substantially changed the base case value was the assumption that patients are provided with group lifestyle intervention (with the same outcomes), which provided an ICER of around $39,000/QALY over 30 years.
Probabilistic sensitivity analysis	The study provides a narrative discussion of probabilistic sensitivity analysis, and concludes that results are robust.

Bibliographic reference	**Eddy, David M., Leonard Schlessinger, and Richard Kahn. "Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes." Annals of Internal medicine 143.4 (2005): 251-264.**
Applicability	**Partially Applicable** This study compares the relevant outcomes, but is only partially applicable due to the non-UK setting and lack of outcomes stratified by patient subgroups
Limitations	**Minor limitations** This study is categorised as having only minor limitations, due to using a validated economic model with appropriately sourced data, and an appropriately long timeline.
Conflicts	**The analysis was funded by Kaiser Permanente. The validation of the Archimedes model was funded by a grant from the American Diabetes Association, supported in part by Bristol-Myers Squibb**

1

Bibliographic reference	**Gillett, Michael, et al. "Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation." Health technology assessment 16.33 (2012).**
Evaluation design	

Interventions	Lifestyle intervention (as per Finnish DPS)
Comparators	Control
Base-line cohort characteristics	Adults with impaired glucose tolerance of age 45-65 years
Type of Analysis	Cost-utility
Structure	Individual patient simulation (Sheffield type 2 diabetes model)
Cycle length	N/A
Time horizon	Lifetime
Perspective	Healthcare system
Country	UK
Currency unit	GBP

Bibliographic reference	**Gillett, Michael, et al. "Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation." Health technology assessment 16.33 (2012).**

Cost year	2008
Discounting	Not specified – assumed 3.5%
Other comments	-

Results

Strategy	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
Control	£14,104	11.1986	-	-	-
Lifestyle	£14,224	11.2649	£121	0.0663	£1,819

Data sources

Base-line data	Baseline disease natural history data were taken from the Finnish DPS and UKDPS
Effectiveness data	Data on the effectiveness of interventions were taken from the Finnish DPS
Cost data	Cost data were sourced from a mixture of the Finnish DPS (converted into GBP) and from standard NHS unit cost sources
Utility data	Utility gains from weight loss and utility decrements relating to comorbidities were taken from a range of UK studies and economic analyses, including from the UKPDS

Uncertainty

One-way sensitivity analysis	Sensitivity analyses of assumptions regarding treatment pathways, treatment benefit, diabetes progression, and cardiovascular risk showed that the cost effectiveness of lifestyle intervention is robust. A 'pessimistic scenario', which included assumptions that diabetes incidence curves for the two interventions converged at year 20, lifestyle intervention was less effective, only 0.001 utility loss per kg weight gained, and three annual visits are required for reinforcement of lifestyle changes after year four, resulted in an ICER of £16,720/QALY.
Probabilistic sensitivity analysis	N/A

Bibliographic reference	**Gillett, Michael, et al. "Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation." Health technology assessment 16.33 (2012).**
Applicability	**Partially applicable** This study is relevant to the NHS, but is categorised as partially applicable due to not considering metformin and lacking outcomes stratified by patient subgroups.
Limitations	**Minor limitations** This study is categorised as having only minor limitations, due to using a detailed model with appropriately sourced data and an appropriately long time horizon.
Conflicts	**None listed**

1

2

Bibliographic reference	**Herman, William H., et al. "The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance." Annals of internal medicine 142.5 (2005): 323-332.**
Evaluation design	

Interventions	Lifestyle intervention, metformin
Comparators	Placebo
Base-line cohort characteristics	Patients in the DPP trial – adults of at least 25 years of age with a BMI of 24 or higher and fasting plasma glucose concentration of 95 to 125mg/dL
Type of Analysis	Cost-utility
Structure	Markov model
Cycle length	1 year
Time horizon	Lifetime
Perspective	Healthcare system/societal
Country	USA

Bibliographic reference	**Herman, William H., et al. "The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance." Annals of internal medicine 142.5 (2005): 323-332.**

Currency unit	USD
Cost year	2000
Discounting	3%
Other comments	-

Results

Outcomes from healthcare system perspective analysis, discounted at 3%:

Strategy	Cost	Effect	Incremental cost (versus placebo)	Incremental QALYs (versus placebo)	ICER (versus placebo)
Placebo	$51,339	10.32	-	-	-
Lifestyle intervention	$51,974	10.89	$635	0.57	$1,124
Metformin	$55,261	10.45	$3,922	0.13	$31,286

Data sources

Base-line data	Complications and comorbid conditions associated with impaired glucose tolerance were derived from the DPP. Complications and comorbid conditions associated with undiagnosed/diagnosed diabetes were derived from the UKPDS
Effectiveness data	Effectiveness data were sourced from the DPP trial
Cost data	Costs of impaired glucose tolerance were taken from a previous analysis of costs associated with DPP outcomes. Data for diabetes were taken from an analysis of costs associated with type 2 diabetes
Utility data	Utilities associated with impaired glucose tolerance were taken from DPP data (elicited using the Self-Administered Quality of Well-Being Index (QWB-SA)). Utilities associated with type 2 diabetes were taken from a previous analysis of health-related quality of life associated with diabetes.

Bibliographic reference	**Herman, William H., et al. "The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance." Annals of internal medicine 142.5 (2005): 323-332.**
Uncertainty	

One-way sensitivity analysis

Scenario	ICER – Lifestyle intervention versus placebo	ICER – Metformin versus placebo
Age 25-44 years	Dominates	9,573
Age 45-54 years	781	30,013
Age 55-64 years	3409	64,904
Age 65-74 years	6646	173,593
Age ≥ 75 years	11,700	273,207
Reduced cost (group therapy for lifestyle and generic metformin)	Dominates	1,755
50% reduced effectiveness	7,886	52,562

Probabilistic sensitivity analysis: N/A

Applicability

Partially Applicable

This study compares the relevant outcomes, but is only partially applicable due to the non-UK setting and lack of outcomes stratified by patient subgroups

Limitations

Minor limitations

This study uses appropriate data sources, model structure, and time horizon, but is limited by the lack of probabilistic sensitivity analysis.

Bibliographic reference	**Herman, William H., et al. "The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance." Annals of internal medicine 142.5 (2005): 323-332.**
Conflicts	**Grant Support: By the Diabetes Prevention Program, National Institutes of Health through the National Institute of Diabetes and Digestive and Kidney Diseases, Office of Research on Minority Health, National Institute of Child Health and Human Development, and National Institute on Aging; Centers for Disease Control and Prevention; Indian Health Service; General Clinical Research Program; National Center for Research Resources; American Diabetes Association; Bristol-Myers Squibb; and Parke-Davis.**

1

Bibliographic reference	**Herman, William H., et al. "Effectiveness and cost-effectiveness of diabetes prevention among adherent participants." The American journal of managed care 19.3 (2013): 194.**
Evaluation design	

Interventions	Lifestyle intervention, metformin
Comparators	Placebo
Base-line cohort characteristics	Patients in the DPP trial – adults of at least 25 years of age with a BMI of 24 or higher and fasting plasma glucose concentration of 95 to 125mg/dL who were adherent to their assigned treatment
Type of Analysis	Cost-utility
Structure	In-trial
Cycle length	N/A
Time horizon	10 years
Perspective	Healthcare system/societal
Country	USA
Currency unit	USD
Cost year	2010
Discounting	None in base case, 3% in sensitivity analysis
Other comments	Analysis of DPP and DPPOS outcomes

Bibliographic reference	**Herman, William H., et al. "Effectiveness and cost-effectiveness of diabetes prevention among adherent participants." The American journal of managed care 19.3 (2013): 194.**

Results

Outcomes from healthcare system perspective analysis, undiscounted:

Strategy	Cost	QALYs	Incremental cost (versus placebo)	Incremental QALYs (versus placebo)	ICER (versus placebo)
Placebo	$2,8236	6.67	-	-	-
Lifestyle intervention	$28,028	6.80	-$210	0.14	Dominates
Metformin	$27,151	6.74	-$1,086	0.08	Dominates

Data sources

Base-line data	N/A – costs and utilities taken directly from RCT
Effectiveness data	N/A – costs and utilities taken directly from RCT
Cost data	Medical costs associated with the DPP trial over first 3 years and DPPOS trial over remaining years
Utility data	Utilities were elicited using the Self-Administered Quality of Well-Being Index (QWB-SA) at yearly intervals during the DPP and DPPOS trials

Uncertainty

One-way sensitivity analysis	ICERs with 3% discounting: • Lifestyle versus placebo: $19,988 • Metformin versus placebo: $20,183 Making the assumption that lifestyle intervention is delivered as group treatment (with the same effectiveness) results in lifestyle dominating placebo with no discounting and an ICER of $9,688/QALY versus placebo with a discount rate of 3% per year.
Probabilistic sensitivity analysis	N/A

Applicability

Partially Applicable

This study compares the relevant outcomes, but is only partially applicable due to the non-UK setting and lack of outcomes stratified by patient subgroups

Bibliographic reference	**Herman, William H., et al. "Effectiveness and cost-effectiveness of diabetes prevention among adherent participants." The American journal of managed care 19.3 (2013): 194.**
Limitations	**Minor limitations** This study is categorised as having only minor limitations as, although the time horizon does not extend to patients' entire lifetimes, results demonstrate that lifestyle intervention is clearly cost effective, and extending the time horizon would only result in lower ICERs.
Conflicts	**Grant Support: By the Diabetes Prevention Program, National Institutes of Health through the National Institute of Diabetes and Digestive and Kidney Diseases, Office of Research on Minority Health, National Institute of Child Health and Human Development, and National Institute on Aging; Centers for Disease Control and Prevention; Indian Health Service; General Clinical Research Program; National Center for Research Resources; American Diabetes Association; Bristol-Myers Squibb; and Parke-Davis.**

1

Bibliographic reference	**Palmer, A. J., and D. M. D. Tucker. "Cost and clinical implications of diabetes prevention in an Australian setting: a long-term modeling analysis." Primary care diabetes 6.2 (2012): 109-121.**
Evaluation design	

Interventions	Lifestyle intervention, metformin
Comparators	Standard care (control)
Base-line cohort characteristics	Patients in the DPP/DPPOS trial – adults of at least 25 years of age with a BMI of 24 or higher and fasting plasma glucose concentration of 95 to 125mg/dL
Type of Analysis	Cost-utility
Structure	Markov model
Cycle length	One year
Time horizon	Lifetime
Perspective	3rd party payer perspective
Country	Australia

Bibliographic reference	**Palmer, A. J., and D. M. D. Tucker. "Cost and clinical implications of diabetes prevention in an Australian setting: a long-term modeling analysis." Primary care diabetes 6.2 (2012): 109-121.**

Currency unit	AUD
Cost year	2009
Discounting	5%
Other comments	Analysis using DPP and DPPOS outcomes

Results

Outcomes from healthcare system perspective analysis, undiscounted:

Strategy	Cost	QALYs	Incremental cost (versus placebo)	Incremental QALYs (versus placebo)	ICER (versus placebo)
Control	$62,380	10.82	-	-	-
Lifestyle intervention	$62,091	11.21	-$289	0.39	Dominates
Metformin	$63,597	10.94	$1,217	0.12	$10,142

Data sources

Base-line data	Progression rates from impaired glucose tolerance to type 2 diabetes were derived from the DPP and DPPOS trials.
Effectiveness data	Relative effectiveness data were derived from the DPP and DPPOS trials.
Cost data	Resource utilisation data for patients with impaired glucose tolerance were taken from the DPP and DPPOS trials, coupled with Australian-specific unit costs. Costs of diabetes were taken from a previous economic analysis of type 2 diabetes costs in Australia.
Utility data	State-dependent utilities were taken from Australian-specific age-dependent health state utility data. Treatment-specific improvements in health utility were taken from Herman et al (2005).

Uncertainty

One-way sensitivity analysis

Scenario	ICER – Lifestyle intervention versus placebo	ICER – Metformin versus placebo

Bibliographic reference	**Palmer, A. J., and D. M. D. Tucker. "Cost and clinical implications of diabetes prevention in an Australian setting: a long-term modeling analysis." Primary care diabetes 6.2 (2012): 109-121.**
	<table><tr><td></td><td><table><tr><td>Annual rate of progression to diabetes set to the overall rate across DPP and DPPOS</td><td>$9,531</td><td>$32,400</td></tr><tr><td>Annual rate of progression to diabetes returns to control rate after 10 years</td><td>Dominant</td><td>$9,883</td></tr><tr><td>Costs of interventions increased by 20%</td><td>$2,702</td><td>$17,767</td></tr><tr><td>Generic metformin used</td><td>N/A</td><td>$8,908</td></tr></table></td></tr><tr><td>Probabilistic sensitivity analysis</td><td>At a threshold of $50,000/QALY the probability of metformin and lifestyle intervention being cost effective is 78% and 100%, respectively</td></tr></table>
Applicability	**Partially Applicable** This study compares the relevant outcomes, but is only partially applicable due to the non-UK setting and lack of outcomes stratified by patient subgroups
Limitations	**Minor limitations** This study is categorised as having only minor limitations as it uses appropriate data sources, model structure, and time horizon.
Conflicts	**None listed**

1

Bibliographic reference	Png, May Ee, and Joanne Su-Yin Yoong. "Evaluating the cost-effectiveness of lifestyle modification versus metformin therapy for the prevention of diabetes in Singapore." PloS one 9.9 (2014): e107225.

Evaluation design

Interventions	Lifestyle intervention, metformin
Comparators	Placebo
Base-line cohort characteristics	Patients in the DPP trial – adults of at least 25 years of age with a BMI of 24 or higher and fasting plasma glucose concentration of 95 to 125mg/dL
Type of Analysis	Cost-utility
Structure	Decision tree
Cycle length	N/A
Time horizon	3 years
Perspective	Healthcare system perspective
Country	Singapore
Currency unit	USD
Cost year	2012
Discounting	3%
Other comments	Analysis using DPP outcomes

Results

Strategy	Cost	QALYs	Incremental cost (versus placebo)	Incremental QALYs (versus placebo)	ICER (versus placebo)
Placebo	$8,050	1.98	-	-	-
Lifestyle intervention	$8,896	2.03	$846	0.05	$16,920
Metformin	$8,331	1.99	$281	0.01	$28,100

Bibliographic reference	**Png, May Ee, and Joanne Su-Yin Yoong. "Evaluating the cost-effectiveness of lifestyle modification versus metformin therapy for the prevention of diabetes in Singapore." PloS one 9.9 (2014): e107225.**	
Data sources	**Base-line data**	N/A – costs and utilities taken directly from RCT
	Effectiveness data	N/A – costs and utilities taken directly from RCT
	Cost data	Resource utilisation data were taken from the DPP study, unit costs were taken from Singapore-specific sources
	Utility data	Utilities were taken from the DPP study (elicited using the Self-Administered Quality of Well-Being Index (QWB-SA) at yearly intervals)
Uncertainty	**One-way sensitivity analysis**	Deterministic sensitivity analyses were carried out in which the QALYs associated with each intervention were varied, and showed that ICERs were inversely related to QALY gain.
	Probabilistic sensitivity analysis	N/A
Applicability	**Partially Applicable** This study compares the relevant outcomes, but is only partially applicable due to the non-UK setting and lack of outcomes stratified by patient subgroups	
Limitations	**Potentially serious limitations** This study is limited by a non-lifetime time horizon and a lack of probabilistic sensitivity analysis	
Conflicts	**None listed**	

1

Bibliographic reference	**Zhuo, Xiaohui, et al. "Cost-effectiveness of alternative thresholds of the fasting plasma glucose test to identify the target population for type 2 diabetes prevention in adults aged≥ 45 years." Diabetes care 36.12 (2013): 3992-3998. APA**

Evaluation design

Interventions	Lifestyle intervention
Comparators	Varying thresholds of fasting plasma glucose for lifestyle intervention
Base-line cohort characteristics	Nationally representative sample of nondiabetic US adults aged ≥45 years
Type of Analysis	Cost-utility
Structure	Markov model – individual patient simulation
Cycle length	One year
Time horizon	Lifetime
Perspective	Healthcare system perspective
Country	USA
Currency unit	USD
Cost year	2012
Discounting	3%
Other comments	Analysis using DPP outcomes

Results

FPG threshold (mg/dL)	Cost	QALYs	Incremental cost	Incremental QALYs	ICER
120	$59,100	10.69	-	-	-
115	$59,400	10.70	$300	0.01	$30,100
110	$60,000	10.72	$600	0.02	$32,900
105	$60,900	10.74	$900	0.02	$42,300
100	$62,300	10.77	$1,400	0.03	$60,700
95	$64,100	10.79	$1,800	0.02	$81,800
90	$65,800	10.8	$1,700	0.01	$115,800

Bibliographic reference	**Zhuo, Xiaohui, et al. "Cost-effectiveness of alternative thresholds of the fasting plasma glucose test to identify the target population for type 2 diabetes prevention in adults aged≥ 45 years." Diabetes care 36.12 (2013): 3992-3998.** **APA**
Data sources	**Base-line data**: Data for the natural history model were taken from the National Health and Nutritional Examination Survey **Effectiveness data**: Data on the effectiveness of interventions were taken from DPP study outcomes **Cost data**: Costs of interventions and related medical costs were derived from DPP data and from Herman et al (2005). Additional costs (e.g. costs of tests and initial physician visit) were taken from the Medicare fee schedule **Utility data**: Utilities were taken from the DPP study (elicited using the Self-Administered Quality of Well-Being Index (QWB-SA) at yearly intervals)
Uncertainty	**One-way sensitivity analysis**: A number of alternative scenarios were tested in one way sensitivity analysis. Scenarios which had a considerable effect on ICERs were: • Using a lower-cost, lower-effectiveness intervention (PLAN4WARD) reduced ICERs • Considering only participants 45-49 years old reduced ICERs • Using cost and effectiveness data from the DPPOS as well as DPP increased ICERs • Making the assumption that interventions are 50% less effective after year 3 increased ICERs **Probabilistic sensitivity analysis**: Probabilistic sensitivity analysis showed that as the monetary value of a QALY increases, the probability of testing at each threshold compared to the one above it also increases. However, due to the lack of a specific cost per QALY threshold for the US healthcare system, results are not meaningful in terms of probability of each intervention being cost effective.
Applicability	**Partially Applicable** This study is classified as partly applicable, as it only considers lifestyle interventions (and not metformin) and is based on a non-UK setting
Limitations	**Minor limitations** This study is categorised as having only minor limitations as it uses appropriate data sources, model structure, and time horizon

Bibliographic reference	**Zhuo, Xiaohui, et al. "Cost-effectiveness of alternative thresholds of the fasting plasma glucose test to identify the target population for type 2 diabetes prevention in adults aged≥ 45 years." Diabetes care 36.12 (2013): 3992-3998. APA**
Conflicts	**None listed**

1

Appendix I: Health economic analysis

Authorship: Chloe Thomas, Penny Breeze, Michael Gillett & Alan Brennan

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Acknowledgements: We thank Laura Gray from the University of Leicester for use of the LEADER dataset, and Paul De Ponte from NHS England for providing an updated projected per person cost for the NHS DPP. We are also grateful to the NICE clinical guidelines committee for useful comments, suggestions and expertise throughout the analysis process.

List of Abbreviations

BME	Black or Minority Ethnic
BMI	Body Mass Index
CVD	Cardiovascular Disease
Finnish DPS	Finnish Diabetes Prevention Study
FPG	Fasting Plasma Glucose
HbA1c	Glycated Haemoglobin
HDL	High Density Lipoprotein
HSE	Health Survey for England
ICER	Incremental Cost-Effectiveness Ratio
IMD	Index of Multiple Deprivation
ITT	Intention to Treat
LEADER	Leicester Ethnic Atherosclerosis and Diabetes Risk
NCVIN	National Cardiovascular Intelligence Network
NHS DPP	NHS Diabetes Prevention Programme
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
OLS	Ordinary Least Squares
PHE	Public Health England
PSA	Probabilistic Sensitivity Analysis
PSSRU	Personal and Social Services Research Unit
QALY	Quality Adjusted Life Year
SBP	Systolic Blood Pressure
SES	Socioeconomic Status
SPHR	School for Public Health Research

T2DM	Type 2 Diabetes
UKPDS	United Kingdom Prospective Diabetes Study
US DPP	United States Diabetes Prevention Programme

Introduction

Background

Type-2 diabetes is a major public health priority in the UK. Currently there are over 2.9 million people with diabetes in England [2], and prevalence is increasing with the aging population and higher levels of obesity. Diabetes is estimated to cost the NHS about £14 billion per year (10% of its total budget [3]), of which most goes towards treating complications of the disease such as amputation, blindness, kidney failure and cardiovascular disease.

Current NICE guidelines (PH38) recommend offering intensive lifestyle programmes to all individuals with a fasting plasma glucose level (FPG) of 5.5-6.9 mmol/L or HbA1c of 6-6.4% (42-48 mmol/mol) [4]. These guidelines were based upon a health technology assessment performed by Gillett et al (2012), which found that lifestyle interventions for high risk individuals were likely to be highly cost-effective [5]. Consequently, a national diabetes prevention programme known as The Healthier You: NHS Diabetes Prevention Programme (NHS DPP), consisting of an intensive lifestyle intervention with diet, physical activity and weight loss components has been developed by Public Health England (PHE), NHS England and Diabetes UK and is currently being rolled out across England through four national providers [6]. The NHS DPP interventions are commissioned centrally by NHS England. By 2020 it is expected that 100,000 referrals to the NHS DPP will be available per year. However, recent estimates put the number of individuals in this high risk category in England at over 5 million [7].

Economic evaluations indicate that intensive lifestyle management programmes such as that planned for the NHS DPP are likely to be cost-effective and potentially cost-saving [5;8-10]. Systematic review of pragmatic diabetes prevention interventions has indicated that interventions are likely to be more effective if they follow at least 9-12 of the NICE PH38 guidelines for designing intensive lifestyle-change programmes [4;11]. There is also evidence that diabetes prevention interventions may be differentially effective and cost-effective in different population subgroups [1;11-16].

The School for Public Health Research (SPHR) Diabetes Prevention Model has been developed for flexible analysis of a range of different diabetes prevention interventions [12;17;18]. The model has been previously adapted for NHS England to assess the cost-effectiveness of the NHS DPP and create a financial planning tool that was used to help support the business case for the programme [19;20]. In an additional analysis for PHE, the model adaptation was developed further to assess the potential cost-effectiveness of the

NHS DPP in different population subgroups [1] and to develop a local authority tool to quantify projected cost-savings and health benefits in different local areas [21].

The results of the PHE subgroup analysis indicated that, under assumptions around intervention cost, effectiveness and duration of effect that were the best available at the time of analysis, the NHS DPP was highly likely to be cost-effective and cost-saving over the medium to long term [1]. The analysis suggested that the highest NHS cost-savings and health benefits are likely to be obtained primarily by targeting individuals who are obese; but also those who are at the upper end of the high risk HbA1c band, or who are aged between 40 and 74.

There are some limitations to the PHE analysis in how it relates to current NICE PH38 recommendations. In NICE PH38, high risk individuals can be identified through HbA1c or FPG testing [4]; however the PHE analysis did not examine cost-effectiveness in subgroups defined by baseline FPG. Furthermore, cost-effectiveness in combinatorial subgroups was not estimated, meaning that it is difficult to make recommendations about who should be prioritised. Finally, previous analyses have not examined how the cost-effectiveness of an intensive lifestyle intervention compares to other diabetes prevention strategies such as digitally delivered interventions or prescription of metformin.

Aim and Objectives of this Study

The aim of this analysis was to model the clinical and cost effectiveness of intensive lifestyle-change programmes or metformin in preventing Type 2 diabetes in adults at high risk due to fasting plasma glucose concentrations of 5.5 – 6.9 mmol/L or HbA1c of 42 – 48 mmol/L (6.0% to 6.4%), in different population subgroups. The original brief was also to model the clinical and cost effectiveness of digitally delivered interventions. However, this could not be done due to a lack of data.

Specific objectives were as follows:

1. To present the results of the cost-effectiveness of intensive lifestyle-change programmes or metformin in prevention of type 2 diabetes in adults at high risk.
2. To estimate which population subgroups would derive the maximum benefit and which would derive the least benefit from intensive lifestyle intervention or metformin. Subgroups were defined as follows:
    - FPG 5.5-5.9 mmol/L
    - FPG 6.0-6.4 mmol/L
    - FPG 6.5-6.9 mmol/L
    - HbA1c 6.0-6.1 %
    - HbA1c 6.2-6.4 %
    - Subgroups defined for the Public Health England Diabetes Prevention Programme analysis to include baseline BMI, ethnicity, deprivation, age and gender.
    - A set of mutually exclusive combinatorial subgroups defined by the Guidelines committee.
3. To present the impact of alternative assumptions around intervention effectiveness, duration of intervention effect and stratification of intervention effect by population subgroup.

Methods

1: Structure of the SPHR Diabetes Prevention Model

The SPHR Diabetes Prevention Model was developed to forecast long-term health and health care costs under alternative scenarios for diabetes prevention. A wide range of stakeholders were involved in its development including clinicians, public health commissioners, diabetes and health economic researchers and members of the public with diabetes. A detailed description of the methodology and assumptions used in the model can be found elsewhere [12;17]. Here we present a summary of the model.

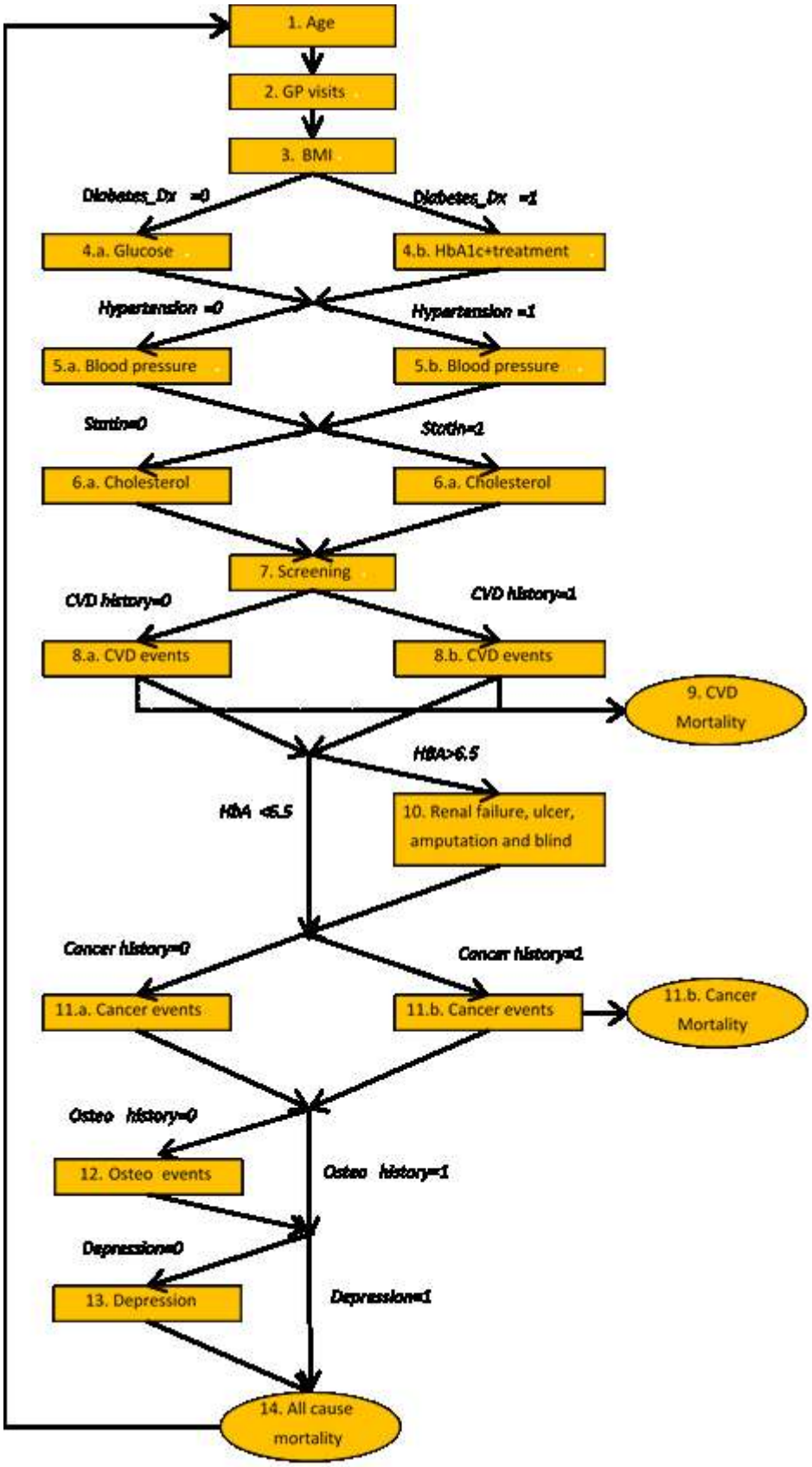
The model is an individual patient simulation model based upon the evolution of personalised trajectories for metabolic factors including body mass index (BMI), systolic blood pressure (SBP), cholesterol and measures of blood glucose (including HbA1c). The baseline population consists of a representative sample of the English population obtained from the Health Survey for England (HSE), an annual survey that is designed to provide a snapshot of the nation's health [22]. The HSE datasets include individual level weights which indicate how representative an individual is within the English population and can be used to derive England-wide results. HSE 2011 was chosen to inform the baseline population in the model due to its focus on diabetes and cardiovascular disease, meaning it incorporates information about relevant metabolic factors. Individuals aged under 16 were excluded from the analysis. Missing anthropometric or metabolic data was imputed using ordinary least squares (OLS) linear regression models.

The model runs in annual cycles (see schematic in Figure 1) over a lifetime horizon. For each person, their BMI, cholesterol levels, SBP and HbA1c fluctuate from year to year, representing natural changes as people age and depending upon personal characteristics such as gender, ethnicity and smoking status. The evolution of these individual level trajectories is based upon a statistical analysis of the Whitehall II cohort, a longitudinal dataset of civil servants [23;24]. Every year in the model, an individual may visit their GP or undergo an opportunistic health check, and be diagnosed with and treated for hypertension, high cardiovascular risk or diabetes, depending upon their personal characteristics. The model simulates a three stage treatment regimen following diabetes diagnosis. First line treatment assumes use of low cost treatments such as metformin; a second treatment (assumed to be Sitagliptin) is added if HbA1c levels rise above 7.4%. Initiation of insulin (third stage treatment) occurs if HbA1c rises above 8.5%.

Individuals with HbA1c ≥ 6.5% are at risk of microvascular complications of diabetes whether or not they are diagnosed with diabetes. The UKPDS Outcomes model risk equations are used to model the annual risk of kidney disease, ulcer, amputation and blindness [25;26]. All individuals in the model are at risk of developing cardiovascular disease (CVD), congestive heart failure, osteoarthritis, depression and breast or colon cancer, or of dying. First cardiovascular event is modelled using the QRISK2 equations [27], modified to take into account increased risk per unit increase in HbA1c [28]. The nature of the first CVD event and the risk of subsequent CVD events are defined using age/gender specific data [29]. All-cause mortality is based upon life tables for England and Wales [30]. Appendix A contains a detailed list of parameters and sources used in the model. Further details of methodology and assumptions are available elsewhere [17].

Utility of each individual in each year of the model is dependent upon their age, gender and medical conditions. Each condition is associated with a utility decrement and a cost. Model costs are at 2014/15 values. Most costs are derived from published literature and inflated to 2014/15 values using the retail price index. Costs for medications were obtained from the British National Formulary [31], and costs for healthcare utilisation were obtained from Personal Social Services Research Unit (PSSRU) unit costs [32]. Appendix A contains a detailed breakdown of unit costs and utilities. The model perspective is that of the NHS and Personal Social Services (PSS).

Figure 45: Model schematic showing what happens in each yearly cycle.

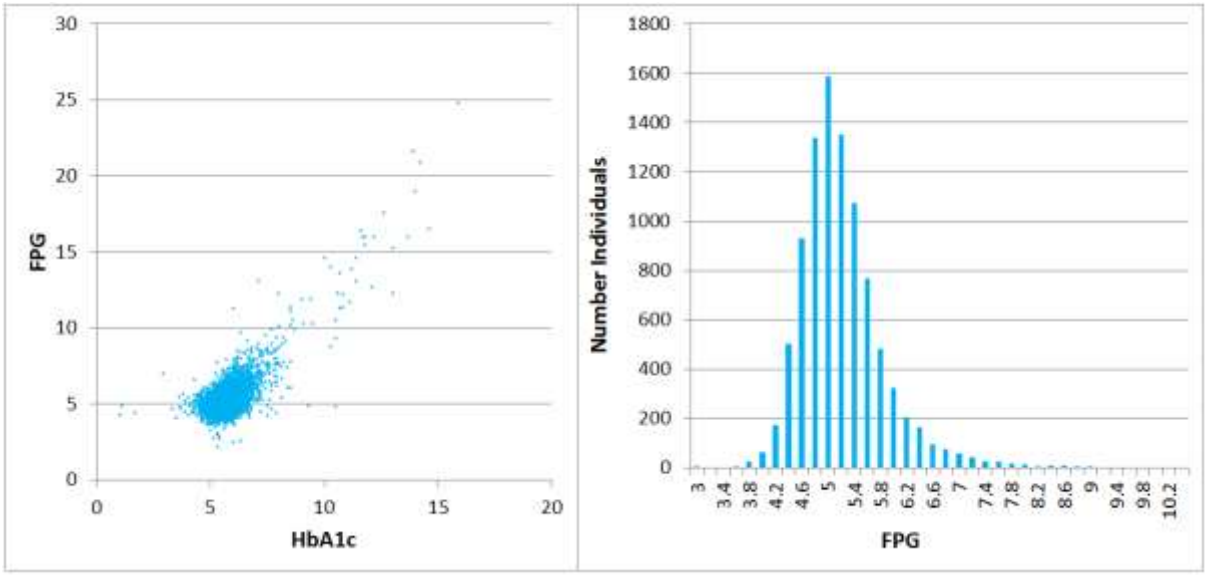


2: Defining Individuals at High Risk of Diabetes

The baseline population was obtained from HSE 2011 data [22]. The aim was to select high risk individuals for simulation if they were not previously diagnosed as diabetic and had either HbA1c 6-6.4% or FPG 5.5-6.9 mmol/L. HSE 2011 includes data on HbA1c, but not on FPG. Furthermore there is no direct correlation between HbA1c and FPG measurements and no robust formulas exist for predicting one measurement from the other. The situation is further complicated by the high level of within subject variation between subsequent measurements. For these reasons it was decided that the pre-existing model HbA1c trajectories, which take within and between subject variation into account, would be used for the process of disease risk estimation and diabetes diagnosis and that FPG trajectories would not be modelled. FPG at baseline, however, would be modelled, to enable selection of the high risk group for simulation and to obtain outcomes from subgroups defined by different FPG cut-off points. Given that HbA1c trajectories are used to define diabetes in the model, the FPG defined high risk group was also restricted to only select individuals with HbA1c < 6.5, as any individuals with HbA1c ≥ 6.5 would be diagnosed with diabetes almost immediately, given the NICE recommendation followed in the model that high risk individuals receive regular diabetes screening [4].

A statistical model estimating FPG from HbA1c and various other personal characteristics was derived from the Leicester Ethnic Atherosclerosis and Diabetes Risk (LEADER) dataset using ordinary least squares multiple regression. The LEADER dataset (kindly made available by Laura Gray, University of Leicester) is comprised of 9,494 individuals from the Leicester area and contains information about FPG, HbA1c and a range of other potentially correlated characteristics such as BMI and ethnicity [33;34]. Scatterplots indicated that FPG appeared to be linearly correlated with various characteristics including HbA1c and had a slightly skewed distribution (Figure 46).

Figure 46: Diagrams showing the correlation of HbA1c with FPG (left) and the distribution of FPG (right) in the LEADER dataset.



The best fitting statistical model is shown in Table 20 and includes HbA1c, HbA1c squared, sex, ethnicity, BMI, BMI squared, smoking status and cholesterol. The inclusion of all these terms was highly significant ($P < 0.001$ apart from cholesterol where $P < 0.01$). Model fit was assessed using the adjusted R^2. The residual term was used to generate a random, normally distributed error term for each simulated individual to ensure between subject variability.

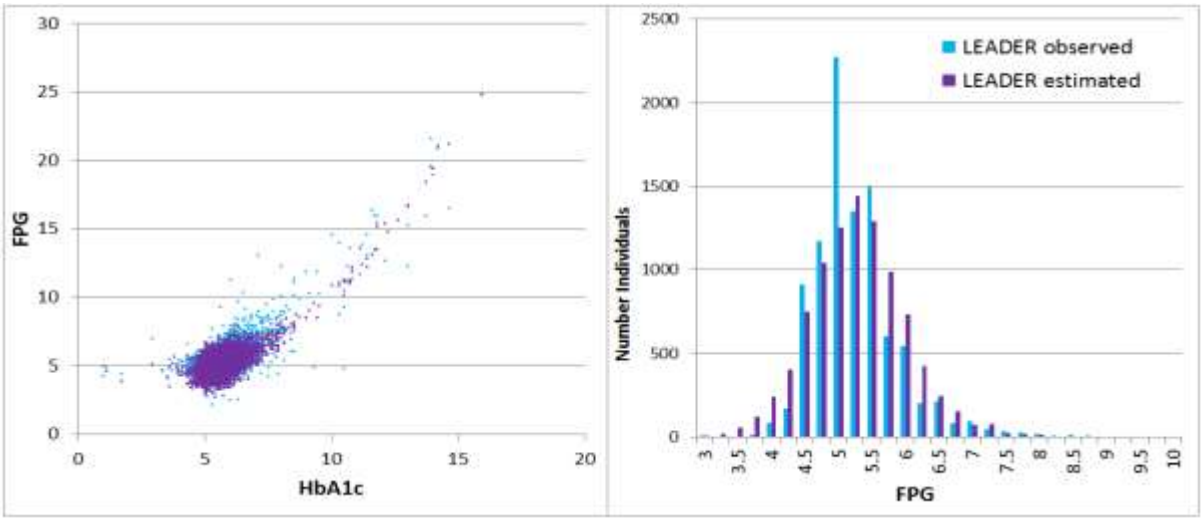
Table 20: Parameters used for estimating FPG, derived from statistical analysis of the LEADER dataset.

Variable	Mean	Standard Error
Intercept	4.57512	0.1856876
HbA1c	-0.863981	0.0411077
HbA1c squared	0.1314879	0.0028148
Sex (0 = women, 1 = men)	0.2189638	0.0122108
Ethnic (0 = white, 1 = BME)	-0.050739	0.0136227
BMI	0.0572292	0.008575
BMI squared	-0.000655	0.0001398
Smoker (0 = non-smoker, 1 = smoker)	-0.111608	0.0159232
Cholesterol	0.0153841	0.0057636
residual	0	0.5684

Error used in adjusted model	0.5	1.1368

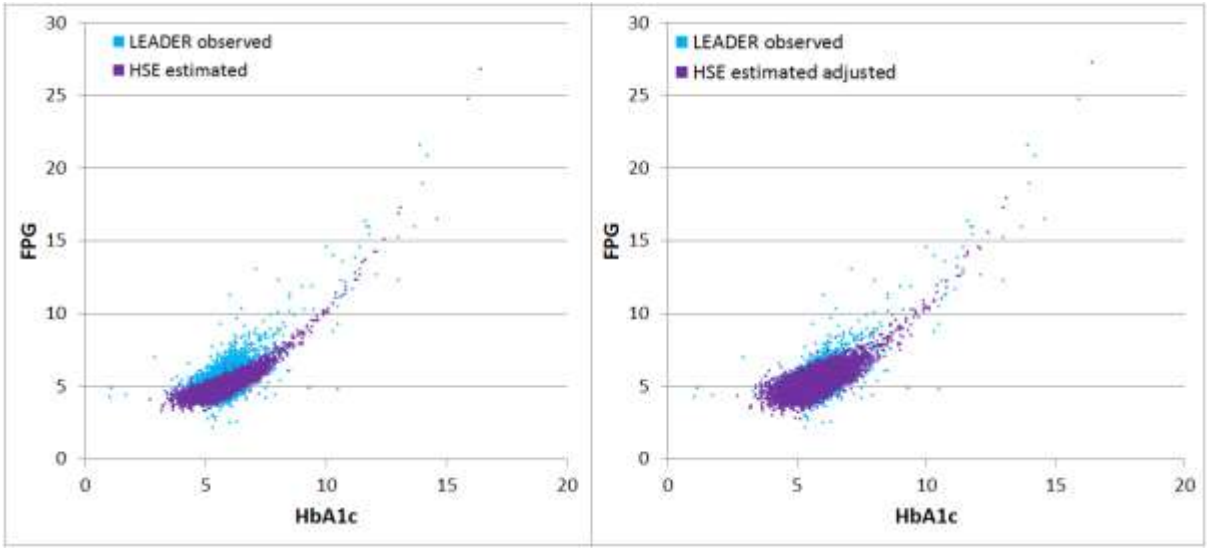
The model was tested to ensure that it was able to estimate FPG values from the LEADER dataset with a reasonable amount of accuracy (Figure 47).

Figure 47: Diagrams indicating that the statistical model is able to predict the correlation of HbA1c with FPG (left) and the distribution of FPG (right) with reasonable accuracy.



The model was then used on the HSE 2011 dataset to predict FPG values from the observed HbA1c values. The datasets contain individuals with different characteristics (in particular, the LEADER dataset contains a high proportion of ethnic minority individuals) and therefore differences between the observed LEADER dataset and the model predictions from the HSE were expected. However, it was thought to be particularly important that a) the correlation between HbA1c and FPG was maintained; b) the distribution of FPG in the total and the high risk populations was similar; c) the distribution of HbA1c within each of the selected FPG subgroups and the total number of individuals in each subgroup was similar. This latter point was particularly important given that the role of the FPG estimation was to enable individuals to be appropriately distributed within subgroups by diabetes risk. It was found that compared to the LEADER estimates, the model estimated much less inter-person variation in the FPG values and that as a result the higher FPG subgroups (particularly FPG 6.5-6.9) contained very few individuals (Figure 48). The error term was therefore adjusted to enable a full range of FPG values to be estimated (Table 20).

Figure 48: Scatterplots show that the statistical model estimates that few individuals from the HSE have high FPG values, whereas adjusting the error term enables these high FPG individuals to be included.



The adjusted model estimates that the HSE contains similar proportions of individuals from HbA1c, FPG and total high risk subgroups to the LEADER dataset (Table 21). It is estimated that around 30% of total individuals are at risk using either the FPG or HbA1c criteria, around 16% are at risk using the HbA1c criteria (this is observed from the HSE) and 23% are at risk using the FPG criteria. Histograms indicate that the adjusted model estimates FPG distribution within the HSE and HbA1c distribution within the FPG subgroups relatively accurately (Figure 49). A comparison of mean and standard deviation for HbA1c distributions in each FPG subgroup is given in Table 22. In all subgroups the predicted mean values are slightly higher than the observed values from LEADER, which is likely to reflect differences in personal characteristics between the two datasets.

Table 21: Proportions of individuals within the high risk group and within particular HbA1c or FPG subgroups in the LEADER dataset and in the HSE 2011. Note that HbA1c subgroup data for the HSE is observed (and imputed), whilst FPG subgroup data is estimated using the statistical model described above.

	LEADER - observed		**HSE - estimated**	
	Number	Percentage	Number	Percentage
TOTAL HIGH RISK	**2831**	**30%**	**2594**	**30%**
HbA1c < 6	1190	13%	1217	14%
HbA1c 6-6.1	994	11%	721	8%
HbA1c 6.2-6.4	647	7%	656	8%

FPG < 5.5	926	10%	576	7%
FPG 5.5-5.9	1328	14%	1503	17%
FPG 6-6.4	406	4%	455	5%
FPG 6.5-6.9	114	1%	57	1%
FPG 7+	57	1%	3	0%

Figure 49: A comparison of observed LEADER data and HSE data estimated using the error adjusted statistical model described above: Histograms showing the distribution of FPG in the total population and the distribution of HbA1c in the three FPG subgroups used in this analysis.

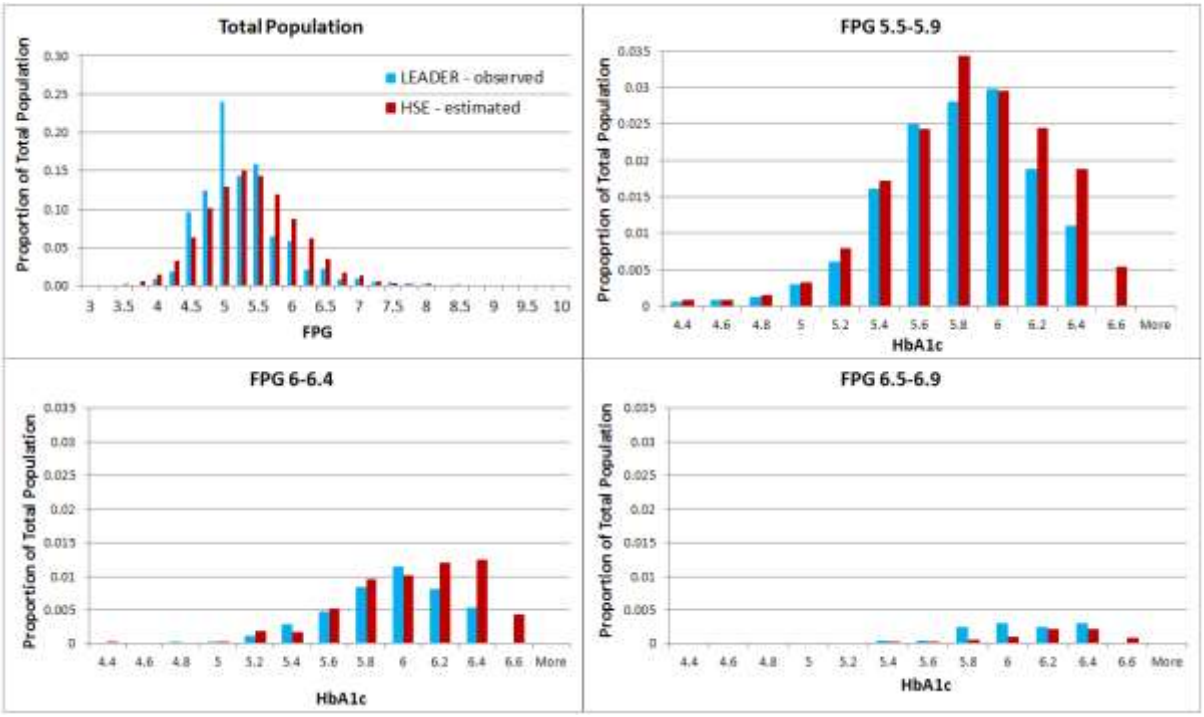


Table 22: A comparison of observed LEADER data and HSE data estimated using the error adjusted statistical model described above: HbA1c mean and standard deviation for each of the FPG subgroups.

Subgroup	LEADER - observed		HSE - estimated	
	Mean	Standard Deviation	Mean	Standard Deviation
FPG 5.5-5.9	5.75	0.38	5.78	0.40
FPG 6-6.4	5.87	0.33	5.94	0.37
FPG 6.5-6.9	6.00	0.32	6.06	0.27

For this analysis the process of identification of high risk individuals was not implicitly modelled, and instead they were assumed to have been identified already by a variety of methods. This means that the model does not include any costs of identifying high risk individuals.

Table 23 summarises the baseline characteristics of the 2,594 high risk individuals from the HSE 2011 identified following imputation of missing data and estimation of FPG. Note that the mean HbA1c of the high risk population is actually less than 6 %, and the mean FPG is only 5.7 mmol/L. This reflects the fact that almost 50% of individuals would not be categorised as high risk using HbA1c criteria alone, and almost 20% of individuals would not be categorised as high risk using FPG criteria alone.

For this analysis the process of identification of high risk individuals was not implicitly modelled, and instead they were assumed to have been identified already by a variety of methods. This means that the model does not include any costs of identifying high risk individuals.

Table 23: Baseline characteristics of the individuals at high risk of diabetes from HSE 2011 (N= 2,594)

Characteristic	Number	Percentage
Male	1,305	50.3%
White Ethnicity	2,345	90.4%
South Asian Ethnicity	108	4.2%
Chinese Ethnicity	6	0.2%
Caribbean Ethnicity	26	1.0%
African Ethnicity	45	1.7%
Other Ethnicity	64	2.5%

Non-smoker	2,231	86.0%
Smoker	363	14.0%
Anti-hypertensive treatment	542	20.9%
Statins	314	12.1%
Pre-existing CVD	198	7.6%
HbA1c 6-6.4	1,377	53.1%
FPG 5.5-6.9	2,015	77.7%
HbA1c 6-6.4 AND FPG 5.5-6.9	798	30.8%
	Mean	**Standard Deviation**
Age (years)	53.6	17.9
BMI (kg/m^2)	28.4	5.4
Total Cholesterol (mmol/l)	5.6	1.1
HDL Cholesterol (mmol/l)	1.5	0.4
HbA1c (%)	5.9	0.4
FPG (mmol/L)	5.7	0.4
Systolic Blood Pressure (mm Hg)	128.3	16.7
EQ-5D (TTO)	0.769	0.294

BMI Body Mass Index; IMD Index of Multiple Deprivation; CVD Cardiovascular Disease; IGR Impaired Glucose Regulation; HDL High Density Lipoprotein; EQ-5D 5 dimensions EuroQol (health related quality of life index) ; TTO Time Trade-Off

3: Defining Population Subgroups for Analysis

Previous work for Public Health England using the SPHR diabetes prevention model has indicated that differences in incremental effectiveness, cost-effectiveness and cost-savings with an intensive lifestyle intervention compared to no intervention are particularly marked between subgroups defined by age, baseline HbA1c and baseline BMI [1]. The previous work did not look at outcomes in subgroups differing by baseline FPG, and did not look at subgroup combinations, which makes it difficult to make recommendations around who is likely to benefit most from the interventions. The approach used for the analysis presented here was to include a number of singly defined subgroups for comparison with the previous work, together with a number of subgroup combinations.

The following single characteristic subgroups were selected for analysis:

- 4 Age groups (Age < 40; Age 40-59; Age 60-74; Age ≥ 75)
- 2 Ethnicity groups (White; BME)
- 2 Gender groups (Male; Female)
- 5 socioeconomic status (SES) groups (Index of Multiple Deprivation [IMD] quintile 1-5)
- 4 BMI groups (BMI < 25 kg/m^2; BMI 25-29.9 kg/m^2; BMI 30-34.9 kg/m^2; BMI ≥ 35 kg/m^2)
- 2 HbA1c groups (HbA1c 6-6.19 %; HbA1c 6.2-6.49 %)
- 3 FPG groups (FPG 5.5-5.9 mmol/L; FPG 6.0-6.5 mmol/L; FPG 6.5-6.9 mmol/L)

Table 24 shows the proportion of high risk individuals (defined by either FPG or HbA1c criteria for age, ethnicity, gender, SES or baseline BMI) in each subgroup. The guidelines committee suggested that baseline BMI cut-off points should be lower in BME individuals in line with the recommendations given in NICE PH46 (BMI < 23 kg/m^2; BMI 23-27.4 kg/m^2; BMI 27.4-34 kg/m^2; BMI ≥ 35 kg/m^2) [35]. This is to take into account the higher risk of diabetes seen in certain ethnic minority groups.

There are potentially thousands of subgroup combinations and it is only possible to look at a small subset within the timescale of the project. There is also a risk in subgroup analysis that results may not be statistically significant if insufficient numbers of individuals are analysed. To mitigate this issue a set of non-overlapping subgroup combinations were chosen that each comprised around 10% of the high risk population as defined by HbA1c (4-8% of total high risk population), and covered the entire high risk population as defined by HbA1c. Equivalent subgroups were chosen for the FPG criteria in order to ensure comparability – this meant that there were more subgroups defined using FPG criteria (13) than HbA1c criteria (9). Note that the FPG 6.5-6.9 subgroups only contain a small number of individuals, meaning that results obtained from these subgroups are likely to be less robust, whilst the FPG 5.5-5.9 subgroups contain a particularly large number of individuals (Table 24).

Table 24: Subgroups chosen for analysis, the numbers of individuals from HSE 2011 within each subgroup and the proportion this represents within the total high risk group (N = 2,594) plus the expected numbers of individuals in England within each subgroup and the proportion this represents within the total high risk group (N = 12.6 million).

Subgroup	Number in HSE 2011	Proportion of high risk in HSE 2011	Estimated Number in England	Proportion of high risk in England
TOTAL	**2,594**	**100%**	**12,590,392**	**100%**
Single Subgroups				
IMD 1 (least deprived)	620	24%	2,891,973	23%
IMD 2	773	30%	3,684,444	29%
IMD 3	307	12%	1,489,447	12%
IMD 4	479	18%	2,393,962	19%
IMD 5 (most deprived)	415	16%	2,130,567	17%
Age < 40	605	23%	3,589,462	29%
Age 40-59	950	37%	4,682,030	37%
Age 60-74	683	26%	2,882,854	23%
Age >= 75	356	14%	1,436,048	11%
BMI < 25 (White) OR BMI < 23 (BME)	658	25%	3,344,427	27%
BMI 25-29 (White) OR BMI 23-27.4 (BME)	1045	40%	5,056,811	40%
BMI 30–34 (White) OR BMI 27.5-34 (BME)	600	23%	2,833,186	23%
BMI >= 35 (White OR BME)	291	11%	1,355,968	11%

Ethnicity White	2345	90%	11,196,429	89%
Ethnicity BME	249	10%	1,393,963	11%
Sex Male	1305	50%	6,904,879	55%
Sex Female	1289	50%	5,685,514	45%
HbA1c 6-6.1	721	28%	3,463,643	28%
HbA1c 6.2-6.4	656	25%	3,089,954	25%
FPG 5.5-5.9	1503	58%	7,358,516	58%
FPG 6-6.4	455	18%	2,248,705	18%
FPG 6.5-6.9	57	2%	266,999	2%
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**1,377**	**53%**	**6,553,596**	**52%**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*36*	*1%*	*154,575*	*1%*
1) HbA1c 6-6.4, BMI >=35	154	6%	703,062	6%
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	153	6%	717,368	6%
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	176	7%	832,948	7%
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	127	5%	520,473	4%
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	123	5%	501,620	4%

6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	124	5%	608,083	5%
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	147	6%	831,705	7%
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	178	7%	911,348	7%
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	195	8%	926,988	7%
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**2,015**	**78%**	**9,874,220**	**78%**
FPG 6.5-6.9, BMI >=35, Age >= 60	*5*	*0.2%*	*20,781*	*0.2%*
1) FPG 5.5-6.9, BMI >=35	234	9%	1,094,401	9%
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	19	1%	93,901	1%
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	124	5%	595,770	5%
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	347	13%	1,619,497	13%
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	12	0.5%	48,373	0.4%
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	77	3%	322,031	3%
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	238	9%	983,831	8%
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	10	0.4%	53,085	0.4%

9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	105	4%	574,907	5%
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	383	15%	2,067,025	16%
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	8	0.3%	36,564	0.3%
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	90	3%	474,011	4%
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	368	14%	1,910,824	15%

In addition to these 22 subgroups, a further two subgroups (one for each blood glucose measure) were defined as a combination of the subgroup characteristics which were found to be most cost-effective in the previous analysis of intensive lifestyle intervention versus control for Public Health England (shown in italics in above table). Note that these only comprise a small proportion of the high risk population and therefore results obtained from these subgroups are likely to be less robust.

The percentage of individuals in the HSE 2011 in each subgroup is not necessarily indicative of the percentage of individuals in England in each subgroup. The HSE contains survey weights which determine how representative each individual is to the population of England [22]. The model uses the individual level survey weights to adjust model results, in order to reflect the expected population composition of England rather than the composition of HSE 2011 (Table 24). The total number of high risk individuals estimated in England using this method is 12.6 million. This is considerably higher than the 5 million estimated by the National Cardiovascular Intelligence Network (NCVIN) [7]. The discrepancy is mainly due to the inclusion of individuals identified at high risk through modelled FPG, which is almost 50% of the estimated high risk population and who were not included in the NCVIN report. However, even if only HbA1c criteria are used to identify high risk individuals, 6.6 million individuals are identified. This is likely to be due to sampling differences: whilst the model is based on a single year of HSE, and imputes missing values for individuals with no blood test data, the NCVIN report combined several years of HSE data and only took data from individuals with available blood results [7], meaning that their results are likely to be more robust with respect to estimates of the number at high risk than the model results. This approach is not possible when obtaining model results as most years of the HSE do not contain data on all parameters needed for all the model risk equations. The population estimates for England presented in Table 24 should therefore be treated with caution.

Table 25 shows the mean age, BMI, HbA1c and FPG, the percentage of white ethnicity, male sex, and most socioeconomically deprived quintile in each of the population subgroups chosen for analysis. The table indicates that some population characteristics are likely to be correlated. For example, BME individuals have a lower mean age, a lower mean BMI and tend to come from more socioeconomically deprived backgrounds than white individuals, whilst older individuals tend to have slightly higher blood glucose as measured by HbA1c, but not by FPG, are more likely to be female, ethnically white and come from less socioeconomically deprived backgrounds than younger individuals.

Table 25: Characteristics of high risk individuals from the HSE 2011 from each of the chosen population subgroups.

	Mean Age (years)	Mean BMI (kg/m^2)	Mean HbA1c (%)	Mean FPG (mmol/L)	Percent Male	Percent BME	Percent IMD Q5
Total	**53.6**	**28.4**	**5.9**	**5.7**	**50%**	**10%**	**16%**
Single Subgroups							
IMD 1 (least deprived)	54.6	28.2	5.9	5.7	49%	5%	0%
IMD 2	55.9	28.4	5.9	5.7	50%	6%	0%
IMD 3	54.6	28.2	5.9	5.7	51%	6%	0%
IMD 4	51.8	28.5	5.9	5.7	53%	14%	0%
IMD 5 (most deprived)	49.0	28.6	5.9	5.6	48%	20%	100%
Age <40	29.3	27.1	5.8	5.7	54%	18%	23%
Age 40-59	49.5	29.0	5.9	5.7	52%	11%	16%
Age 60-74	66.4	28.7	6.0	5.7	47%	3%	10%
Age 75+	81.0	28.2	6.0	5.7	44%	3%	15%
BMI < 25 (White) OR BMI < 23 (BME)	50.8	22.4	5.9	5.6	47%	5%	17%
BMI 25-29 (White) OR BMI 23-27.4 (BME)	54.1	27.2	5.9	5.7	56%	9%	14%
BMI 30–34 (White) OR BMI 27.5-34 (BME)	55.9	31.7	5.9	5.8	49%	17%	17%
BMI >= 35 (White OR BME)	53.1	39.0	5.9	5.7	38%	8%	19%

Ethnicity White	54.7	28.4	5.9	5.7	50%	0%	14%
Ethnicity BME	43.1	28.0	5.9	5.6	50%	100%	34%
Sex Male	52.3	28.1	5.8	5.8	100%	10%	15%
Sex Female	54.8	28.6	6.0	5.6	0%	10%	17%
HBA 6-6.1	55.7	28.2	6.1	5.5	41%	11%	16%
HBA 6.2-6.4	56.7	28.3	6.3	5.7	43%	10%	16%
FPG 5.5-5.9	52.7	28.5	5.8	5.7	52%	10%	15%
FPG 6-6.4	53.5	29.1	5.9	6.2	59%	8%	14%
FPG 6.5-6.9	56.9	30.6	6.1	6.7	67%	9%	14%
Subgroup Combinations: HbA1c Defined							
HbA1c 6-6.4 Total	**56.2**	**28.2**	**6.2**	**5.6**	**42%**	**11%**	**16%**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*68.9*	*38.8*	*6.3*	*5.7*	*39%*	*3%*	*8%*
1) HbA1c 6-6.4, BMI >=35	55.1	39.1	6.2	5.6	30%	10%	20%
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	60.8	31.8	6.3	5.7	44%	19%	12%
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	57.3	31.7	6.1	5.6	41%	19%	16%
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	73.4	27.5	6.3	5.7	46%	2%	13%
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	71.4	27.4	6.1	5.6	41%	3%	14%

6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	43.6	27.0	6.3	5.7	50%	12%	20%
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	42.2	27.0	6.1	5.5	50%	15%	14%
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	50.5	22.0	6.3	5.5	40%	6%	19%
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	55.5	22.2	6.1	5.4	40%	6%	14%
Subgroup Combinations: FPG Defined							
FPG 5.5-6.9 Total	**53.0**	**28.7**	**5.8**	**5.9**	**54%**	**9%**	**15%**
FPG 6.5-6.9, BMI >=35, Age >= 60	*73.0*	*38.2*	*6.0*	*6.6*	*60%*	*0%*	*20%*
1) FPG 5.5-6.9, BMI >=35	52.2	39.2	5.9	5.9	41%	6%	17%
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	56.1	31.8	6.1	6.7	68%	16%	5%
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	55.2	31.7	6.0	6.2	59%	14%	14%
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	54.9	31.8	5.8	5.7	49%	18%	19%
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	73.0	27.5	6.1	6.7	58%	0%	17%
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	71.6	27.7	6.0	6.2	57%	1%	10%
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	71.5	27.4	5.9	5.7	55%	5%	10%
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	40.8	28.2	6.1	6.6	70%	10%	10%

9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	40.2	27.2	5.9	6.2	66%	9%	12%
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	42.2	27.1	5.7	5.7	63%	13%	15%
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	52.5	24.2	6.1	6.7	88%	0%	0%
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	51.5	22.6	5.9	6.2	60%	8%	19%
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	49.9	22.7	5.8	5.7	50%	3%	15%

4: Specifying Interventions

Intervention Effectiveness

In the SPHR Diabetes Prevention Model interventions are assumed to impact directly upon individual risk factors such as BMI, blood pressure, cholesterol and HbA1c. In the model these changes then impact upon incidence rates of type 2 diabetes and related diseases. Intervention effectiveness data was taken from the NICE clinical reviews carried out as part of this project.

The reviews were specified to extract five key outcomes for input into the model: change in weight, systolic blood pressure (SBP), total cholesterol, HbA1c and diabetes incidence in intervention compared to control, at two time points: 12-24 months and 24 months plus. The reviews also extracted information about reduction in FPG; however as the model does not simulate individual trajectories of FPG, this information was not incorporated into the model. The model uses trajectories of BMI rather than weight; however, all individuals in the model have a height measurement and therefore the corresponding BMI reduction could be calculated for each individual.

The 12-24 month time point corresponded in most studies to around one year. Given that the model acts in annual cycles, metabolic data from this time point was programmed into the model to represent the benefits of the intervention over the first year and continuing into the second year. Mean length of follow-up for the 24 months plus time point was around three years, and was therefore programmed into the model to represent the benefits of the intervention after three years. It was assumed that at two years post intervention implementation, metabolic reductions would be halfway between those observed at year one and year three.

The model structure does not allow observed diabetes incidence reductions to be programmed directly into it. Instead, the diabetes incidence data was used in two ways:

1. To validate the model predictions of diabetes incidence reduction given the observed changes in metabolic trajectories programmed into the model.
2. If necessary, to calibrate the HbA1c trajectories to enable the observed diabetes incidence reduction to be replicated in the model with a reasonable degree of tolerance.

The previous subgroup cost-effectiveness analysis carried out for PHE [1] used effectiveness data from an evidence review commissioned by PHE [11]. The NICE review provided a more

robust, specific and up-to-date estimate of intervention effectiveness, which was thought to be preferable to the PHE estimates for the following reasons:

1. The NICE review used only those studies in which the intensive lifestyle intervention fulfils 9-12 NICE guidelines as defined in PH38 [4] and as specified for the NHS DPP [36]. The PHE review analysed a wider range of studies, although a subgroup analysis with limited outcomes was included incorporating only those studies which fulfilled 9-12 guidelines [11]. However, the NICE review included a larger number of studies than the PHE 9-12 NICE guidelines subgroup analysis due to the incorporation of two studies published more recently, plus an additional two studies that met NICE review study criteria but did not meet PHE review study criteria.
2. The NICE review included only randomised controlled trials with a comparison against control, whereas the PHE analysis included some studies without controls [11].
3. The NICE review included only studies that carried out an intention to treat (ITT) analysis, whereas the PHE review included a mixture of ITT and completer studies [11]. The NICE effectiveness estimates therefore incorporated observed rates of intervention drop-out and non-adherence from the included studies.
4. The NICE review collected data for the full range of outcomes required in the model, whereas the PHE review only collected weight loss (and some limited HbA1c data) [11]. This meant that other outcomes had to be extrapolated from an earlier systematic review [8].
5. The NICE review analysed data from two time points, whereas the PHE review only analysed data for short-term (one year) outcomes [11].

Intensive Lifestyle Intervention

Nine ITT analysis studies were found in the clinical review to inform data around effectiveness of the intensive lifestyle intervention (Table 26). The US Diabetes Prevention Programme (US DPP) is by far the largest study with 3,234 participants [14], which is slightly higher than the total number of participants in all the other studies added together.

Table 26: Studies included in the intensive lifestyle intervention effectiveness data used in the model, and their baseline characteristics. N/R = not recorded.

Study	N	Mean BMI (kg/m^2)	Mean Age (years)	Mean HbA1c (%)	Mean FPG (mmol/L)	Ref.
Ackermann et al, 2015	509	36.8	51.0	6.05	N/R	[37]
Davies et al, 2016	880	32.6	63.9	6.1	5.65	[38]

Katula et al, 2011	301	32.7	57.9	N/R	5.88	[39]
Kulzer et al, 2009	182	31.5	56.3	5.7	5.87	[40]
Ma et al, 2013	241	33.9	53.6	N/R	5.55	[41]
Mensink et al, 2003	88	29.6	56.7	5.9	5.89	[42]
Oldroyd et al, 2006	78	N/R	57.9	N/R	6.10	[43]
Tuomilehto et al, 2001	522	31.3	55.0	5.65	6.15	[44]
US DPP (various articles)	3,234	34.0	50.6	5.91	5.90	[14;45;46]

Data from the US DPP has previously been used to inform the PH38 NICE guidelines [4], as the large size of the study means that the data is very robust [14]. However, the lifestyle intervention given was very intensive both by the standards of what can be offered routinely in the NHS and in comparison with other trials, and correspondingly the US DPP shows much higher effectiveness than the other included studies (Table 27). In the US DPP, individuals underwent a 16 lesson curriculum in the first 24 weeks following referral, covering diet, exercise, and behaviour modification in order to help them achieve and maintain a 7% reduction in body weight and regular engagement in physical activity [14]. Whilst, the NHS DPP should offer at least 16 hours of contact time over at least 13 sessions, spread over a minimum of 9 months [36], the US DPP curriculum was taught on a one-to-one basis, was flexible, culturally sensitive, and individualized, whilst the NHS DPP could consist of group sessions, meaning that there will be little opportunity for tailoring the approach to each individual's needs. Most importantly, the US DPP incorporated regular maintenance sessions, with face to face sessions at least once every two months for the remainder of the trial, and phone contact in between these visits [14]. In the NHS DPP on the other hand, no maintenance beyond 9 months is specified other than for the provider to ensure that links are made with local or national activities and services to enable individuals to continue with lifestyle improvements [36].

Table 27: Effectiveness data for each study at each timepoint: Mean estimates of metabolic changes in intensive lifestyle arm compared to control arm. N/R = not recorded.

Study	**Weight Change (kg)**		**HbA1c Change (%)**		**Systolic Blood Pressure Change (mmHg)**		**Total Cholesterol Change (mmol/L)**	
Time Point	**Yr 1**	**Yr 3**	**Yr 1**	**Yr 3**	**Yr 1**	**Yr 3**	**Yr 1**	**Yr 3**

Ackermann et al, 2015	-2.3	N/R	-0.04	N/R	-1.1	N/R	0.04	N/R
Davies et al, 2016	-0.3	-0.3	-0.04	-0.07	1.2	0.6	-0.07	-0.11
Katula et al, 2011	-3.5	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Kulzer et al, 2009	-2.4	N/R	-0.10	N/R	-3.6	N/R	-0.22	N/R
Ma et al, 2013	-3.9	N/R	N/R	N/R	-1.3	N/R	-0.17	N/R
Mensink et al, 2003	-2.2	-1.2	-0.05	0.01	-0.5	-0.1	-0.10	0.15
Oldroyd et al, 2006	-2.6	-3.3	N/R	N/R	N/R	N/R	N/R	0.10
Tuomilehto et al, 2001	-3.5	-2.6	-0.20	-0.20	-4.0	-5.0	0.00	-0.20
US DPP (various)	-6.3	-4.1	-0.18	-0.17	N/R	-3.0	N/R	-0.05

Whilst the US DPP is more intensive than any of the other studies, the intensity of the Finnish Diabetes Prevention Study (Finnish DPS; Tuomilehto et al, 2001 [44]) was also high compared with the remaining studies and corresponded to relatively large effectiveness estimates (Table 27). In the Finnish DPS, individuals had seven sessions with a nutritionist during the first year of the study and one session every three months thereafter, plus individualised guidance on increasing physical activity and supervised, individually tailored, circuit-type resistance-training sessions [44]. Most of the other studies also included an element of maintenance beyond the first year of the study, which may not be reflected in the NHS DPP.

The guidelines committee agreed that given the differences between the US DPP and the NHS DPP, effectiveness data from the US DPP was unlikely to accurately represent the expected effectiveness of the NHS DPP. However, they thought that the Finnish DPS should be included in estimates of intervention effectiveness. A conservative scenario was therefore modelled which used effectiveness estimates that included the Finnish DPS but excluded the US DPP. Given that the US DPP has been previously used to inform PH38, an optimistic scenario was also modelled in which the US DPP was included in the effectiveness estimates. Finally, in order to reflect the likely lower level of maintenance and adherence to intervention in real life roll-out of the NHS DPP, a pessimistic scenario was modelled in which the Finnish DPP was also excluded. The effectiveness data used in the model, which were synthesised by a meta-analysis of studies identified in the clinical review, are presented in Table 28. Note from Table 27 that different studies contribute to the different effectiveness outcomes at different time points, with certain outcomes under the pessimistic

scenario derived from as few as two studies. Uncertainty around some of these estimates is therefore quite high.

Table 28: Intensive Lifestyle Intervention: Effectiveness data used in the model

	One year follow-up			Three years follow-up		
	Mean	Lower	Upper	Mean	Lower	Upper
Optimistic Scenario: Including US DPP and Finnish DPS						
Progression to diabetes (risk ratio)	**0.34**	0.15	0.75	**0.57**	0.37	0.88
Change in weight (kg)	**-2.97**	-4.75	-1.19	**-2.29**	-4.08	-0.49
Change in HbA1c (%)	**-0.10**	-0.18	-0.03	**-0.13**	-0.20	-0.05
Change in SBP (mm Hg)	**-1.33**	-3.35	0.70	**-2.26**	-4.58	0.06
Change in Cholesterol (mmol/L)	**-0.04**	-0.10	0.02	**-0.08**	-0.16	0.01
Conservative Scenario: Including Finnish DPS but excluding US DPP						
Progression to Diabetes (risk ratio)	**0.34**	0.15	0.75	**0.63**	0.37	1.08
Change in weight (kg)	**-2.41**	-3.44	-1.38	**-1.71**	-3.17	-0.24
Change in HbA1c (%)	**-0.07**	-0.12	-0.02	**-0.09**	-0.21	0.02
Change in SBP (mm Hg)	**-1.33**	-3.35	0.70	**-1.72**	-5.85	2.41
Change in Cholesterol (mmol/L)	**-0.04**	-0.10	0.02	**-0.09**	-0.22	0.05
Pessimistic Scenario: Excluding US DPP and Finnish DPS						
Progression to Diabetes (risk ratio)	**0.39**	0.10	1.50	**0.80**	0.50	1.28
Change in weight (kg)	**-2.15**	-3.14	-1.15	**-1.30**	-2.89	0.30
Change in HbA1c (%)	**-0.04**	-0.08	-0.01	**-0.04**	-0.13	0.05
Change in SBP (mm Hg)	**-0.06**	-1.53	1.40	**0.44**	-1.98	2.86
Change in Cholesterol (mmol/L)	**-0.06**	-0.13	0.02	**-0.02**	-0.19	0.14

The data suggests that weight loss compared to control is maximal at 12 months in all three scenarios, then declines over the next two years. Statistically significant reductions in HbA1c are seen at year one, whilst changes in total cholesterol and SBP are not quite significant (Table 28), which may be due in part to the smaller number of studies that collected this data. At three years, these reductions in metabolic factors are maintained or even increased

in most scenarios; the exception is in the pessimistic scenario where the observed change in SBP compared to control is actually positive.

Metformin for Diabetes Prevention

Only one intention to treat study; the US DPP, was found in the clinical review to inform data around effectiveness of the intensive lifestyle intervention (Table 29).

Table 29: Study included in the metformin effectiveness data used in the model, and its baseline characteristics.

Study	N	Mean BMI (kg/m^2)	Mean Age (years)	Mean HbA1c (%)	Mean FPG (mmol/L)	Ref.
US DPP (various articles)	3,234	34.0	50.6	5.91	5.90	14;45;46

The US DPP reports that 72% of individuals took at least 80% of their prescribed medication [14]. Individuals were strongly encouraged to adhere to their medication within the US DPP trial and this rate of adherence is unlikely to be achieved in practice. Adherence to metformin for diabetes treatment has been shown to be correlated with outcomes [47], and therefore effectiveness estimates could be expected to be reduced if adherence is lower than observed in the US DPP. Estimates of real world adherence to metformin for prevention are not available as it is currently not standard practice to prescribe metformin for this purpose. Adherence to metformin for diabetes treatment has been estimated at 76% of individuals taking treatment as prescribed, in a systematic review from 2004 [48]; however, it is likely that drug adherence for prevention will be lower than this. The use of statins in primary prevention of cardiovascular disease could be considered to parallel the use of metformin for diabetes prevention. A recent meta-analysis found that adherence to statins was only 57% using criteria of the number of prescriptions filled [49]. Actual adherence is likely to be much lower than this when individuals who miss a proportion of their prescribed treatment are included.

The effectiveness data used in the model is presented in Table 30. Given that estimates of adherence were not available but were likely to be lower than that included within the US DPP effectiveness estimates, it was assumed that the observed effectiveness data represented an optimistic scenario. A conservative scenario was also estimated by reducing

the effectiveness proportionally in line with the difference in effectiveness seen between the optimistic and conservative intensive lifestyle intervention data.

Table 30: Metformin for diabetes prevention: Effectiveness data used in the model.

	One year follow-up			Three years follow-up		
	Mean	Lower	Upper	Mean	Lower	Upper
Optimistic Scenario: Data from US DPP						
Progression to diabetes (risk ratio)				**0.71**	0.61	0.82
Change in weight (kg)	**-2.27**	-2.68	-1.86	**-1.70**	-2.12	-1.28
Change in HbA1c (%)	**-0.09**	-0.12	-0.06	**-0.09**	-0.12	-0.06
Change in SBP (mm Hg)						
Change in Cholesterol (mmol/L)						
Conservative Scenario: Less Effective						
Progression to Diabetes (risk ratio)				**0.79**	0.62	1.00
Change in weight (kg)	**-1.84**	-1.94	-2.17	**-1.27**	-1.65	-0.63
Change in HbA1c (%)	**-0.06**	-0.08	-0.04	**-0.06**	-0.12	0.03
Change in SBP (mm Hg)						
Change in Cholesterol (mmol/L)						

The data suggests that, similarly to intensive lifestyle intervention, weight loss is maximal in the first year and then declines by year three, whilst reduction in HbA1c due to metformin appears to be constant between one and three years following intervention implementation. The US DPP does not present 12 month estimates of cholesterol and SBP change compared with baseline. However, by the three year time-point, no differences in cholesterol or SBP are observed. Given that no other evidence that metformin affects blood pressure or cholesterol could be found, changes in these metabolic factors were not implemented in the model.

Digitally Delivered Intervention

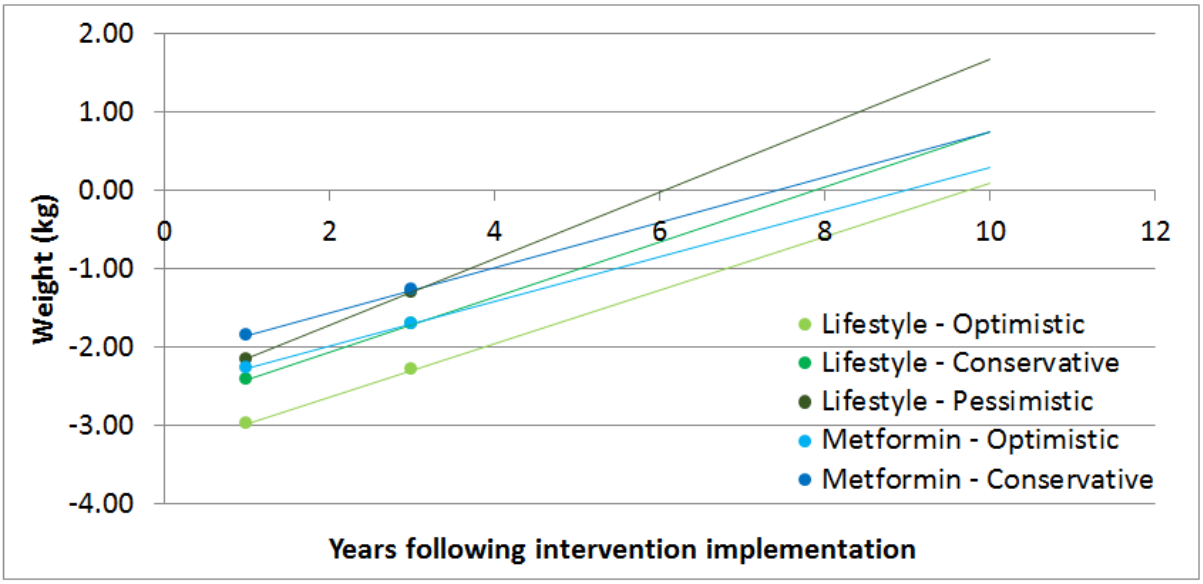
No data was available to estimate the effectiveness of a digitally delivered intervention, and therefore this was not modelled.

Duration of Intervention Effect

The review extracted effectiveness estimates from one year and three year time-points, but did not look at effectiveness over the long-term. A series of assumptions around duration of intervention effect, based on limited data, were therefore implemented.

In all three lifestyle and two metformin scenarios considered, the initial weight loss at year one is partially regained by year three. If it is assumed that this weight regain trend is linearly projected into subsequent years, then it is estimated that weight will be fully regained over a period that ranges between six years for the pessimistic lifestyle intervention to ten years for the optimistic lifestyle intervention (Figure 50).

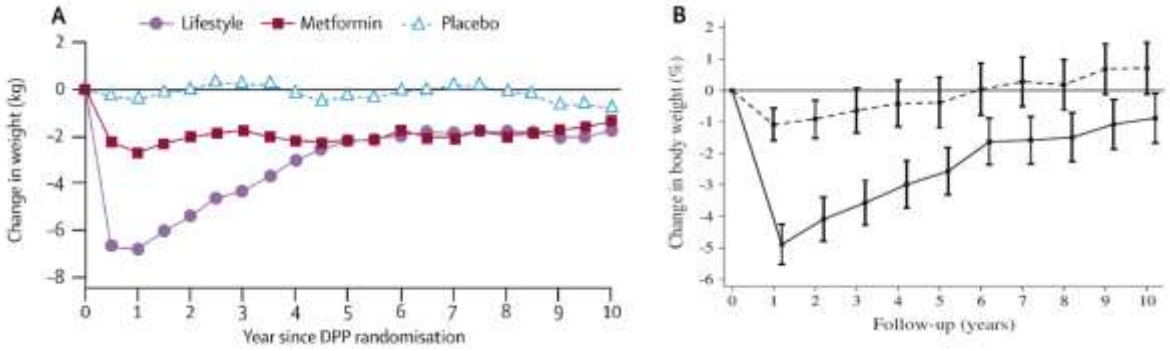
Figure 50: Diagram showing weight regain following intensive lifestyle intervention, linearly projected from one and three year observed data



Long-term follow-up data from both the US DPP and Finnish DPS indicates that individuals who have undergone an intensive lifestyle intervention or taken metformin for diabetes prevention do appear to regain weight linearly for 5-6 years, but then this tails off in the intensive lifestyle intervention so that at year ten weight is still lower (although non-significantly so) than in control individuals [45;50] (Figure 51). This supports modelling a 9-10 year period of linear weight regain as a reasonable approximation of the data for the

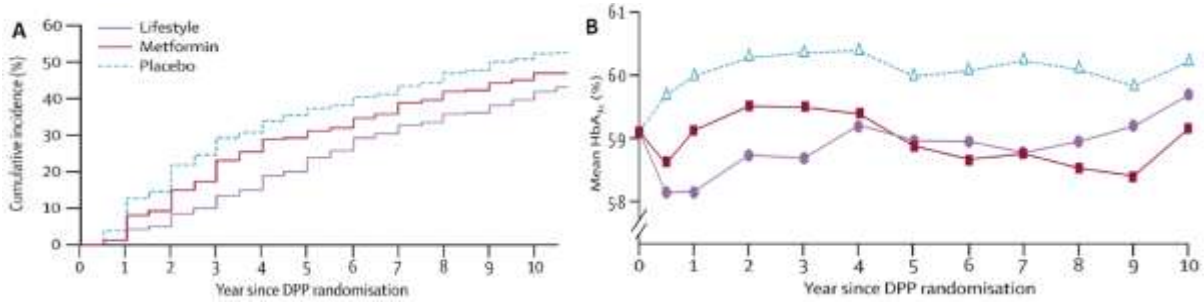
optimistic scenarios. Weight regain rates with metformin treatment are apparently dependent upon adherence to metformin, with individuals who only partially adhere regaining weight by year four, and those who poorly adhere regaining weight by year 2 [45]. This supports having a more rapid average regain in the conservative metformin scenario. Few other studies report weight loss data beyond three years; although there is evidence to support a weight regain period of no longer than five years for a one year dietary intervention for individuals with impaired glucose tolerance [51], suggesting that the weight regain period could be shorter than estimated even in the pessimistic lifestyle intervention scenario. However, the intervention used in that study does not fulfil the 9-12 NICE guidelines criteria and does not include a physical activity component.

Figure 51: Figures from A) the US DPP and B) the Finnish DPS showing weight regain over ten years [45;50].



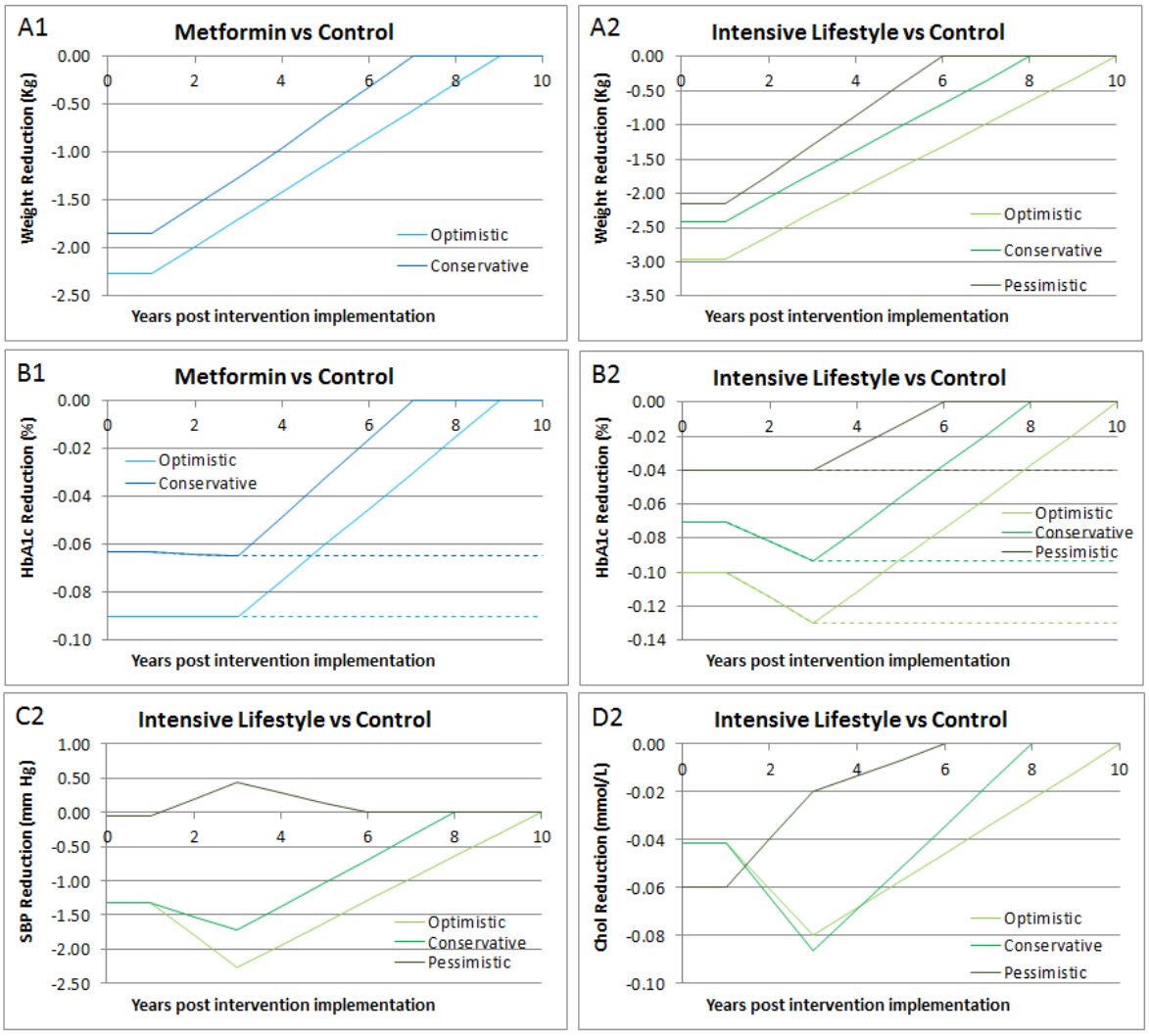
There is no data on long-term trajectories of SBP and total cholesterol, but there is some evidence from the US DPP which suggests that HbA1c reductions due to intensive lifestyle intervention or metformin treatment may be maintained for at least ten years [45] (Figure 52). This is supported by diabetes incidence reduction data from both the US DPP and Finnish DPS [45;50], which indicate that cumulative diabetes incidence is persistently lower in the intervention arms compared with the control arm, suggesting that HbA1c may not return to baseline in the same way that weight does. However, as previously mentioned, both of these studies provided a lot of follow-up support and maintenance to participants to help them adhere to the interventions. There is evidence from the US DPP that those who stopped taking metformin rapidly became at much higher risk of diabetes, suggesting that the reduction in HbA1c was lost following non-adherence [45]. It is also unclear whether the persistent reduction of HbA1c following intensive lifestyle intervention would be retained if individuals do not adhere to the lifestyle recommendations as well as they do in the US DPP, as is likely in practice.

Figure 52: Figures from the US DPP showing A) Cumulative diabetes incidence; B) HbA1c trajectories, over ten years [45].



For consistency with the weight regain period, it was assumed in the basecase set of scenarios that following year three, reduction in HbA1c, SBP and Cholesterol would linearly decline, reaching zero at the same point as the weight was fully regained. However, given the suggestion that HbA1c reductions might be maintained indefinitely, an alternative set of scenarios were also modelled in which it was assumed that the year three HbA1c reduction was maintained until either death or diabetes diagnosis. Once diagnosed with diabetes, individuals follow trajectories based upon the UK PDS Outcomes Study and are assumed to no longer benefit from any intervention effects. Diagrams showing the difference between control and intervention for all four metabolic trajectories and all intervention scenarios over the first ten model years are shown in Figure 53.

Figure 53: Metabolic trajectories implemented to model intervention effect. A = weight reduction; B = HbA1c reduction; C = SBP reduction; D = cholesterol reduction. Dotted lines in B indicate alternative scenario of persistent HbA1c reduction.



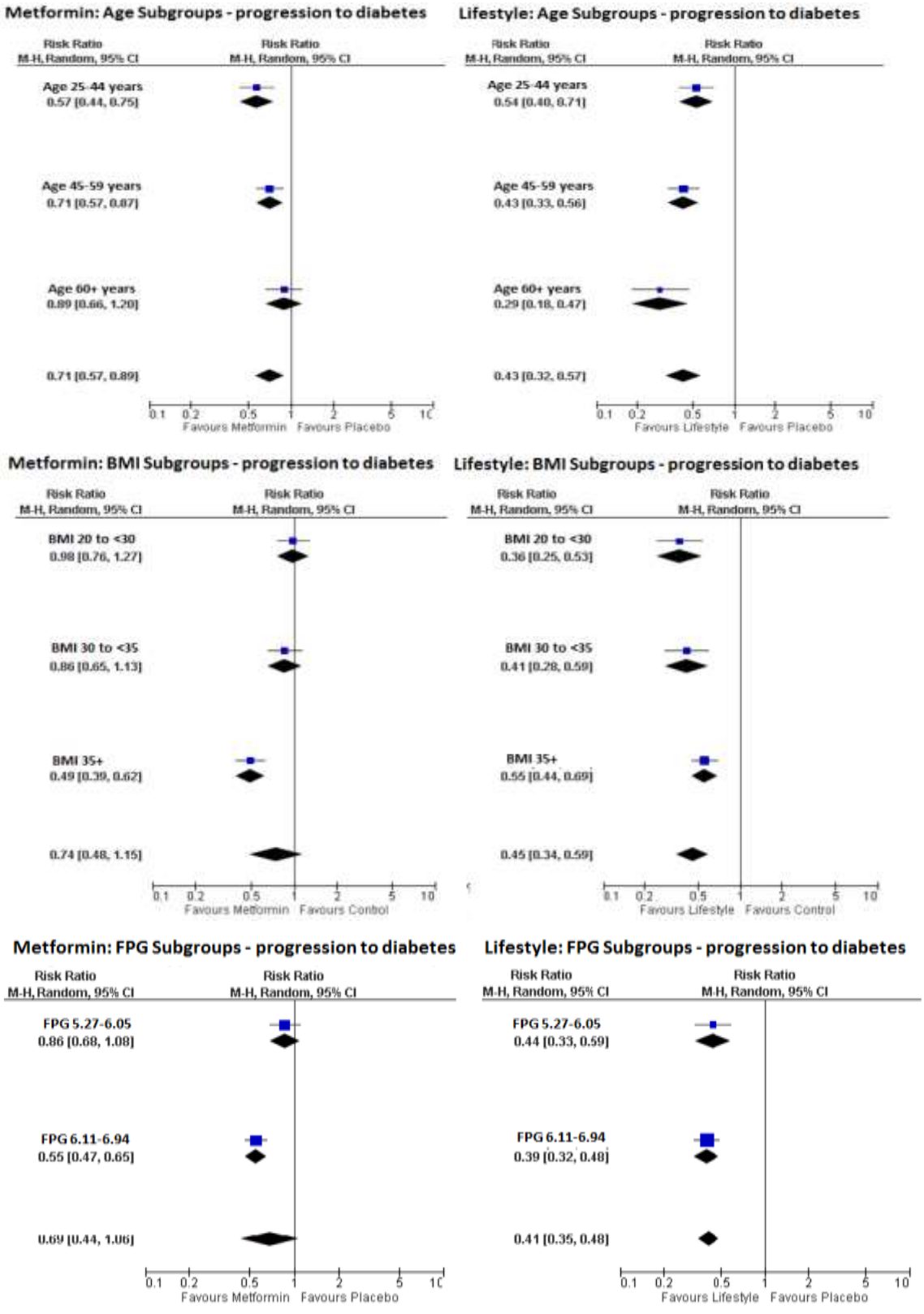
Stratifying Intervention Effectiveness by Personal Characteristics

Stratifying HbA1c

There is evidence that diabetes prevention interventions may be differentially effective in different population subgroups [11;14;16]. Of the studies included in the clinical review, only the US DPP describes differential effectiveness in different population subgroups, and this is measured by reduction in incidence of diabetes (Figure 54 & [14]). Most of the differences between subgroups observed in the US DPP are not significant. However, the study did observe a significantly greater effect of metformin versus control among people with higher baseline BMI or higher baseline FPG. A significantly greater effect of intensive lifestyle intervention versus metformin was also observed amongst people who were older or had

lower baseline BMI, reflecting the opposite trends seen for the age and BMI subgroups between the two interventions.

Figure 54: Forest plots from the within study subgroup analysis derived from data from the US DPP comparing progression to diabetes in interventions versus control for age, BMI and FPG subgroups. Note the trends by BMI and age are in opposite directions for metformin and for intensive lifestyle intervention, resulting in significant differences between the two interventions.



The SPHR Diabetes Prevention Model implements diabetes incidence reductions indirectly through changes in HbA1c; however, there is currently no evidence about whether the magnitude of HbA1c reduction due to either intensive lifestyle intervention or metformin differs by subgroup. To reflect the observed differences in diabetes incidence reduction between subgroups seen in the US DPP, a calibration process was therefore undertaken to find the optimal stratification of HbA1c trajectories by baseline BMI, FPG and age. Calibration of HbA1c trajectories by ethnic group was not performed, due to the non-significance of these subgroup differences in the US DPP, and the number of multiple different ethnic minority groups. It was decided that calibration should be done for both interventions for consistency, even though none of the intensive lifestyle intervention subgroup differences were significant compared with control. The process was undertaken via trial and error using the following steps:

1. Using data from the US DPP alone, the observed intensive lifestyle and metformin intervention effects on HbA1c at one year and three years were programmed into the model in the same way as described above. The proportional effect of each personal characteristic on the HbA1c reduction was then estimated; fairly imprecisely in the first round of calibration according to the observed direction of slope, but in later rounds was adjusted to better match the observed data. Linear stratification of HbA1c by baseline BMI, age and then baseline FPG were sequentially applied around the model population mean values for these characteristics as follows:

   Personalised Intervention Effect = Mean Intervention Effect

   + Mean Intervention Effect * BMI Effect * (Individual BMI – Mean BMI)

   + Mean Intervention Effect * Age Effect * (Individual Age – Mean Age)

   + Mean Intervention Effect * FPG Effect * (Individual FPG – Mean FPG)

   Where: Mean Intervention Effect = -0.18% (Lifestyle) OR -0.09% (Metformin)

   BMI/Age/FPG Effect = estimated proportion effect size

   Individual BMI = the baseline BMI of each individual in the population

   Mean BMI = 28.4 kg/m^2 (the mean BMI from the HSE 2011)

2. The model was run for 100 loops of 2,594 high risk individuals and three year diabetes incidence results averaged over model runs.

3. Diabetes incidence risk reductions due to intervention effect were calculated for the total population and for each subgroup.
4. Model predicted diabetes incidence reduction was compared with values observed in the US DPP trial through visualisation on graphs (see Figure 55) and the linear stratification values tweaked to enable them to better reflect the observed data in the next round of calibration.
5. Steps 2-4 were repeated until a reasonable estimate of diabetes incidence reduction rates was obtained (Table 31). This allowed a set of stratification variables to be estimated that could be used in the model for all intervention scenarios (Table 32).

Table 31: Observed (black) and estimated following calibration (red) risk ratios for diabetes incidence reduction at three years post intervention implementation for each intervention versus control in different population subgroups

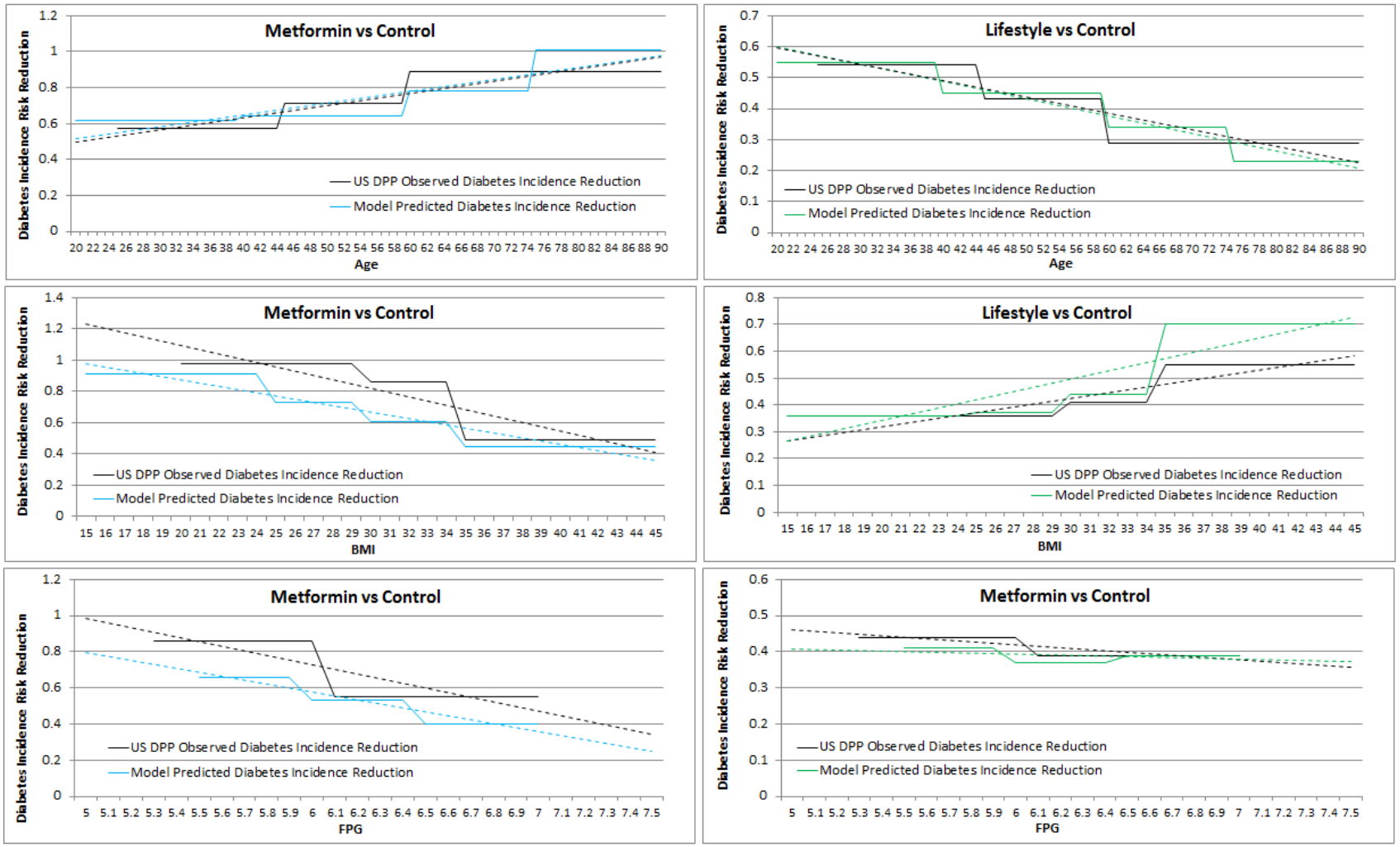
	US DPP	Model	US DPP	Model
Subgroup	**Intensive Lifestyle vs Control**		**Metformin vs Control**	
Total Population	**0.44**	**0.42**	**0.71**	**0.72**
Age 25-44	0.54	0.55	0.57	0.62
Age 45-59	0.43	0.45	0.71	0.64
Age 60+	0.29	0.30	0.89	0.86
Ethnic White	0.50	0.42	0.75	0.72
Ethnic African American	0.41	0.45	0.58	0.67
Ethnic Asian	0.30		0.64	
BMI 20- <30	0.36	0.36	0.98	0.80
BMI 30- <35	0.41	0.44	0.86	0.61
BMI 35+	0.55	0.70	0.49	0.45
FPG 5.27 -6.05	0.44	0.41	0.86	0.66
FPG 6.11 - 6.94	0.39	0.37	0.55	0.52

Table 32: Stratification variables applied to HbA1c by age, BMI and FPG for each intervention. Each variable represents the additional proportional HbA1c change per unit of personal characteristic above the population mean.

	Intensive Lifestyle Intervention	Metformin
Age Variable (per year)	0.015	-0.038

BMI Variable (per 1 kg/m^2)	-0.050	0.120
FPG Variable (per 1 mmol/l)	0.400	1.500

Figure 55: Observed and model predicted diabetes incidence risk reduction by subgroups defined by age, baseline BMI or baseline FPG for Metformin or intensive lifestyle intervention compared with control. Dotted lines indicate linear projections of incidence risk ratios.



There were several problems with this calibration process. Firstly, there is some correlation between FPG, age and BMI in the high risk population, so modifying the stratification variable for one characteristic had some impact on the others. This however was relatively small so did not pose too much of a problem. Secondly, it is clear that the relationship between HbA1c change and each personal characteristic is unlikely to be linear, particularly for BMI (Figure 55). However, there was insufficient time to develop a more complex model of the relationships. Finally, differences in population composition between the modelled HSE 2011 and the US DPP meant that it was not possible to accurately simulate diabetes incidence reduction over all subgroups and the total population simultaneously. The populations differ particularly by BMI (mean BMI in the US DPP is 34 kg/m^2 [14], whereas it is only 28.4 kg/m^2 in the model population), which means that the estimated BMI stratification does not match the observed BMI stratification slope particularly well (Figure 55). Due to these limitations and the uncertainty around the accuracy of the US DPP data, it was decided that a set of scenarios would be modelled that included HbA1c stratification and compared against a second set of modelled scenarios in which all individuals received the mean amount of HbA1c reduction no matter what their personal characteristics.

The estimated diabetes incidence reduction at three years in the total population, in each of the five intervention scenarios with or without HbA1c stratification, is compared with observed diabetes incidence risk reduction from the modelled studies in Table 33. This indicates that the model is able to estimate diabetes incidence risk reduction at three years fairly accurately in all five scenarios (exact matches are not expected for intensive lifestyle intervention as different studies report HbA1c reduction and diabetes incidence reduction), and provides an external validation of the evolution of HbA1c trajectories in the model. Adding stratification of HbA1c by personal characteristic does affect the total population diabetes incidence reduction; for metformin the model predicts total diabetes incidence risk reduction more accurately following stratification, whereas for intensive lifestyle intervention the model predicts total diabetes incidence risk reduction slightly more accurately if stratification is not performed.

Table 33: Comparison of observed and model predicted three year diabetes incidence risk reduction in the total population for each intervention.

	Observed (95% CI)	**Predicted: HbA1c not Stratified**	**Predicted: HbA1c Stratified**
Pessimistic lifestyle intervention	0.80 (0.50-1.28)	0.83	0.84
Conservative lifestyle intervention	0.63 (0.37-1.08)	0.67	0.69
Optimistic lifestyle intervention	0.57 (0.37-0.88)	0.55	0.58

Conservative metformin intervention	0.79 (0.62-1.00)	0.73	0.78
Optimistic metformin intervention	0.71 (0.61-0.82)	0.64	0.73

Stratifying Weight Loss

As part of the clinical review, a crude estimate of mean weight loss following intensive lifestyle intervention versus control, across studies with different mean baseline BMI, baseline age and baseline blood glucose (HbA1c and FPG) was carried out. As this uses the study means, rather than individual values, to estimate subgroup effects, the results must be interpreted with caution. Whilst none of the findings indicate significant differences between subgroups, there is a trend for weight loss to be higher in studies with high mean baseline BMI than in studies with low mean baseline BMI (Table 34). If assumed to be linear, this trend implies a 0.14kg additional weight loss for each unit of baseline BMI higher than the weighted study mean BMI of 32.5 kg/m^2, or 0.14kg lower weight loss for each unit of baseline BMI below 32.5 kg/m^2.

Table 34: Inter-study subgroup analysis: Mean weight loss found in studies of intensive lifestyle intervention versus control, separated into subgroups due to study mean baseline Age, BMI, FPG or HbA1c. Not estimable indicates that none of the selected studies fall into that subgroup.

Included Studies	Mean	Lower	Upper
All with age data	***-3.03***	*-4.63*	*-1.44*
Age < 40	**Not estimable**		
Age 40-59	**-3.37**	-4.66	-2.08
Age 60-74	**-0.21**	-0.84	0.42
Age 75+	**Not estimable**		
All with BMI data	***-3.07***	*-4.78*	*-1.37*
BMI < 25	**Not estimable**		
BMI 25-29	**-2.34**	-3.27	-1.41
BMI 30-34	**-3.28**	-5.93	-0.64
BMI 35+	**-3.37**	-5.96	-0.78
All with FPG data	***-2.83***	*-4.77*	*-0.89*
FPG 5-5.9	**-3.1**	-5.28	-0.91
FPG 6-6.4	**-1.76**	-5.14	1.62

FPG 6.5-6.9	**Not estimable**		
All with HbA1c data	***-2.95***	*-4.84*	*-1.07*
HbA1c < 6	**-3.81**	-5.49	-2.13
HbA1c 6-6.1	**-1.6**	-3.23	0.04
HbA1c 6.2-6.4	**Not estimable**		

Previous work for Public Health England using the SPHR diabetes prevention model to analyse an intensive lifestyle intervention has assumed that intervention effectiveness is higher in individuals with high baseline BMI. This assumption was based on a similarly designed inter-study subgroup analysis carried out as part of the recent PHE evidence review [11]. For consistency with the previous piece of work, stratification of weight loss was therefore applied in the model to the intensive lifestyle intervention. This was implemented by applying personalised intervention effects for each individual dependent upon their baseline BMI, calculated using the following equation:

Personalised Intervention Effect = Mean Intervention Effect

+ BMI Effect * (Individual BMI – Mean BMI)

Where: Mean Intervention Effect = -3.03 kg

BMI Effect = -0.14 kg

Cholesterol and SBP trajectories were stratified in line with weight trajectories, due to the known correlations between weight, cholesterol and SBP. HbA1c trajectories however, were not stratified in line with weight loss trajectories given their calibration to the diabetes incidence reduction data discussed above.

It is less clear whether weight loss due to metformin is stratified by baseline BMI or by other personal characteristics. Two relevant studies were found which indicated that whilst percentage weight loss due to metformin may not be significantly associated with baseline BMI, absolute weight loss (as implemented in the model) is likely to be [52;53]. This was significant in one study, which looked at the effectiveness of metformin on weight loss in non-diabetic individuals with obesity, and where the mean weight loss ranged from 3.4kg in those with BMI 27-32.6 kg/m^2 to 8.5kg in those with BMI ≥ 37.5 kg/m^2 [53]. The second study examined weight loss in individuals with diabetes in China and concluded that the smallest percentage decrease from baseline body weight was observed in the normal weight

subgroup [52]. Stratification of weight loss was therefore applied in the model to the metformin intervention. Given the lack of evidence to suggest such weight loss stratification would differ in any way from that applied to the lifestyle intervention, personalised intervention effects were calculated in the same way as described above for the lifestyle intervention, using the same BMI effect of -0.14 kg. One difference was implemented: the BMI around which the stratification effect was applied was assumed to be 34 kg/m^2, which is the mean BMI of individuals in the US DPP study from which the metformin effectiveness data is derived.

Table 35 and Table 36 show the mean reductions in weight, SBP, cholesterol and HbA1c seen in each modelled subgroup following implementation of the intensive lifestyle intervention conservative scenario (Table 35), or the metformin conservative scenario (Table 36), assuming that HbA1c is stratified in line with the calibration described above and that weight/SBP/cholesterol reductions are stratified by BMI. It is important to note that the mean baseline BMI of the modelled high risk population is only 28.4 kg/m^2; considerably lower than the mean baseline BMI in either the reviewed lifestyle intervention studies (32.5 kg/m^2) or in the metformin study (US DPP – 34 kg/m^2). The lower BMI implies that the intervention will be less effective in the English population than in the study population. One consequence of stratifying intervention effectiveness by baseline BMI is therefore to reduce the mean weight loss (and SBP and cholesterol reduction) following intervention in the total high risk population compared with the figures shown in Table 27 and Table 30.

Table 35: Intensive lifestyle intervention conservative scenario with HbA1c stratification: Mean weight, SBP, cholesterol and HbA1c reduction at one year in each of the chosen population subgroups.

Subgroup	Weight Reduction (kg)	SBP Reduction (mm Hg)	Cholesterol Reduction (mmol/L)	HbA1c Reduction (%)
TOTAL	**-1.96**	**-1.06**	**-0.033**	**-0.069**
Single Subgroups				
IMD 1 (least deprived)	-1.93	-1.05	-0.033	-0.072
IMD 2	-1.96	-1.06	-0.033	-0.072
IMD 3	-1.93	-1.05	-0.033	-0.072
IMD 4	-1.98	-1.07	-0.033	-0.066
IMD 5 (most deprived)	-1.99	-1.08	-0.034	-0.062
Age < 40	-1.80	-0.98	-0.030	-0.047
Age 40-59	-2.03	-1.11	-0.034	-0.063

Age 60-74	-1.99	-1.09	-0.034	-0.082
Age >= 75	-1.93	-1.05	-0.033	-0.101
BMI < 25 (White) OR BMI < 23 (BME)	-1.23	-0.67	-0.021	-0.083
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-1.81	-0.99	-0.031	-0.075
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-2.36	-1.29	-0.040	-0.062
BMI >= 35 (White OR BME)	-3.23	-1.76	-0.055	-0.033
Ethnicity White	-1.96	-1.07	-0.033	-0.071
Ethnicity BME	-1.90	-1.04	-0.032	-0.059
Sex Male	-1.92	-1.05	-0.033	-0.071
Sex Female	-1.97	-1.08	-0.033	-0.068
HbA1c 6-6.1	-1.94	-1.05	-0.033	-0.068
HbA1c 6.2-6.4	-1.95	-1.06	-0.033	-0.072
FPG 5.5-5.9	-1.98	-1.07	-0.033	-0.069
FPG 6-6.4	-2.04	-1.11	-0.035	-0.080
FPG 6.5-6.9	-2.22	-1.21	-0.038	-0.091
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-1.94**	**-1.06**	**-0.033**	**-0.070**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-3.20*	*-1.75*	*-0.054*	*-0.041*
1) HbA1c 6-6.4, BMI >=35	-3.24	-1.77	-0.055	-0.032
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-2.37	-1.29	-0.040	-0.065
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-2.35	-1.28	-0.040	-0.060
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.85	-1.01	-0.031	-0.094
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.83	-1.00	-0.031	-0.090
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.78	-0.97	-0.030	-0.063
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.78	-0.97	-0.030	-0.057
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-1.18	-0.65	-0.020	-0.083

9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-1.20	-0.66	-0.020	-0.083
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-2.00**	**-1.09**	**-0.034**	**-0.072**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-3.13*	*-1.71*	*-0.053*	*-0.062*
1) FPG 5.5-6.9, BMI >=35	-3.26	-1.78	-0.055	-0.034
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-2.37	-1.29	-0.040	-0.083
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-2.36	-1.29	-0.040	-0.072
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-2.37	-1.29	-0.040	-0.060
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.85	-1.01	-0.031	-0.133
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.87	-1.02	-0.032	-0.112
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.83	-1.00	-0.031	-0.095
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.93	-1.05	-0.033	-0.078
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.80	-0.99	-0.031	-0.071
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.80	-0.98	-0.030	-0.062
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-1.43	-0.79	-0.024	-0.115
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-1.25	-0.68	-0.021	-0.104
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-1.27	-0.69	-0.021	-0.085

Table 36: Metformin conservative scenario with HbA1c stratification: Mean weight, SBP, cholesterol and HbA1c reduction at one year in each of the chosen population subgroups.

Subgroup	Weight Reduction (kg)	SBP Reduction (mm Hg)	Cholesterol Reduction (mmol/L)	HbA1c Reduction (%)

TOTAL	**-1.35**	**0.00**	**0.000**	**-0.065**
Single Subgroups				
IMD 1 (least deprived)	-1.33	0.00	0.000	-0.061
IMD 2	-1.35	0.00	0.000	-0.059
IMD 3	-1.32	0.00	0.000	-0.066
IMD 4	-1.36	0.00	0.000	-0.069
IMD 5 (most deprived)	-1.37	0.00	0.000	-0.075
Age < 40	-1.23	0.00	0.000	-0.111
Age 40-59	-1.40	0.00	0.000	-0.081
Age 60-74	-1.37	0.00	0.000	-0.035
Age >= 75	-1.33	0.00	0.000	0.002
BMI < 25 (White) OR BMI < 23 (BME)	-0.79	0.00	0.000	-0.018
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-1.24	0.00	0.000	-0.054
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-1.65	0.00	0.000	-0.089
BMI >= 35 (White OR BME)	-2.32	0.00	0.000	-0.161
Ethnicity White	-1.35	0.00	0.000	-0.063
Ethnicity BME	-1.31	0.00	0.000	-0.083
Sex Male	-1.32	0.00	0.000	-0.070
Sex Female	-1.36	0.00	0.000	-0.059
HbA1c 6-6.1	-1.33	0.00	0.000	-0.045
HbA1c 6.2-6.4	-1.34	0.00	0.000	-0.055
FPG 5.5-5.9	-1.36	0.00	0.000	-0.067
FPG 6-6.4	-1.41	0.00	0.000	-0.118
FPG 6.5-6.9	-1.54	0.00	0.000	-0.174
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-1.33**	**0.00**	**0.000**	**-0.050**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-2.29*	*0.00*	*0.000*	*-0.065*
1) HbA1c 6-6.4, BMI >=35	-2.33	0.00	0.000	-0.133
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-1.66	0.00	0.000	-0.071

3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-1.65	0.00	0.000	-0.067
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.26	0.00	0.000	-0.013
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.25	0.00	0.000	-0.015
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.21	0.00	0.000	-0.073
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.21	0.00	0.000	-0.054
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-0.75	0.00	0.000	-0.015
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-0.77	0.00	0.000	-0.010
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-1.38**	**0.00**	**0.000**	**-0.081**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-2.24*	*0.00*	*0.000*	*-0.082*
1) FPG 5.5-6.9, BMI >=35	-2.34	0.00	0.000	-0.195
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-1.66	0.00	0.000	-0.195
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-1.65	0.00	0.000	-0.145
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-1.66	0.00	0.000	-0.087
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.26	0.00	0.000	-0.033
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.28	0.00	0.000	-0.034
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-1.25	0.00	0.000	-0.018
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.32	0.00	0.000	-0.219
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.23	0.00	0.000	-0.140
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-1.22	0.00	0.000	-0.079
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-0.95	0.00	0.000	-0.076

12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-0.81	0.00	0.000	-0.033
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-0.82	0.00	0.000	-0.022

Intervention Uptake

Intervention uptake has not been considered in this analysis. Whilst an estimate of NHS DPP uptake at 32% of those offered the intervention was applied in the PHE cost-effectiveness analysis [1], it is assumed for the current analysis that there are no additional costs of identifying or referring individuals to interventions that they do not wish to take up. Under this assumption, if uptake were to be included, cost-effectiveness estimates would not change from those presented here as the model would produce proportional changes in costs and QALYs that cancel out when calculating relative cost-effectiveness of different interventions or across different subgroups. Uptake estimates are useful for budget impact assessment; however, currently no estimates of NHS DPP uptake by different subgroups of the population are available, and no estimates of potential uptake of metformin for diabetes prevention were identified in the evidence review.

Intervention Costs

It is assumed that the intensive lifestyle intervention costs reflect the cost of the NHS DPP. Previous work with the model for PHE used a cost of £270 per participant, which came from NHS England's impact assessment and represents the mean cost to NHS England for each individual undergoing the NHS DPP, incorporating expected retention rates of participants [19].

Now that the NHS DPP is being rolled out across England a revised cost of £223 per participant has been provided by NHS England (personal communication from Paul De Ponte, Analytics Lead for the NHS DPP, NHS England). This cost is based on the agreed four provider prices for Wave 1, weighted according to market share (based on projected referrals to each provider for the first year, 2016/17) and the milestone payments negotiated with each provider. Whilst payments are based on participant retention rates, these are not yet known as insufficient time has elapsed to evaluate the programme, so remain the same as those estimated in the impact assessment [19]. The cost is assumed to be a one-off cost, incurred in the first year of the model.

It was assumed that costs of metformin treatment for diabetes prevention would incorporate not only the medication cost, but also costs of regular blood tests and contact time with health care professionals. The dose of metformin used in the US DPP study was 850 mg

twice daily [14], whilst NICE PH38 guidelines recommend 1,500-2,000 mg daily [4]. However, the guidelines committee suggested that some individuals would be unlikely to be able to tolerate this level of dosage. Costs were therefore based on 1,500mg daily metformin, which is the same level assumed for first line treatment of diabetes in the model. It was assumed, in line with metformin for diabetes treatment already implemented in the model, that 15% of individuals would be taking modifiable release metformin due to gastrointestinal intolerance. This produced an average annual cost per person of £28.24 using drug costs from the British National Formulary[31].

It is recommended in NICE guidelines PH38 that individuals taking metformin for prevention undergo twice yearly renal function monitoring and three monthly HbA1c testing in the first 6-12 months [4]. However, PH38 also recommends that all identified individuals at high risk of diabetes should undergo annual HbA1c and lipid testing (annual screening for HbA1c and lipids in all high risk individuals is already implemented in the model), and the guidelines committee suggested that renal function testing should also be given to all individuals at high risk of diabetes whether taking metformin or not, but possibly more frequently in the elderly. When costing an intervention it is important to only consider those costs that are additional to those incurred by individuals in the control arm. The guidelines committee advised that the only additional tests for individuals taking metformin would be annual liver function tests and B12 tests. Whilst the guidelines committee suggested that a B12 test could cost as much as £10, no reference source for this could be identified; B12 and liver function tests were therefore costed at £3.13 each, according to the costs of 'other tests' in the national schedule of NHS reference costs [54].

Managing an individual taking metformin will incur additional costs of healthcare professional time. In line with the costings for metformin for diabetes treatment already implemented in the model, it was assumed that an annual appointment with an advanced nurse practitioner would also be required, costed at £25.52 per surgery consultation from the Personal and Social Services Research Unit (PSSRU) unit costs [32]. Whilst the costs of metformin for diabetes treatment in the model also include ten minutes of healthcare assistant time to take blood samples for testing, this was not included in the intervention cost as it was assumed that the extra blood samples for liver function and B12 testing would be taken at the same time as the annual HbA1c and lipid tests given to all individuals at high risk of diabetes, and that therefore any additional cost would be negligible. The total annual costs of metformin treatment were therefore estimated at £60.01 (Table 37).

Table 37: Costs of metformin for diabetes prevention implemented in the model. Note that individuals will also receive an additional annual HbA1c test, lipid test and kidney function test. However, this is not incorporated into intervention

costs as all high risk individuals are expected to receive these whether taking metformin or not.

	Annual Cost
ANNUAL COSTS	**£60.01**
Metformin 3 x 500mg daily, 15% taking modifiable release due to GI intolerance	£28.24
Appointment with advanced nurse practitioner	£25.52
Liver function testing	£3.13
B12 testing	£3.13
PLUS EXTRA COST IN YEAR 1	**£78.35**
2 appointments with advanced nurse practitioner	£51.03
2 appointments with health care assistant	£6.80
2 additional HbA1c tests	£6.00
2 additional lipid tests	£2.00
2 additional Liver function tests	£6.26
2 additional B12 tests	£6.26

It was thought that the first year of treatment would incur additional costs, due to the requirement for three monthly blood testing over the first 6-9 months during titration of optimal metformin dosage. An additional two tests for HbA1c, lipids, liver function and B12 were therefore assumed to be required in the first year, together with an additional two appointments with an advanced nurse practitioner and an additional two lots of ten minute appointments with a healthcare assistant. The total extra cost of metformin treatment in year one was estimated at £78.35 (Table 37).

Not all individuals will adhere to metformin treatment. Data from the US DPP suggests that in the second phase of the study (starting three years after intervention initiation), only 70.1% of individuals in the metformin arm of the trial took metformin in any amount [46], and therefore were likely to incur costs. However, it seems plausible that all individuals who are willing to take up the metformin intervention initially would incur prescription costs in the first year. It was therefore assumed that in year one individuals would incur the full metformin cost, whilst in year four onwards individuals would only incur 70% of the metformin cost on average. In years two and three a linear decline in adherence and therefore cost was assumed. Individuals diagnosed with diabetes at any time point stop incurring costs of metformin for

diabetes prevention and instead incur costs of metformin for diabetes treatment, which are not counted as intervention costs. Base case, upper bound and lower bound costs where appropriate are shown in Table 38.

Table 38: Base case, upper and lower values of intervention costs per person taking up the intervention, and year in which the intervention cost is incurred

	When Cost Incurred	Base Case Cost	Upper Value	Lower Value
Intensive Lifestyle Intervention	Year 1	£223	N/A	N/A
Metformin for Prevention (only incurred in individuals without diabetes)	Year 1	£138.36	£160.96	£117.84
	Year 2	£54.01	£59.88	£48.68
	Year 3	£48.01	£53.23	£43.27
	Year 4 onwards	£42.01	£46.57	£37.86

5: Scenarios Modelled

As described earlier in these methods, 20 different scenarios were modelled in order to explore uncertainty around intervention effectiveness, duration of effect and stratification of effectiveness by personal characteristics (Table 39). These parameters were chosen for sensitivity analysis as they were particularly likely to impact upon subgroup ordering and the relative effectiveness of the intensive lifestyle intervention compared with metformin. Given the large number of subgroups and scenarios investigated, it was not practical to do further scenario analysis around other model parameters; however, previous work with the model has indicated that decision uncertainty is not particularly affected by deterministic sensitivity analysis involving non-intervention model parameters [12;18].

Table 39: Scenarios modelled for this analysis.

A: HbA1c Not Stratified; Returns to Baseline 1A: Pessimistic Intensive Lifestyle Intervention 2A: Conservative Intensive Lifestyle Intervention 3A: Optimistic Intensive Lifestyle Intervention 4A: Conservative Metformin Intervention 5A: Optimistic Metformin Intervention	**B: HbA1c Stratified; Returns to Baseline** 1B: Pessimistic Intensive Lifestyle Intervention 2B: Conservative Intensive Lifestyle Intervention 3B: Optimistic Intensive Lifestyle Intervention 4B: Conservative Metformin Intervention 5B: Optimistic Metformin Intervention
C: HbA1c Not Stratified; Persists 1C: Pessimistic Intensive Lifestyle Intervention 2C: Conservative Intensive Lifestyle Intervention 3C: Optimistic Intensive Lifestyle Intervention 4C: Conservative Metformin Intervention 5C: Optimistic Metformin Intervention	**D: HbA1c Stratified; Persists** 1D: Pessimistic Intensive Lifestyle Intervention 2D: Conservative Intensive Lifestyle Intervention 3D: Optimistic Intensive Lifestyle Intervention 4D: Conservative Metformin Intervention 5D: Optimistic Metformin Intervention

6: Running the Model

This analysis modelled a single cohort of high risk individuals, representing the English population, who either receive an intensive lifestyle intervention, metformin for diabetes prevention or no intervention, and all the downstream cost savings and health benefits that this produces in subsequent years. Individuals who are currently not at risk but may become high risk in subsequent years were not modelled.

Probabilistic sensitivity analysis (PSA) was carried out on all 20 scenarios; firstly in order to account for non-linearity in the model by providing an accurate estimate of mean cost-effectiveness results; and secondly to describe the uncertainty in parameter inputs of the model and how this translates into uncertainty in the outcomes of the model. A suitable distribution was selected for each parameter, based upon its mean and standard error. Random sampling simultaneously across all input parameter distributions allowed parameter uncertainty to be quantified. It is important to note that the estimate of uncertainty as obtained through PSA is of two types; parameter uncertainty and stochastic uncertainty that occurs due to the randomness present in the model and that is related to the number of individuals in the sample. This means that subgroups that comprise only a small proportion of the population have wider uncertainty around their outcomes than larger subgroups, as random events have a disproportional effect on results when they cannot be averaged out over many individuals. 2000 different random samples of parameter values were selected, and each was applied to the 2,594 high risk individuals from HSE 2011. Results for each individual were weighted using the individual level weights from the HSE 2011, to ensure their representativeness for the population of England. Model outcomes for each subgroup were extracted from the total results following each run. Mean outcomes estimates did not differ significantly whether results were averaged from 1000 or 2000 PSA runs, indicating that sufficient PSA samples had been taken. A list of model parameters, their distribution for PSA and their source is provided in Appendix A.

The SPHR Diabetes Prevention Model allows a variety of different outcomes to be gathered at various time points. For this analysis, lifetime costs and quality-adjusted life-years (QALYs) were gathered. All costs and QALYs were discounted by 3.5% as advised by NICE Centre for Health Technology guidelines [55]. Sensitivity analysis for all scenarios was also carried out in which a discount rate of 1.5% was used in line with previous NICE guidance for Public Health [56]. For easy comparison between subgroups, costs and QALYs were divided by the number of individuals given the intervention to obtain a per person result. In addition to these outcomes, estimates of diabetes incidence reduction at different time points following intervention were collected. Finally, to enable budget impact analysis, estimates of

costs and savings for each of the first five years following intervention implementation were gathered for each subgroup.

Intervention cost-effectiveness was assessed primarily using the incremental net monetary benefit (NMB) approach, assuming a threshold of £20,000 per QALY gained. NMB is particularly useful for comparing interventions where incremental cost-effectiveness ratios (ICERs) are negative, which occurs when interventions are cost-saving and QALY gaining. Incremental NMB is calculated as follows:

Incremental NMB (£/QALY) = (Incremental QALYs * QALY value (£)) – Incremental Costs (£)

Results

All the results in this section are presented as mean values of probabilistic sensitivity analysis, using a discount rate of 3.5%. A set of results charts using a discount rate of 1.5% can be found in Appendix 2. Whilst reducing the discount rate has a substantial impact in increasing the total QALYs gained and the total costs saved, it has only a subtle effect on the ordering of subgroups, resulting in slightly more benefits being accrued in younger rather than older individuals.

1: Cost-effectiveness of Intensive Lifestyle Intervention in Population Subgroups

In order to answer the question of which subgroups benefit most from an intensive lifestyle intervention, incremental monetary net benefit compared with control was calculated for each subgroup. The results are presented as follows:

A. Investigation of the impact on subgroup results of altering study effectiveness.
B. Investigation of the impact on subgroup results of HbA1c stratification.
C. Investigation of the impact on subgroup results of different assumptions around the duration of HbA1c reduction following intervention implementation.

1A: Investigating the Impact of Study Effectiveness on Lifestyle Intervention

The results presented in this section compare the effect of optimistic, conservative and pessimistic assumptions around intervention effectiveness, in the basecase scenario where the intervention effect on HbA1c is not stratified and returns to baseline at the same point as weight is fully regained. Summary results for the total population are shown in Table 40. Full results for each subgroup can be found in Appendix 3.

Table 40: Per person summary results for the total population when intensive lifestyle intervention is compared with control and HbA1c is neither stratified nor persistent.

Scenario	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)	Probability Cost-Effective
Optimistic	-£533	0.049	£1,520	-£10,816	100%
Conservative	-£244	0.031	£863	-£7,866	97%
Pessimistic	£24	0.013	£244	£1,802	79%

The most important findings to note are as follows:

A1.1 Intensive lifestyle intervention is predicted to be cost-effective compared to control, in all subgroups, in all three scenarios of intervention effectiveness (Figure

56). The NMB is about seven fold higher in the optimistic scenario compared with the pessimistic scenario.

A1.2 Subgroup ordering by NMB is very similar in all three scenarios of intervention effectiveness (Figure 56 and Figure 57).

The most cost-effective subgroup defined using a single characteristic in all three scenarios is the HbA1c 6.2-6.4 subgroup (Figure 56). The probability that it is more cost-effective to intervene specifically in this subgroup, rather than in anyone from the high risk population is close to 100% (

A1.3 Figure 58). In general, there is a trend for the intervention to be more cost-effective in those with higher HbA1c.

A1.4 A BMI trend is seen in which it is about 50% more cost-effective to intervene in those in the highest BMI group than those in the lowest BMI group.

A1.5 The most cost-effective combinatorial subgroup in all three scenarios is the 'HbA1c 6.2-6.4, overweight, aged < 60 subgroup'. Note, it is likely that if higher BMI combinatorial subgroups had been defined by both age and HbA1c in the same way as the over-weight subgroup, we would expect them to show results at least as cost-effective as this 'HbA1c 6.2-6.4, overweight, aged < 60 subgroup', because high cost-effectiveness is also seen in the 'HbA1c 6.2-6.4 and obese' subgroup, and in the 'HbA1c 6-6.4, BMI 35+' subgroup.

A1.6 In general, the results suggest that it is more cost-effective to intervene in subgroups with high HbA1c than with low HbA1c, with high FPG than with low FPG, with high BMI than with low BMI, in those of middle age (40-74) than those of high or low age, in females rather than males, in those with BME rather than white ethnicity and in those from more socioeconomically deprived backgrounds.

A1.7 The least cost-effective subgroups are those with individuals aged 75+ or <40, and those with FPG 5.5-5.9, particularly if BMI is also low.

A1.8 The results also suggest that it is more cost-effective to intervene in subgroups defined by HbA1c than those defined by FPG. In fact, cost-effectiveness is twice as high in the HbA1c 6-6.4 subgroup than in the FPG 5.5-6.9 subgroup. This is due to the cut-off points defined by each group, rather than HbA1c providing a fundamentally better test. The FPG 5.5-6.9 subgroup defines a relatively broad subgroup of individuals (almost 50% of the population), while the HbA1c 6.6.4 subgroup is comparatively much narrower.

A1.9 The results from subgroups defined using a single characteristic differ somewhat from the results obtained in the PHE subgroup analysis [1]. The PHE analysis found that the high BMI subgroups were most cost-effective, followed by the high HbA1c groups and those of middle age. The primary reason for the difference is that the analysis here additionally includes high risk individuals defined through FPG but not HbA1c as described above (whereas in the PHE analysis the population modelled were all HbA1c ≥ 6%), and it is this FPG defined subpopulation who reduce the cost-effectiveness of subgroups defined by BMI alone. A second factor is that the implemented stratification of weight loss by BMI is smaller than that used in the PHE analysis (-0.14kg instead of -0.23kg extra weight loss per unit BMI).

Figure 56: Mean incremental NBM per person of intensive lifestyle compared to control in different population subgroups under optimistic, conservative or pessimistic estimates of intervention effectiveness, assuming that HbA1c effect is neither stratified nor persistent. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

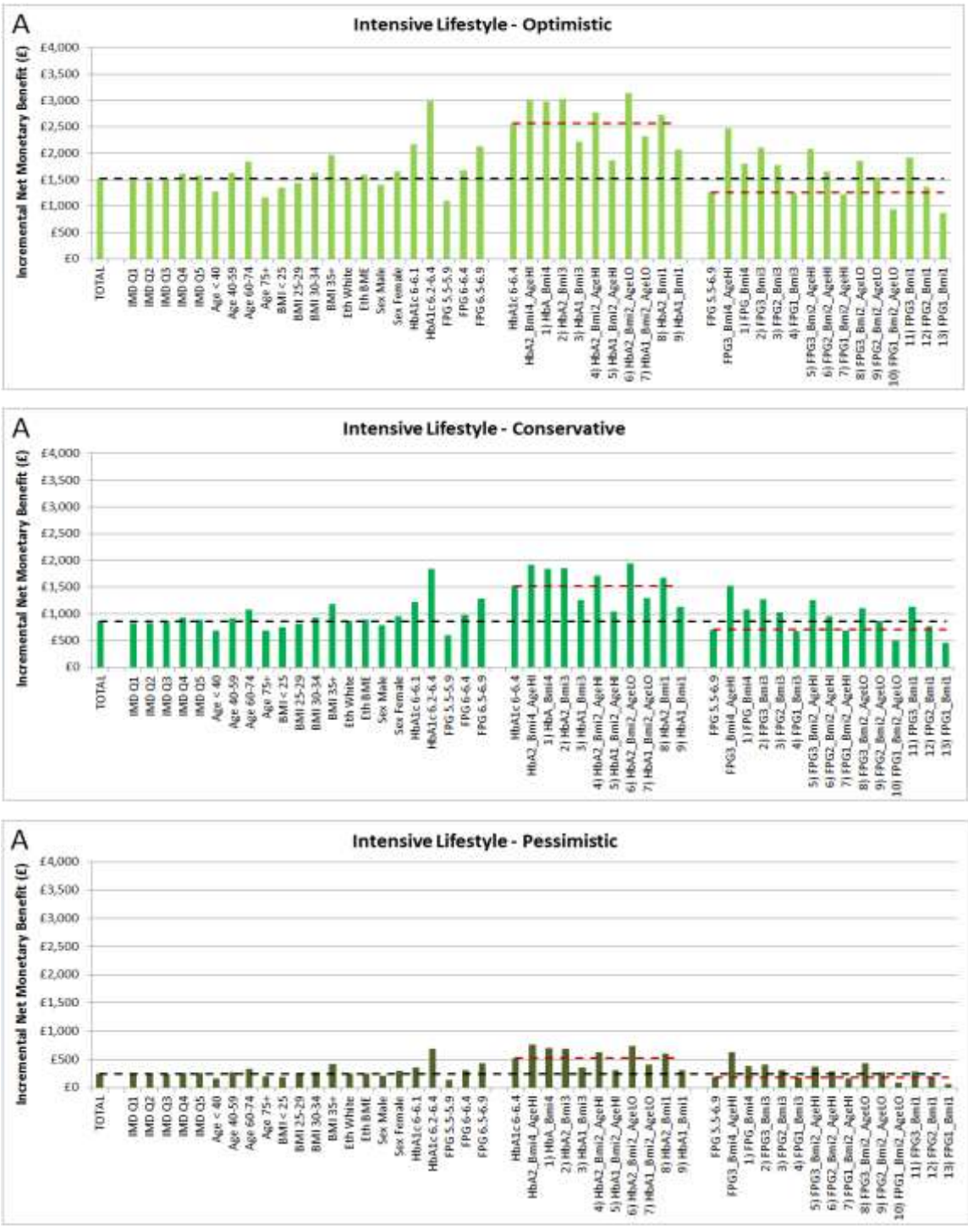


Figure 57: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is neither stratified nor persistent. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

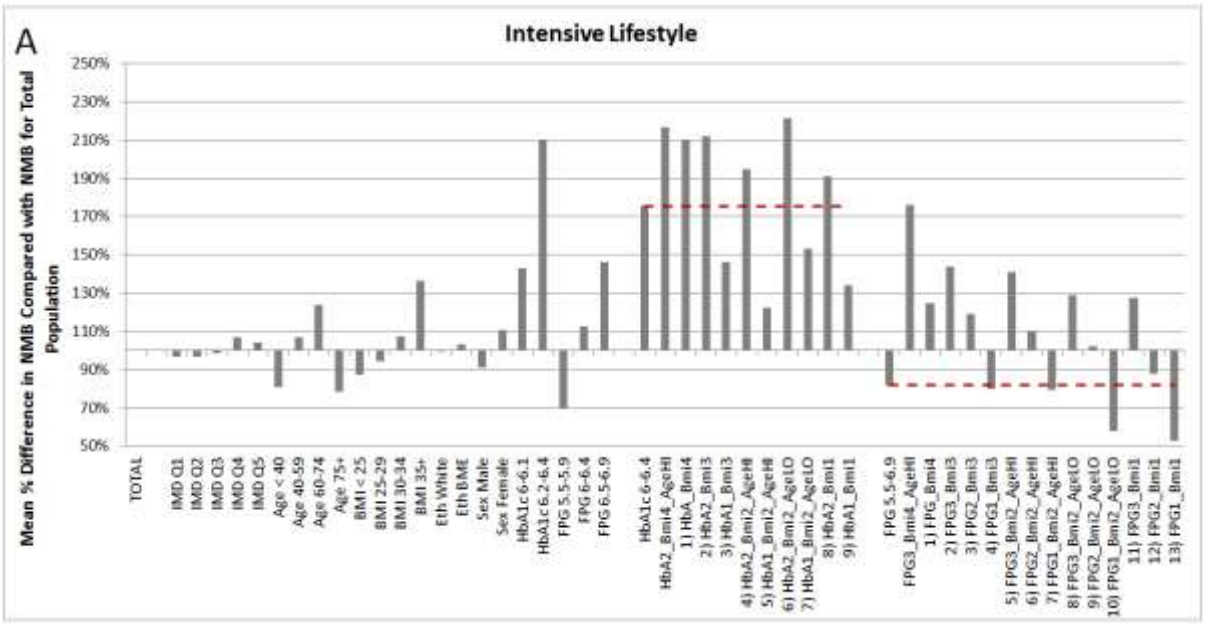
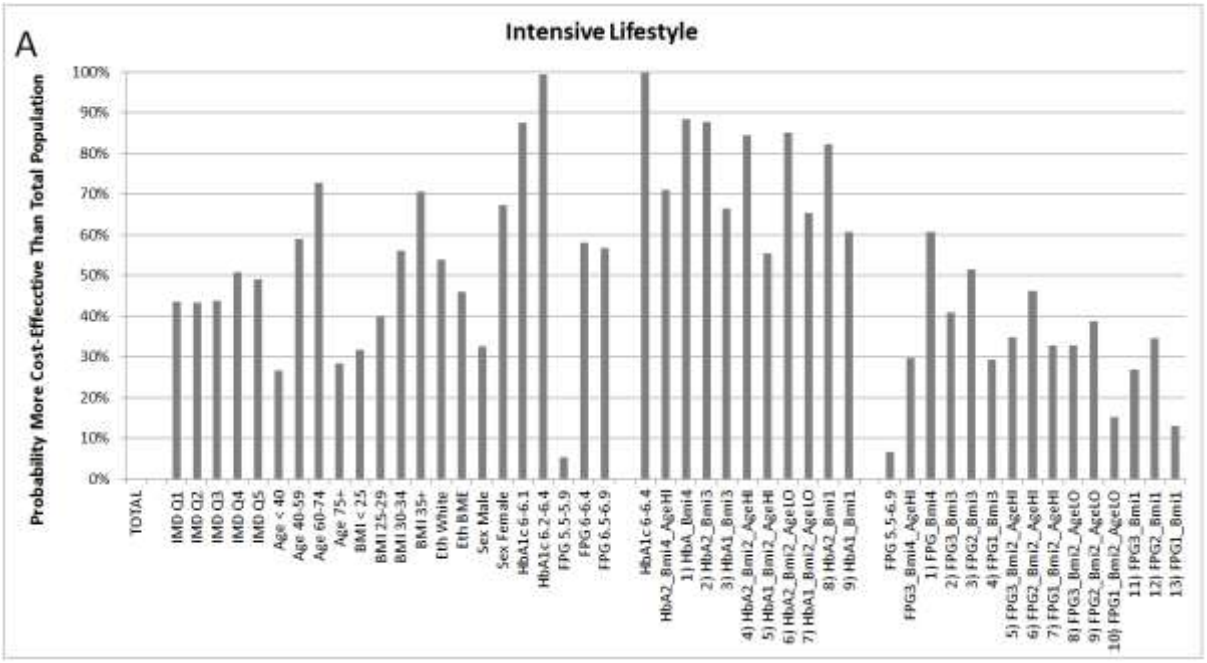


Figure 58: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is neither stratified nor persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



1B: Investigating the Impact of HbA1c Stratification (by age, BMI and FPG) on Intensive Lifestyle Intervention

The next set of results look at the effect of optimistic, conservative and pessimistic assumptions around intervention effectiveness, in a scenario where the intervention effect on HbA1c is stratified by age, baseline BMI and baseline FPG. Summary results for the total population are found in Table 41. Full results for each subgroup can be found in Appendix 3.

Table 41: Per person summary results for the total population when intensive lifestyle intervention is compared with control and HbA1c is stratified but not persistent.

Scenario	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)	Probability Cost-Effective
Optimistic	-£442	0.049	£1,414	-£9,084	100%
Conservative	-£188	0.031	£805	-£6,112	97%
Pessimistic	£45	0.013	£223	£3,367	79%

The most important findings of these results compared with the non-stratified results are presented below:

B1.1 Overall the results with stratification are very similar to the results in section 1A above without stratification of effectiveness. Total NMB is very slightly lower if HbA1c is assumed to be stratified (compare Table 40 and Table 41).

B1.2 The intensive lifestyle intervention remains cost-effective in all subgroups and in all three effectiveness scenarios if it is assumed that HbA1c effect is stratified by personal characteristics (Figure 59). The NMB is about seven fold higher in the optimistic scenario compared with the pessimistic scenario, as found without stratification (see A1.1).

B1.3 Subgroup ordering by NMB is very similar between the three scenarios of intervention effectiveness (Figure 60), as found without stratification (see A1.2).

B1.4 The most cost-effective subgroup defined using a single characteristic is the HbA1c 6.2-6.4 subgroup, whether or not the HbA1c effect is stratified (compare Figure 57 and Figure 60). The probability that it is more cost-effective to intervene specifically in this subgroup, rather than in anyone from the high risk population is close to 100% (Figure 61). In general, there is a trend for the intervention to be more cost-effective in those with higher HbA1c whether or not HbA1c is stratified (see A1.3).

B1.5 Stratification does have an impact on the ordering of subgroups below the most cost-effective subgroup. The second most cost-effective subgroup defined using a single characteristic in this scenario is the FPG 6.5-6.9 subgroup. This is due to the stratification of the HbA1c intervention effect by FPG; which causes individuals with higher baseline FPG to have a greater reduction in HbA1c than those with lower baseline FPG (see Table 32 in the Methods section for details).

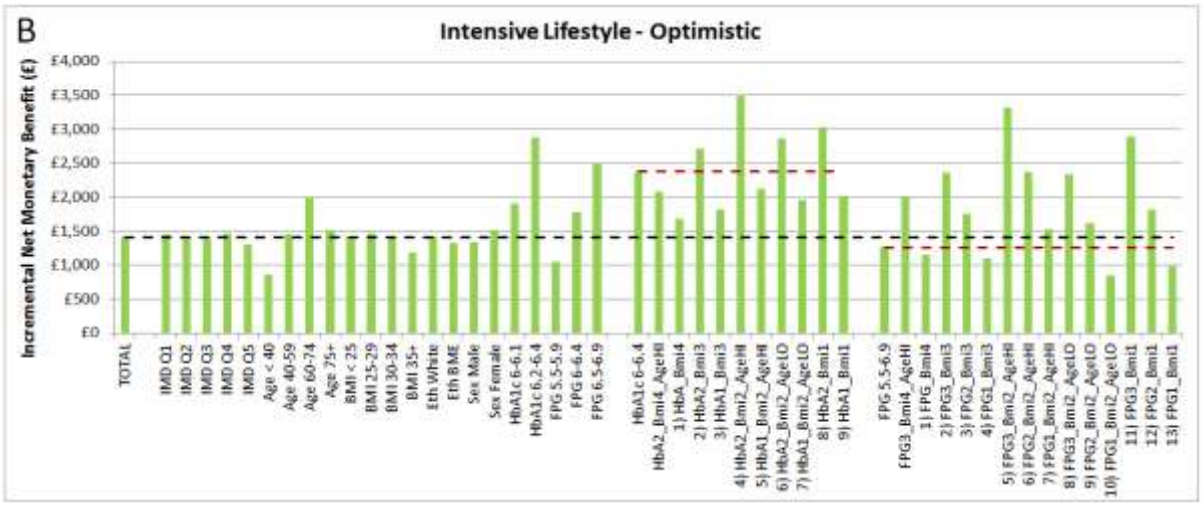
B1.6 It is more cost-effective to intervene in the middle aged (40-74) population than in older or younger populations whether or not the HbA1c effect is stratified (see A1.6). However, whereas without stratification, lowest cost-effectiveness is seen in individuals aged 75+, with stratification the lowest cost-effectiveness is seen in individuals aged under 40. This is due to the greater HbA1c reduction implemented in older people when HbA1c is stratified (see Table 32 in the Methods section for details).

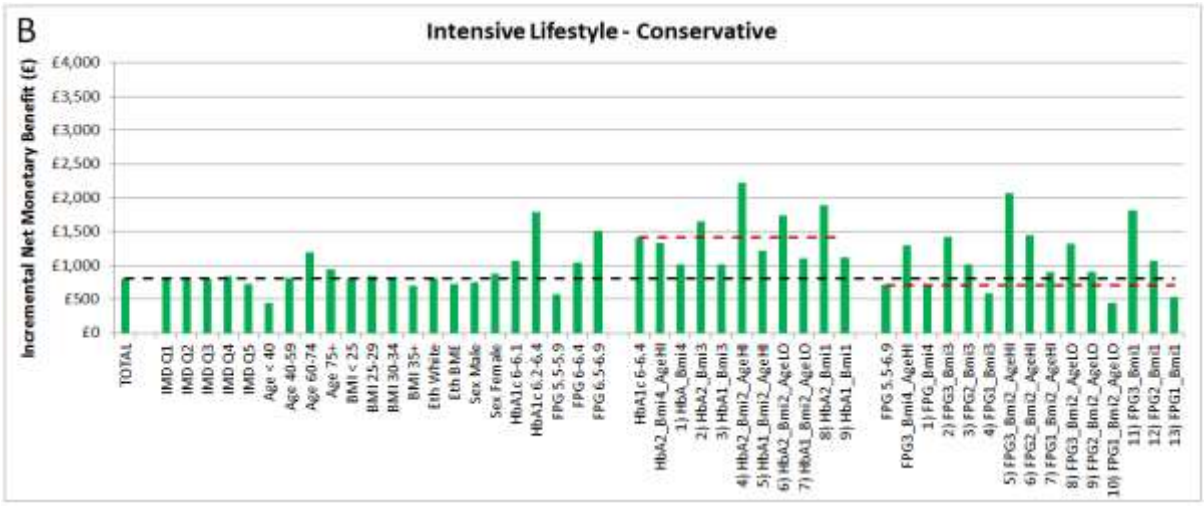
B1.7 The high cost-effectiveness seen in the highest BMI subgroups without stratification (see A1.4) is no longer present when HbA1c effects are stratified. Instead, the BMI 35+ subgroup is less cost-effective than the other BMI groups. This is due to the greater HbA1c reduction implemented in people with low BMI when HbA1c is stratified (see Table 32 in the Methods section for details).

B1.8 The most cost-effective combinatorial subgroup when HbA1c is stratified are those who have ‘HbA1c 6.2-6.4, are overweight and who are aged over 60’. This is the same whether HbA1c is stratified or not (see A1.5). High cost-effectiveness is also seen in the ‘HbA1c 6.2-6.4 and normal weight’ subgroup, and in the ‘HbA1c 6.2-6.4, overweight and aged under 60’ subgroup. This differs from the situation where HbA1c effect is not stratified, by favouring the lower BMI combinatorial subgroups over the higher BMI ones.

B1.9 In general, the results suggest that it is more cost-effective to intervene in subgroups with high HbA1c than with low HbA1c, with high FPG than with low FPG, in those with high than with low age, in those with lower BMI than those with very high BMI, in females rather than males and in those of white rather than BME ethnicity. Model results suggest that socioeconomic deprivation does not impact upon the cost-effectiveness of intensive lifestyle interventions.

Figure 59: Mean incremental NBM per person of intensive lifestyle compared to control in different population subgroups under optimistic, conservative or pessimistic estimates of intervention effectiveness, assuming that HbA1c effect is stratified but not persistent. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.





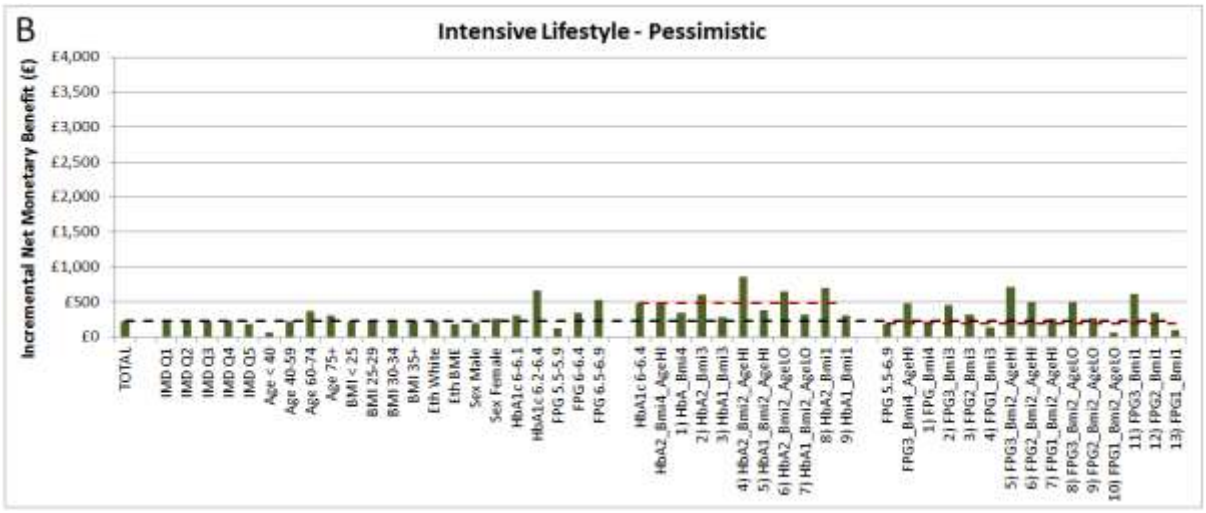


Figure 60: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is stratified but not persistent. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

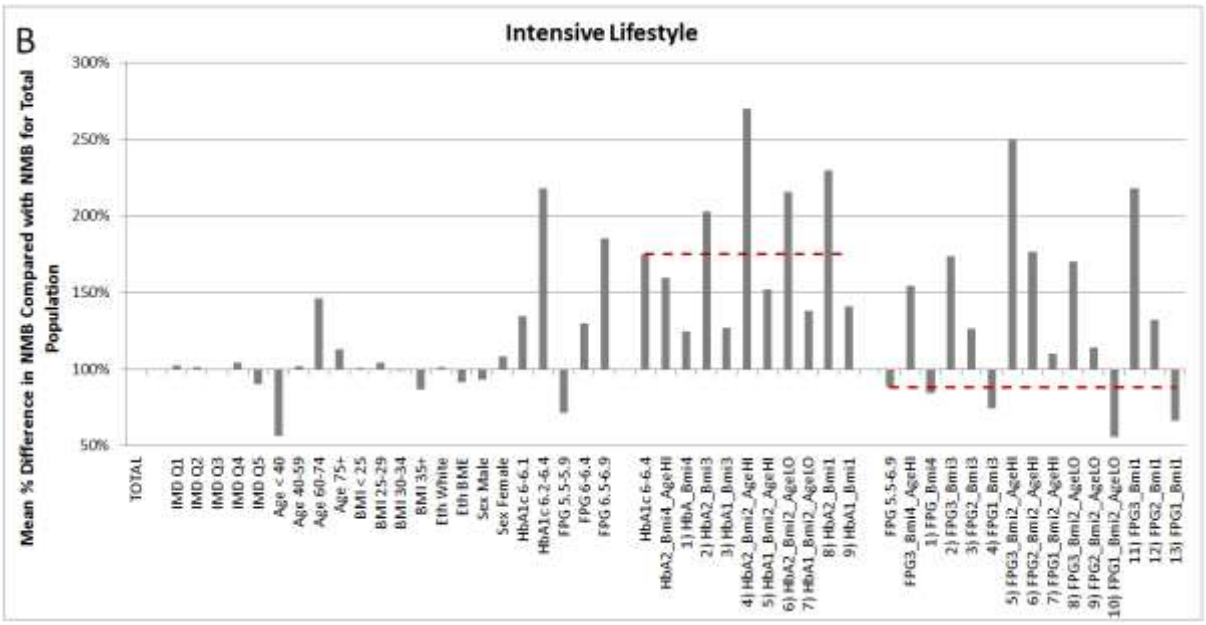
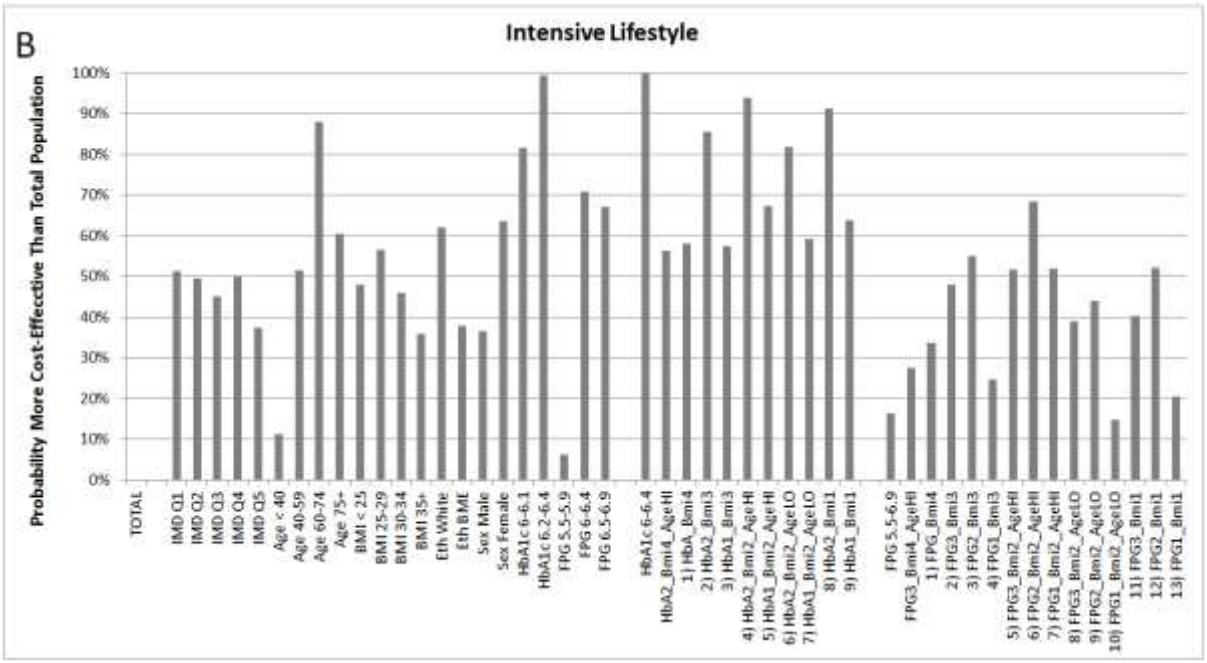


Figure 61: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is stratified but not persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME);

BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



1C: Investigating the Impact of Assumptions regarding Persistence of HbA1c Effect on Lifestyle Intervention

These results describe a comparison of the six scenarios (already presented in Figure 56 to Figure 61 in sections 1A and 1B) in which HbA1c effect goes back to where it would have been without intervention in line with the weight regain period, with an equivalent six scenarios in which the HbA1c effect is assumed to be persistent until death or diagnosis of diabetes. Summary results for the total population are found in Table 42. Full results for each subgroup can be found in Appendix 3.

Table 42: Per person summary results for the total population when intensive lifestyle intervention is compared with control and HbA1c is persistent and either not stratified, or stratified.

Scenario	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)	Probability Cost-effective
HbA1c Not Stratified					
Optimistic	-£2,524	0.119	£4,897	-£21,279	100%
Conservative	-£1,770	0.085	£3,466	-£20,862	94%
Pessimistic	-£749	0.040	£1,551	-£18,687	83%
HbA1c Stratified					
Optimistic	-£2,015	0.112	£4,247	-£18,061	100%
Conservative	-£1,396	0.080	£2,998	-£17,439	95%
Pessimistic	-£563	0.038	£1,320	-£14,859	83%

The most important of these results when persistence (but not stratification) of HbA1c effectiveness is assumed are presented below:

C1.1 If the HbA1c effect is assumed to be persistent, the cost-effectiveness of an intensive lifestyle intervention is three to six fold higher than if the HbA1c effect is assumed to return to baseline in line with weight regain. This occurs whether or not HbA1c is stratified and in all of the effectiveness scenarios (compare Table 42 with Table 40 and Table 41).

C1.2 Subgroup ordering does not differ significantly between the three effectiveness estimates (the ordering of subgroups in the six scenarios shown in Figure 62 and Figure 63 is similar), but these do differ very considerably when compared with the scenarios in which HbA1c effect is not persistent (compare with Figure 56 and Figure 59).

C1.3 In these scenarios assuming persistence of HbA1c effectiveness, the most cost-effective subgroup defined using a single characteristic when HbA1c effect is persistent but not stratified is the age < 40 subgroup (Figure 64), closely followed by the HbA1c 6-6.1 subgroup and the HbA1c 6.2-6.4 subgroup. The particularly high cost-effectiveness seen in young people is due to the persistence of the HbA1c effect throughout their longer lifetime, meaning that young individuals can benefit for many years more than older people. This age effect overwhelms the trends on HbA1c and BMI seen when the HbA1c effect is not persistent (see A1.3 and A1.4). Therefore, when persistence is assumed, only small differences in cost-effectiveness are seen in subgroups that differ by HbA1c or BMI.

C1.4 The BME subgroup also shows high cost-effectiveness when the HbA1c effect is persistent but not stratified (Figure 64). This is likely due to the relatively low mean age of this population (43 years) compared to the white high risk population (55 years: see Table 25).

C1.5 The most cost-effective combinatorial subgroup when the HbA1c effect is persistent but not stratified is the 'HbA1c 6-6.1, overweight and age < 60' subgroup. Other combinatorial subgroups where age < 60 is specified are also highly cost-effective, indicating the overwhelming importance of the age component.

C1.6 In general, if persistence is assumed then the results suggest that it is more cost-effective to intervene in subgroups with low age than high age, with high FPG than low FPG and in BME than in white ethnic individuals. Socioeconomic deprivation, BMI, gender and baseline HbA1c do not have a particularly strong impact upon the cost-effectiveness of intensive lifestyle interventions when HbA1c effect is persistent but not stratified.

The most important results when both persistence and stratification (by age, BMI and FPG) of HbA1c effectiveness is assumed are presented below:

D1.1 The results when both persistence and stratification are assumed are similar to those when persistence is assumed without stratification, with some differences due to the stratification effects.

D1.2 The most cost-effective subgroup defined using a single characteristic when HbA1c effect is both persistent and stratified is the FPG 6.5-6.9 subgroup (Figure 65). The difference from the findings in C1.3 is due to the stratification of the HbA1c intervention effect by FPG, which means that individuals with higher baseline FPG receive a greater reduction in HbA1c effect (see Table 32 in the Methods section for details).

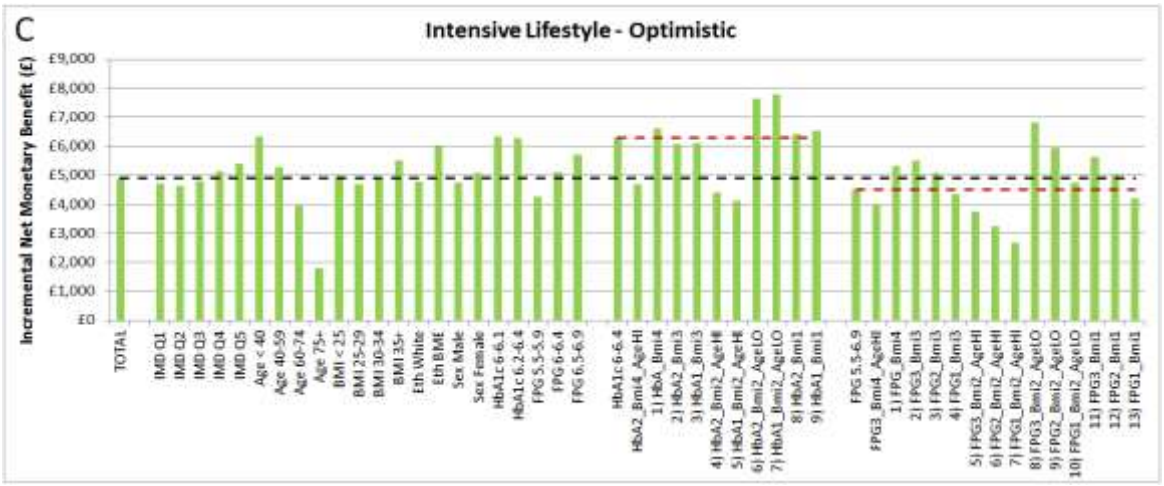
D1.3 Other highly cost-effective subgroups defined using a single characteristic include the age 40-59 subgroup, the normal weight BMI subgroup, the high HbA1c

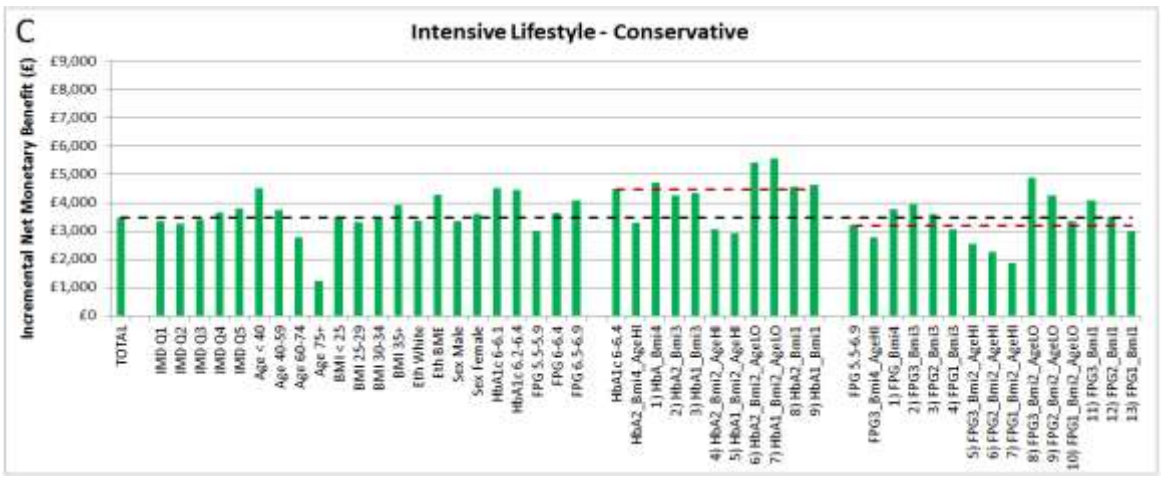
subgroup and the BME subgroup (Figure 65). Low BMI is more cost-effective than high BMI due to the greater HbA1c reduction implemented in people with low BMI when HbA1c is stratified (see Table 32). The age 40-59 subgroup is more cost-effective than higher age subgroups despite a greater HbA1c reduction implemented in older people (see Table 32); in this case the benefits to younger people of a persistent HbA1c effect over their longer lifetime partially outweigh the lower reduction in HbA1c conferred by the intervention.

D1.4 The most cost-effective combinatorial subgroup when assuming the HbA1c effect is both persistent and stratified is those who have 'FPG 6.5-6.9 and who are of normal weight'. High cost-effectiveness is also seen in the 'FPG 6.5-6.9, age < 60 and overweight' subgroup. This differs from the other scenarios in which HbA1c defined subgroups tend to be more cost-effective than FPG defined ones (see A1.5, B1.8 and C1.5).

D1.5 In general, the results when it is assumed that HbA1c effect is both persistent and stratified suggest that it is more cost-effective to intervene in subgroups of middle age (40-59) rather than higher or lower age, with low BMI than high BMI, with high FPG than low FPG, of high HbA1c than low HbA1c and in BME than in white ethnic individuals. In these scenarios, the impacts of socioeconomic deprivation and gender upon the cost-effectiveness of intensive lifestyle interventions are relatively small.

Figure 62: Mean incremental NBM per person of intensive lifestyle compared to control in different population subgroups under optimistic, conservative or pessimistic estimates of intervention effectiveness, assuming that HbA1c effect is persistent but not stratified. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.





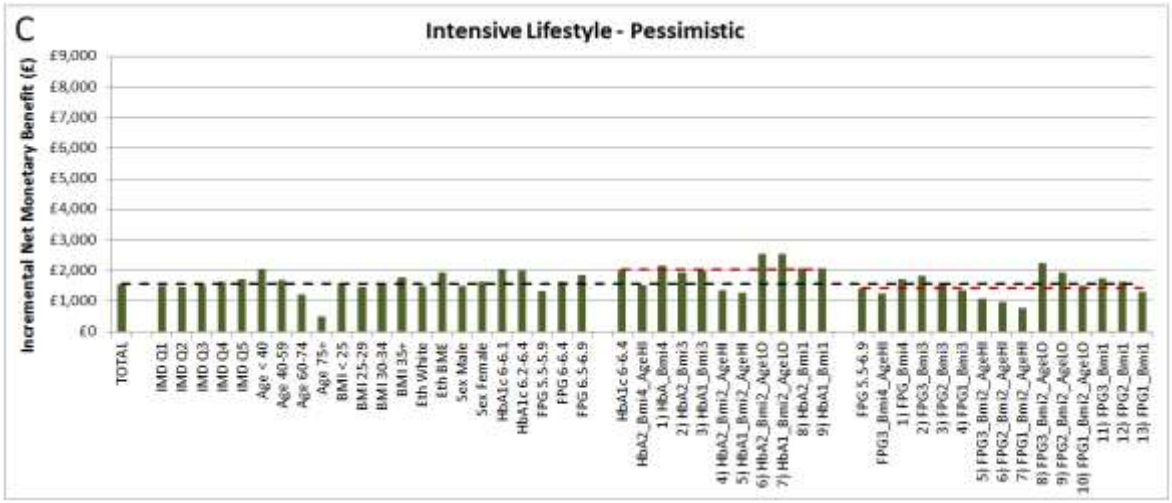
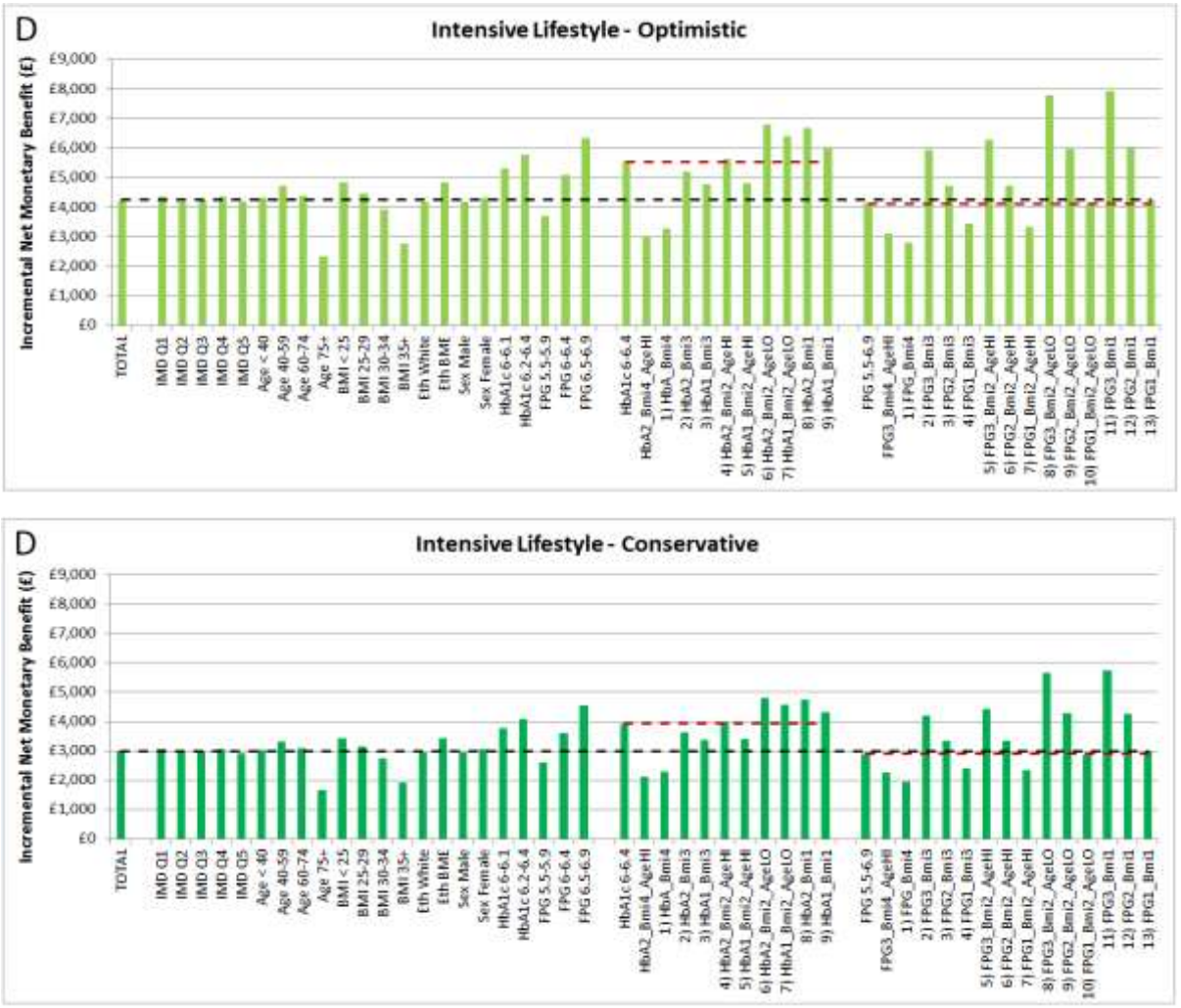


Figure 63: Mean incremental NBM per person of intensive lifestyle compared to control in different population subgroups under optimistic, conservative or pessimistic estimates of intervention effectiveness, assuming that HbA1c effect is persistent and stratified. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



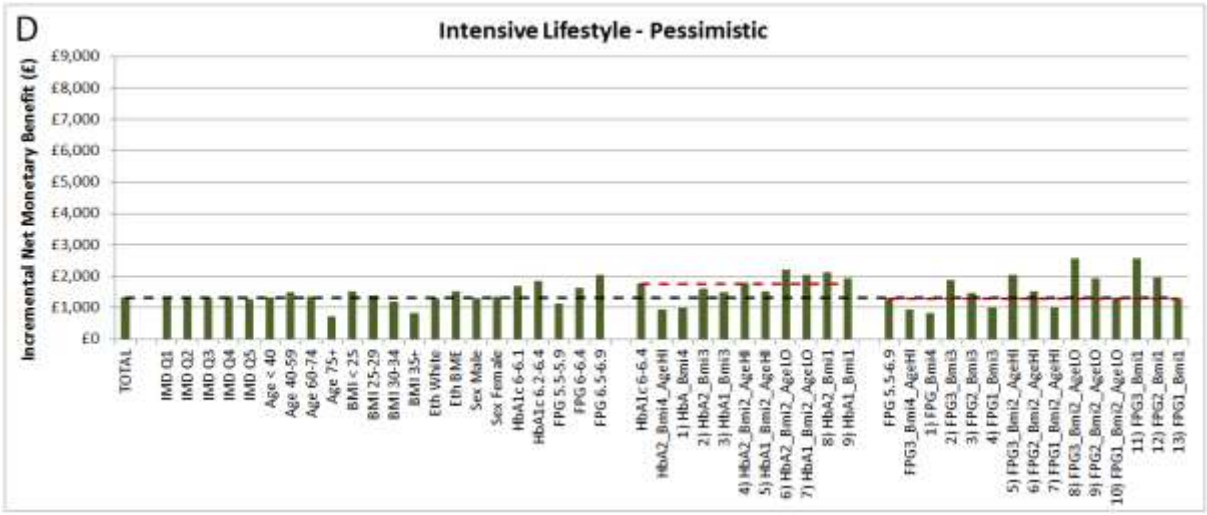


Figure 64: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is persistent but not stratified. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

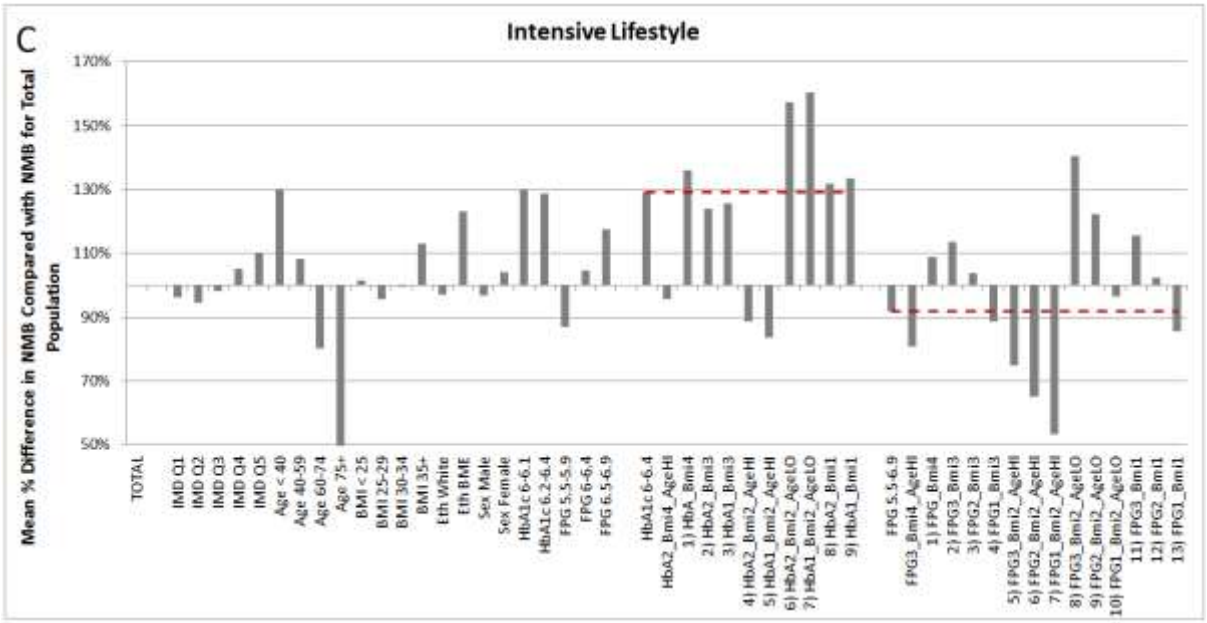


Figure 65: The mean proportional difference in incremental NBM of each subgroup compared to the total population assuming that HbA1c effect is persistent and stratified. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI

25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

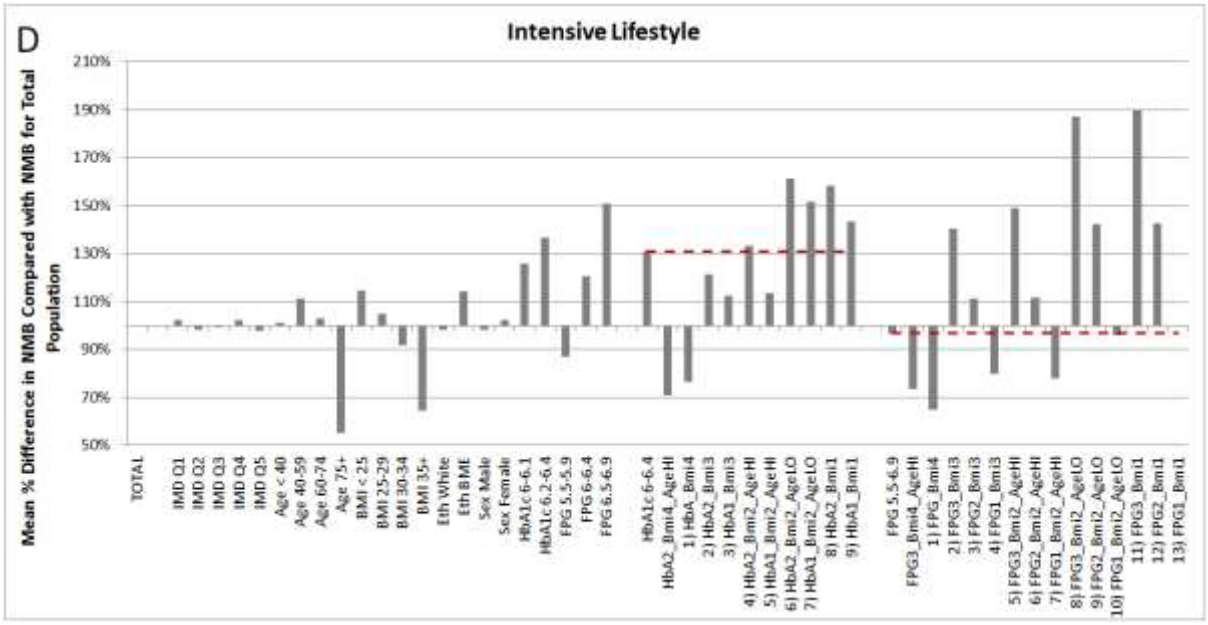


Figure 66: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is persistent but not stratified. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

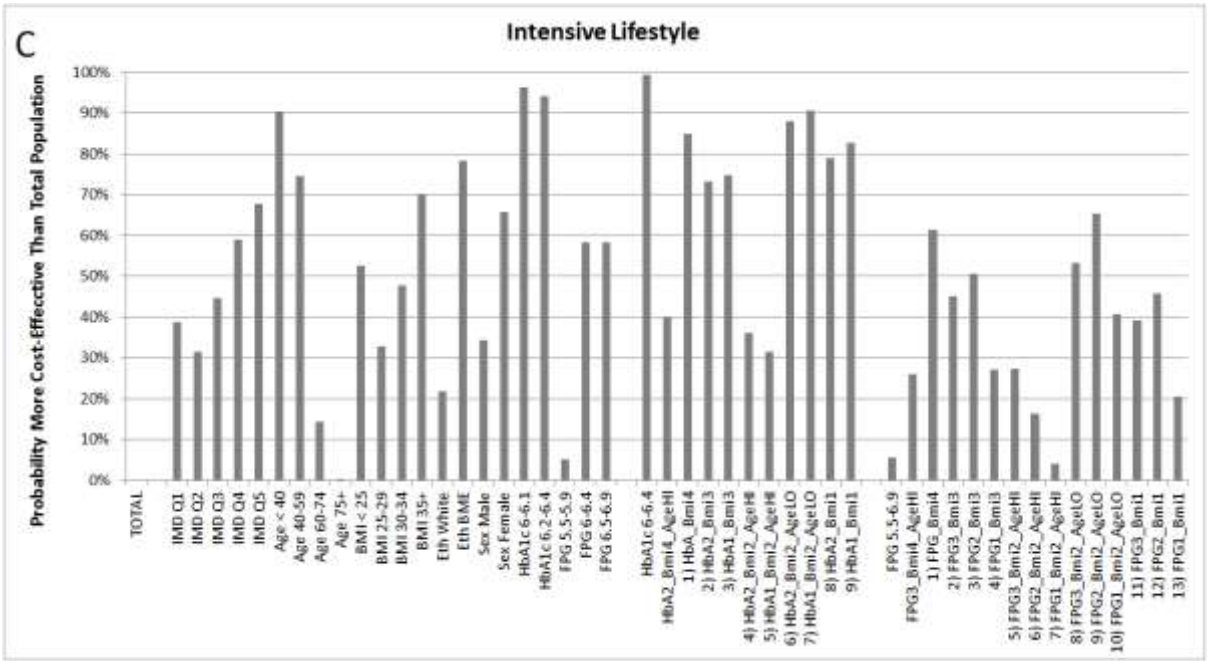
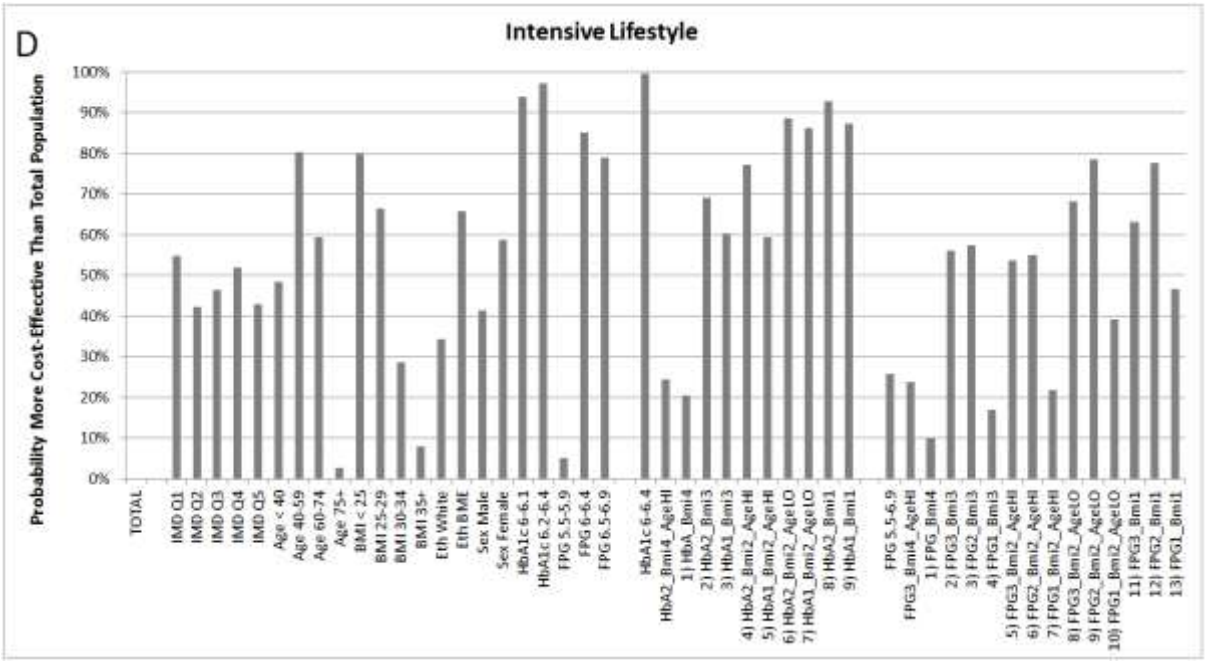


Figure 67: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is persistent and stratified. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



2: Cost-effectiveness of Metformin in Population Subgroups

In order to answer the question of which subgroups could benefit most from metformin for diabetes prevention, a similar set of results were presented as those described above for intensive lifestyle intervention:

2A: Investigating the Impact of Study Effectiveness on Metformin

The results presented in this section compare the effect of optimistic and conservative assumptions around intervention effectiveness, in the basecase scenario where the intervention effect on HbA1c is not stratified and returns to baseline at the same point as weight is fully regained. Summary results are shown in Table 43. Full results for each subgroup can be found in Appendix 3.

Table 43: Per person summary results for the total population when Metformin is compared with control and HbA1c is neither stratified nor persistent.

Scenario	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)	Probability Cost-effective
Optimistic	£4	0.033	£655	£127	99%
Conservative	£203	0.020	£202	£10,024	81%

The most important findings to note are as follows:

A2.1 Metformin is predicted to be cost-effective compared to control in all subgroups with optimistic effectiveness estimates, but not with conservative effectiveness estimates, where it is predicted not to be cost-effective in subgroups where FPG is low, particularly if BMI and age are also low (Figure 68).

A2.2 Subgroup ordering by NMB is very similar in both scenarios of intervention effectiveness (Figure 68 and Figure 69).

A2.3 The most cost-effective subgroup defined using a single characteristic in both scenarios when HbA1c effect is neither persistent nor stratified is the HbA1c 6.2-6.4 subgroup, the same as that found to be most cost-effective in the equivalent set of lifestyle intervention scenarios (see A1.3).

A2.4 The most cost-effective combinatorial subgroup in all three scenarios when HbA1c effect is neither persistent nor stratified is the 'HbA1c 6.2-6.4, overweight, age <60' subgroup, the same as that found to be most cost-effective in the equivalent set of lifestyle intervention scenarios (see A1.5).

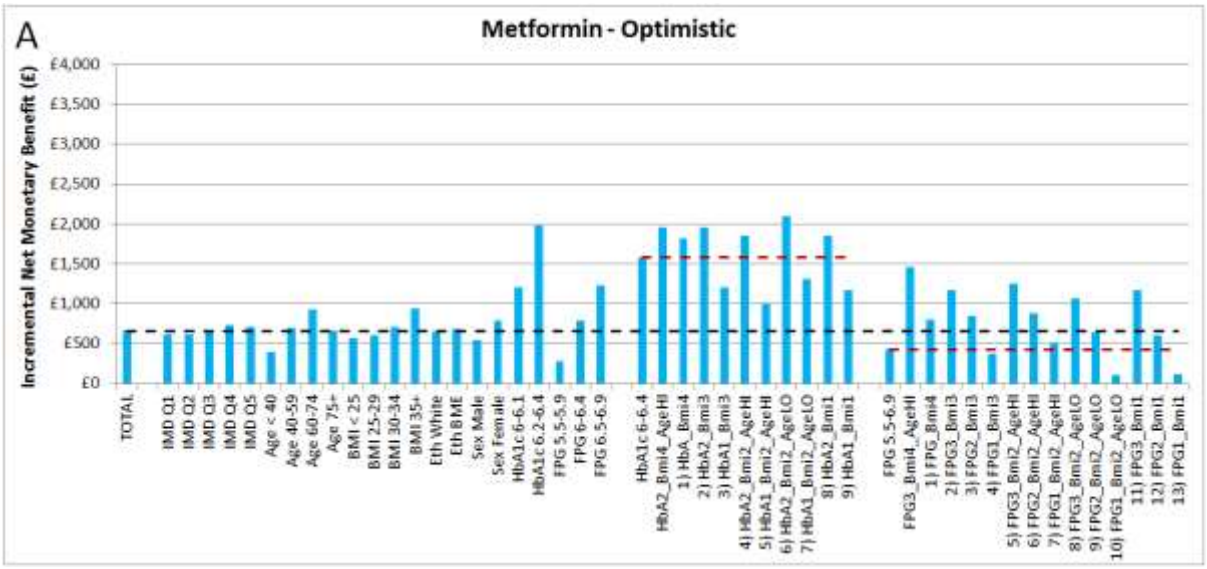
A2.5 Subgroup ordering in general is very similar to the equivalent scenarios for intensive lifestyle intervention when HbA1c effect is neither persistent nor stratified

(see section A1); the only exception is with age, where metformin is less cost-effective in the age < 40 subgroup than in the age 75+ subgroup; whilst intensive lifestyle intervention is slightly less cost-effective in the age 75+ subgroup than in the age < 40 subgroup (see A1.7). These differences appear to occur because young individuals incur higher lifetime intervention costs on average when taking metformin than older individuals, due to their longer lifespan and the requirement to keep paying for the intervention annually (unlike intensive lifestyle intervention, which incurs a one-off cost in the first year).

A2.6 In general, assuming neither stratification nor persistence, the results suggest that it is more cost-effective to give metformin to subgroups with high HbA1c rather than low HbA1c, high FPG rather than low FPG, high age rather than low age, high BMI rather than low BMI, high rather than low socioeconomic deprivation and to females rather than males. No clear difference is seen between subgroups defined by ethnicity.

A2.7 The least cost-effective subgroups when HbA1c effect is neither persistent nor stratified appear to be those with FPG 5.5-5.9, in combination with low BMI and young age.

Figure 68: Mean incremental NMB per person of metformin compared to control in different population subgroups under optimistic or conservative estimates of intervention effectiveness, assuming that HbA1c is neither stratified nor persistent. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



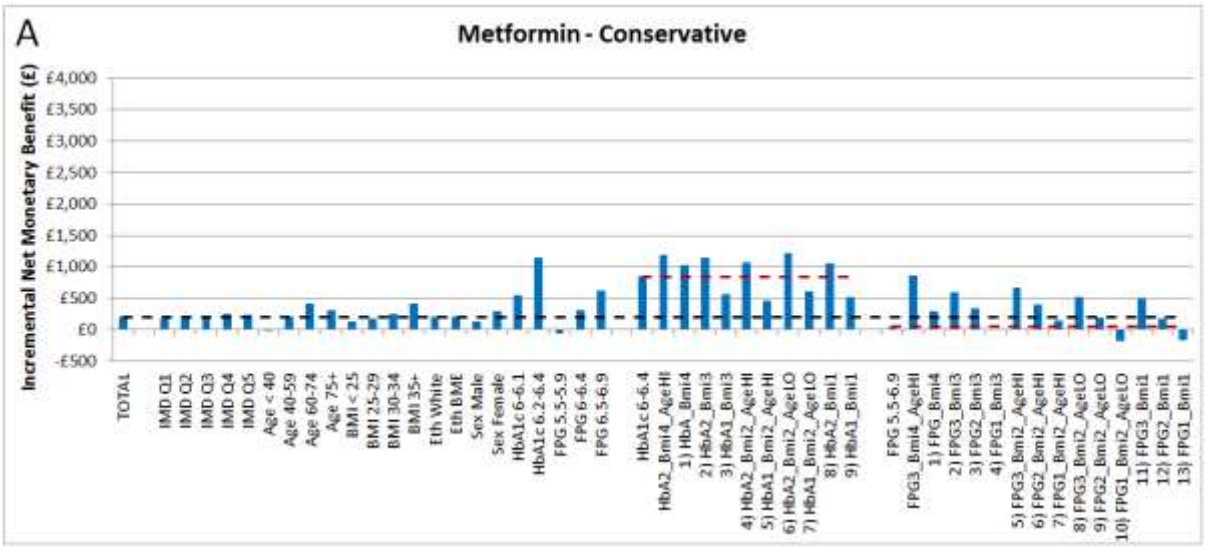


Figure 69: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is neither stratified nor persistent. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 =

BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

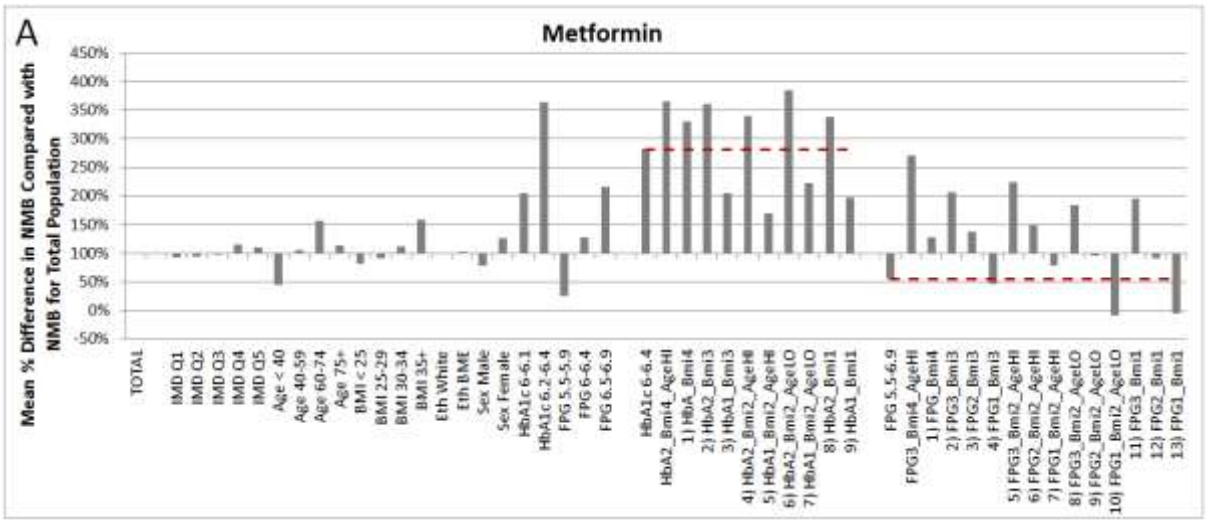
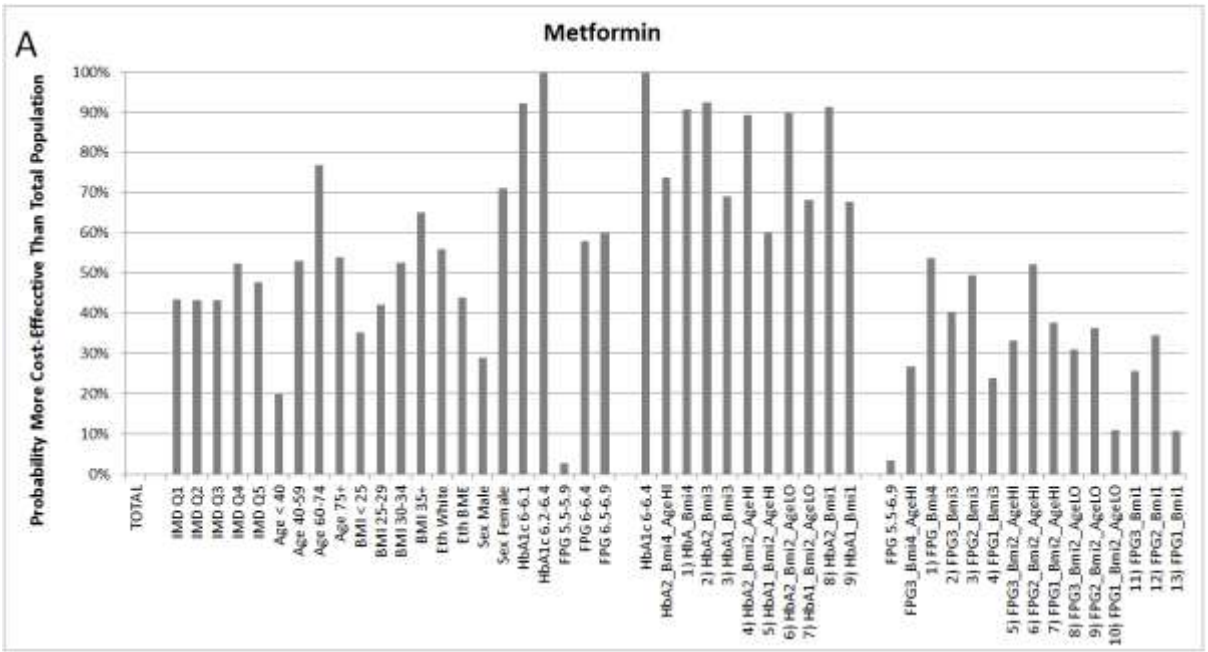


Figure 70: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is neither stratified nor persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



2B: Investigating the Impact of HbA1c Stratification (by age, BMI and FPG) on Metformin

The next set of results look at the effect of conservative and pessimistic assumptions around metformin effectiveness, in a scenario where the intervention effect on HbA1c is stratified by age, baseline BMI and baseline FPG. Summary results are shown in Table 44. Full results for each subgroup can be found in Appendix 3.

Table 44: Per person summary results for the total population when metformin is compared with control and HbA1c is stratified but not persistent.

Scenario	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)	Probability Cost-effective
Optimistic	£27	0.026	£486	£1,040	96%
Conservative	£207	0.016	£116	£12,835	68%

The most important findings of these results compared with the non-stratified results are presented below:

B2.1 Metformin is cost-effective in most but not all subgroups in either conservative or optimistic scenarios if it is assumed that HbA1c effect is stratified by personal characteristics. In particular, under this scenario it is not cost-effective in those aged 75+ or who are of normal weight (Figure 71).

B2.2 Total net monetary benefit across the whole population is considerably lower when the HbA1c effect is stratified than when it is not (compare Table 43 and Table 44). This differs from intensive lifestyle intervention in which stratification of HbA1c had only a very small effect on the magnitude of NMB (see B1.1).

B2.3 Subgroup ordering by NMB is very similar between conservative and optimistic scenarios of intervention effectiveness (Figure 71).

B2.4 Stratification has an impact on the ordering of subgroups. The most cost-effective subgroup defined using a single characteristic is the FPG 6.5-6.9 subgroup when HbA1c effect is stratified (Figure 72), compared with the HbA1c 6.2-6.4 subgroup when HbA1c effect is not stratified (see A2.3). This is due to the stratification of the HbA1c intervention effect by FPG, which means that individuals with higher baseline FPG receive a greater reduction in HbA1c effect (see Table 32 in the Methods section for details).

B2.5 Metformin is also highly cost effective in the HbA1c 6.2-6.4 subgroup and in the BMI 35+ subgroup when HbA1c effect is stratified but not persistent. The much stronger BMI effect seen when HbA1c is stratified is due to the greater HbA1c

reduction implemented in people of higher BMI (see Table 32 in the Methods section for details).

B2.6 It is more cost-effective to intervene in the young (age < 60) population than in older populations if HbA1c when HbA1c effect is stratified but not persistent. This is due to the greater HbA1c reduction implemented in younger people (see Table 32 in the Methods section for details).

B2.7 The most cost-effective combinatorial subgroup when HbA1c is stratified but not persistent is the 'HbA1c 6.2-6.4, BMI 35+' subgroup (Figure 72). High cost-effectiveness is also seen in the 'FPG 6.5-6.9 and BMI 35+' subgroup, and in the 'FPG 6.5-6.9, obese and age <60' subgroup.

B2.8 In general, the results assuming stratification effects suggest that it is more cost-effective to intervene in subgroups with high HbA1c than with low HbA1c, with high FPG than with low FPG, with high BMI than low BMI, in lower age than higher age, in individuals of BME than white ethnicity and with high rather than low socioeconomic deprivation. There is little or no consistent difference in cost-effectiveness by gender.

Figure 71: Mean incremental NBM per person of metformin compared to control in different population subgroups under optimistic or conservative estimates of intervention effectiveness, assuming that HbA1c effect is stratified but not persistent. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

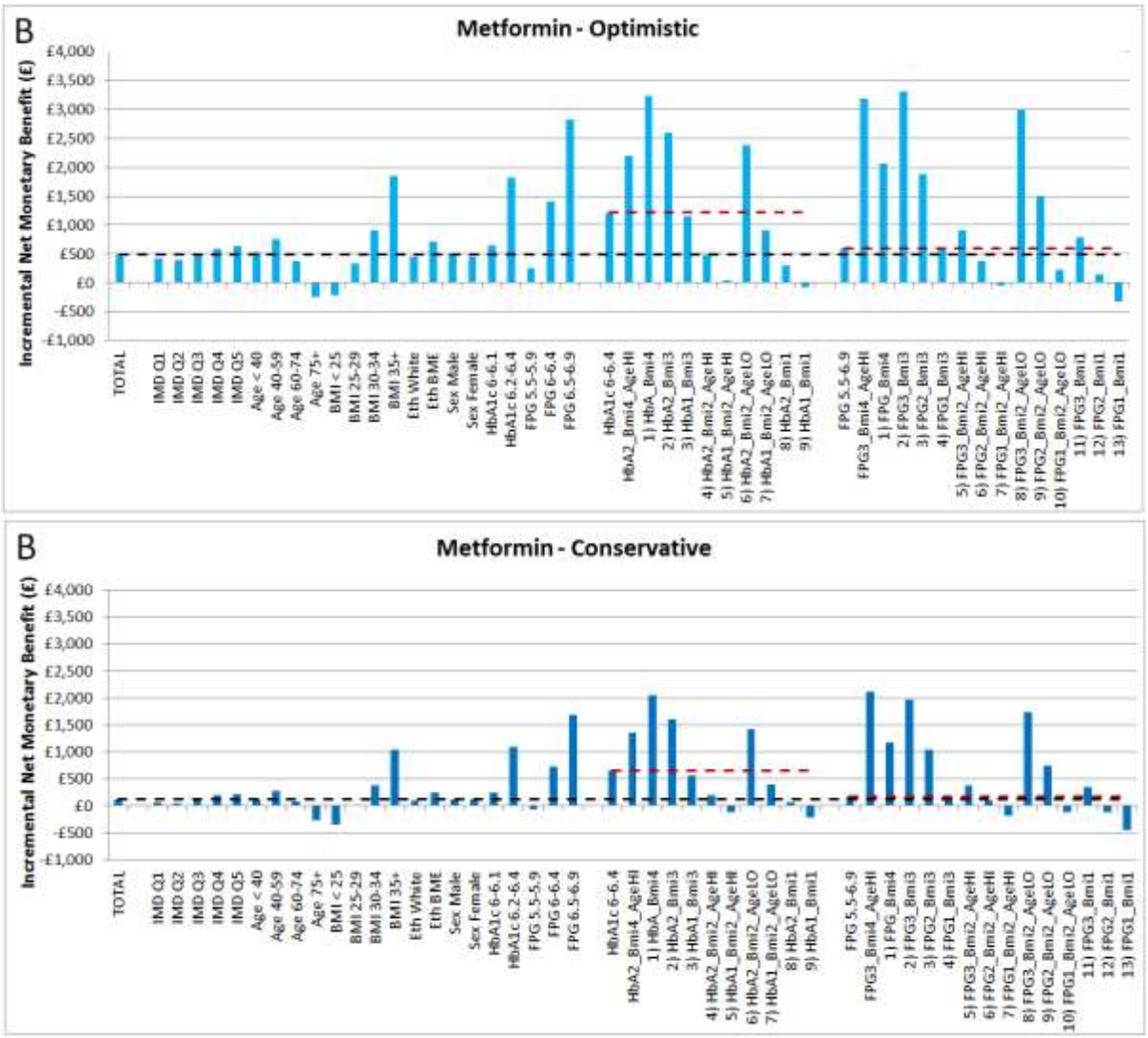


Figure 72: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is stratified but not persistent. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

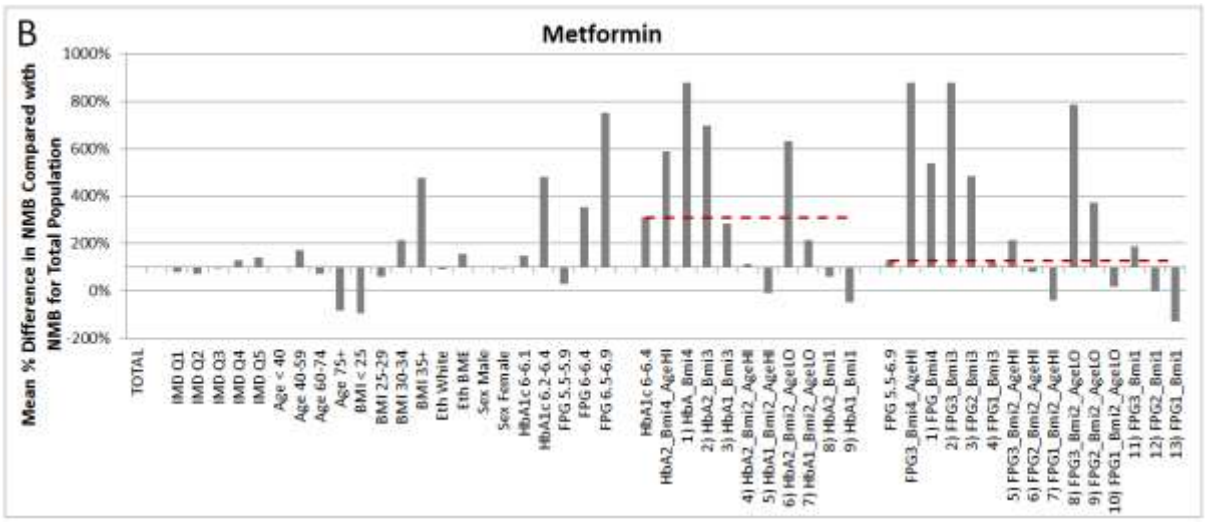
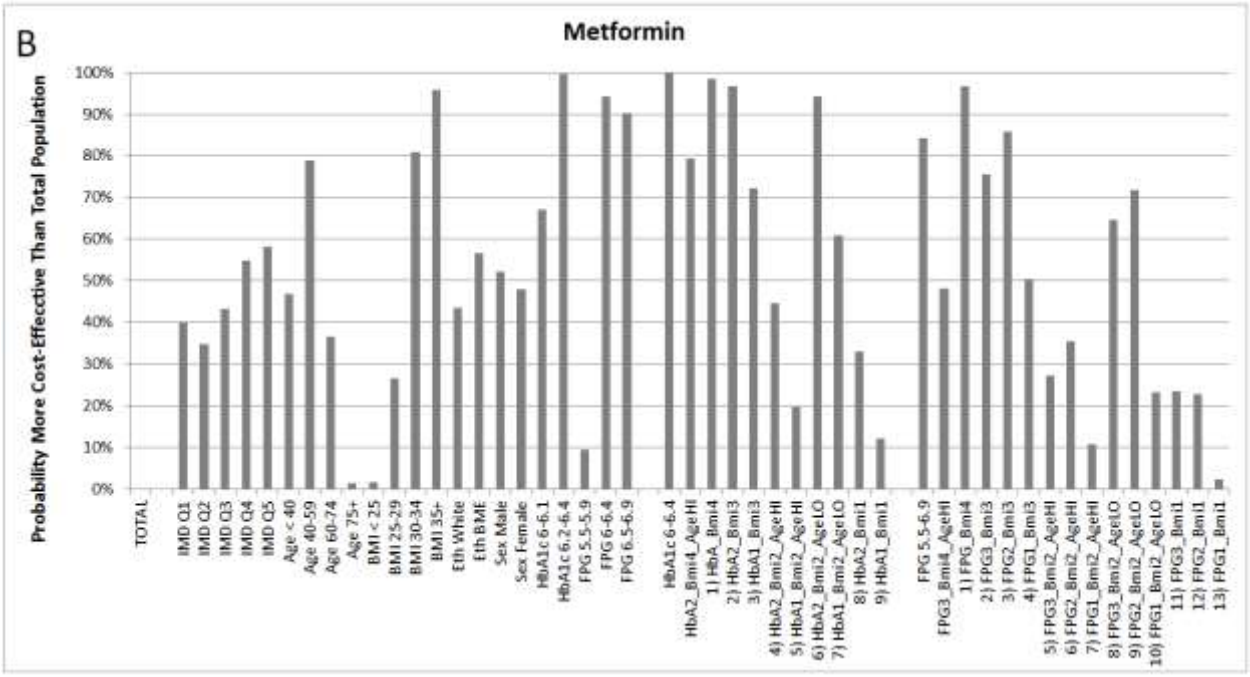


Figure 73: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is stratified but not persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME);

BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



2C: Investigating the Impact of Assumptions regarding Persistence of HbA1c Effect on Metformin

These results describe a comparison of the four scenarios in which HbA1c effect goes back to baseline in line with weight regain as already presented in Figure 68 to Figure 73 with an equivalent four scenarios in which HbA1c effect is persistent. Summary results are presented in Table 45. Full results for each subgroup can be found in Appendix 3.

Table 45: Summary results for the total population when metformin is compared with control and HbA1c is persistent and either not stratified or stratified.

Scenario	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)	Probability Cost-effective
HbA1c Not Stratified					
Optimistic	-£1,504	0.083	£3,171	-£18,045	100%
Conservative	-£953	0.059	£2,128	-£16,212	100%
HbA1c Stratified					
Optimistic	-£1,757	0.088	£3,517	-£19,971	100%
Conservative	-£1,214	0.063	£2,475	-£19,245	100%

The most important of the results assuming persistence but not stratification are presented below:

C2.1 If the HbA1c effect is assumed to be persistent, the cost-effectiveness of metformin intervention ranges from five to twenty fold higher than if the HbA1c effect is assumed to return to baseline in line with weight regain (compare Table 45 with Table 43 and Table 44).

C2.2 Subgroup ordering does not differ significantly between the two effectiveness estimates (the ordering of subgroups in the four scenarios shown in Figure 74 and Figure 75 is similar), but these do differ very considerably when compared with the scenarios in which HbA1c effect is not persistent (i.e. when comparing with Figure 68 and Figure 71).

C2.3 The most cost-effective subgroup defined using a single characteristic when HbA1c effect is persistent but not stratified is the HbA1c 6.2-6.4 subgroup – the same as that found to be most cost-effective when the HbA1c effect is not persistent (see A2.3).

C2.4 Particularly high cost-effectiveness is also seen in the age < 40 subgroup (Figure 76). The particularly high cost-effectiveness seen in young people is due to the persistence of the HbA1c effect throughout their longer lifetime meaning that

young individuals can benefit for many years more than older people. This age effect overwhelms the trends on BMI and to some extent on HbA1c seen when the HbA1c effect is not persistent.

C2.5 High cost-effectiveness is also seen in the BME group. This is likely due to the relative low age of this population (43 years) compared to the white high risk population (55 years: see Table 25).

C2.6 The most cost-effective combinatorial subgroup when the HbA1c effect is persistent but not stratified is the 'HbA1c 6-6.1, overweight and age < 60' subgroup. Other combinatorial subgroups where age < 60 is specified are also highly cost-effective, indicating the overwhelming importance of the age component.

C2.7 In general, the results for this scenario suggest that it is more cost-effective to intervene with metformin in subgroups with low age than high age, with high FPG than low FPG and in BME than in white ethnic individuals. Socioeconomic deprivation, BMI, gender and baseline HbA1c do not have a particularly strong impact upon the cost-effectiveness of intensive lifestyle interventions.

C2.8 The subgroup ordering is very similar for metformin as it is for intensive lifestyle intervention when HbA1c persistence but not stratification is assumed (see section C1).

The most important results assuming both persistence and stratification are presented below:

D2.1 As with intensive lifestyle intervention (see D1.1), the most cost-effective subgroup defined using a single characteristic when HbA1c effect is both persistent and stratified is the FPG 6.5-6.9 subgroup (Figure 77). This is due to the stratification of the HbA1c intervention effect by FPG, which means that individuals with higher baseline FPG receive a greater reduction in HbA1c effect (see Table 32 in the Methods section for details).

D2.2 Other highly cost-effective subgroups defined using a single characteristic include the age < 40 subgroup and the BMI 35+ subgroup (Figure 77). High BMI is more cost-effective than low BMI due to the greater HbA1c reduction implemented in people receiving metformin with high BMI when HbA1c is stratified (see Table 32). Low age is more cost-effective than high age, partly due to the greater HbA1c reduction implemented in younger people when HbA1c is stratified (see Table 32) and partly due to the benefits to younger people of a persistent HbA1c effect over their longer lifetime.

D2.3 The most cost-effective combinatorial subgroup when the HbA1c effect is both persistent and stratified is the 'FPG 6.5-6.9, age < 60 and overweight' subgroup. Other combinatorial subgroups that are also highly cost-effective include the 'FPG 6.5-6.9, obese' subgroup and the 'FPG 55-6.9, BMI 35+' subgroup.

D2.4 In general, the results when assuming both persistence and stratification suggest that it is more cost-effective to intervene in subgroups with low age than high age, with high BMI than low BMI, with high FPG than low FPG, with high HbA1c than low HbA1c, in males rather than females, in BME than in white ethnic individuals and with high rather than low socioeconomic deprivation.

Figure 74: Mean incremental NBM per person of metformin compared to control in different population subgroups under optimistic or conservative estimates of intervention effectiveness, assuming that HbA1c effect is persistent but not stratified. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

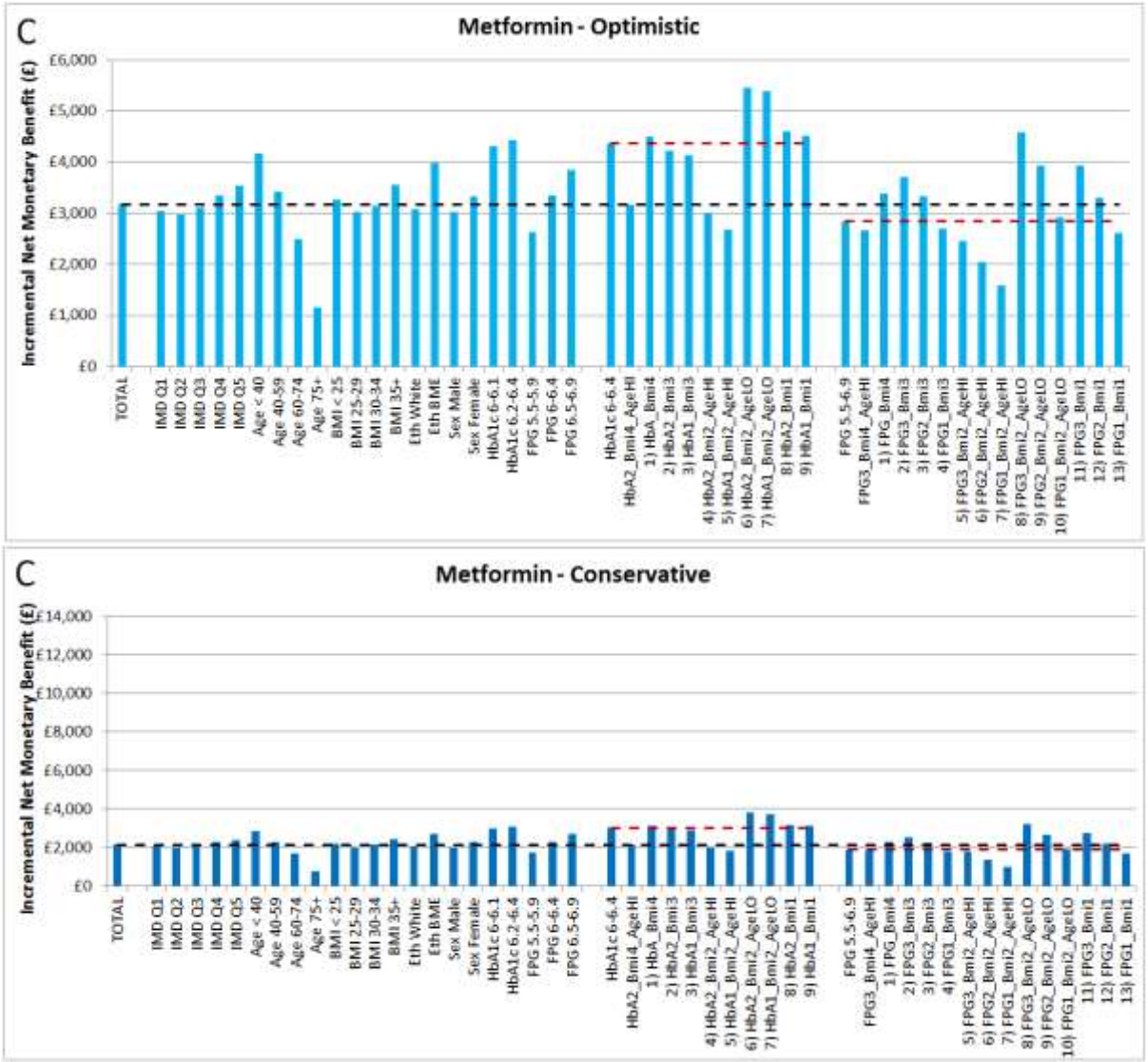
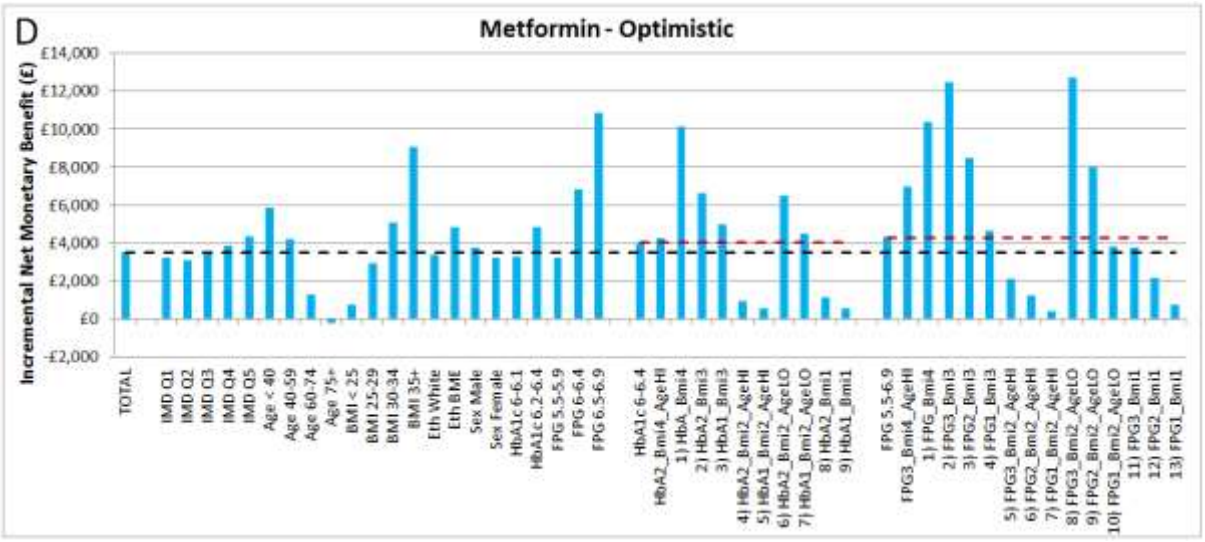


Figure 75: Mean incremental NBM per person of metformin compared to control in different population subgroups under optimistic or conservative estimates of intervention effectiveness, assuming that HbA1c effect is persistent and stratified. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



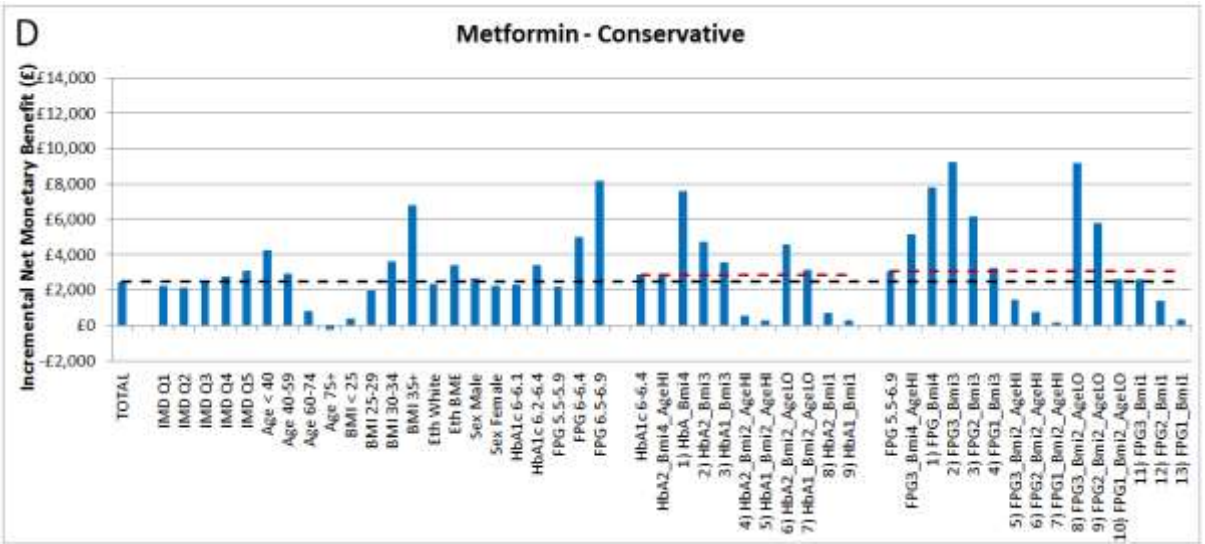


Figure 76: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is persistent but not stratified. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 =

BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

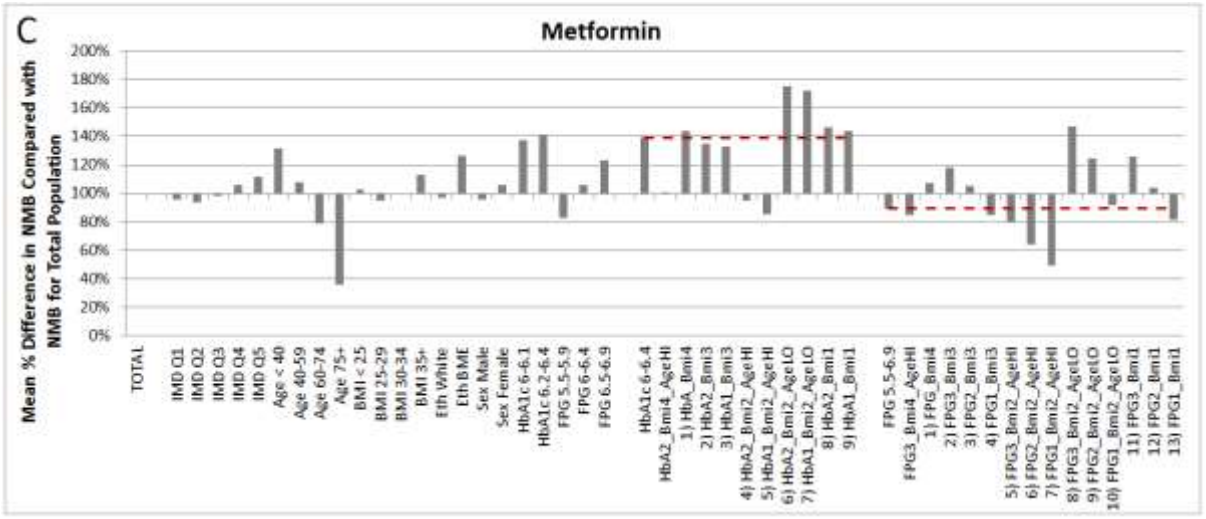


Figure 77: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is persistent and stratified. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

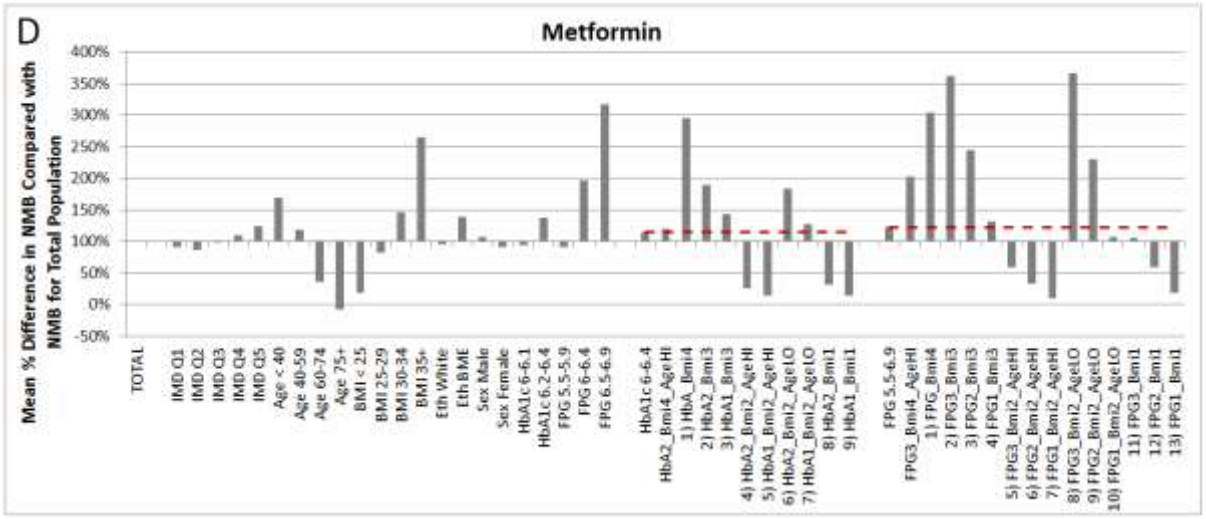


Figure 78: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is persistent but not stratified. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME);

BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

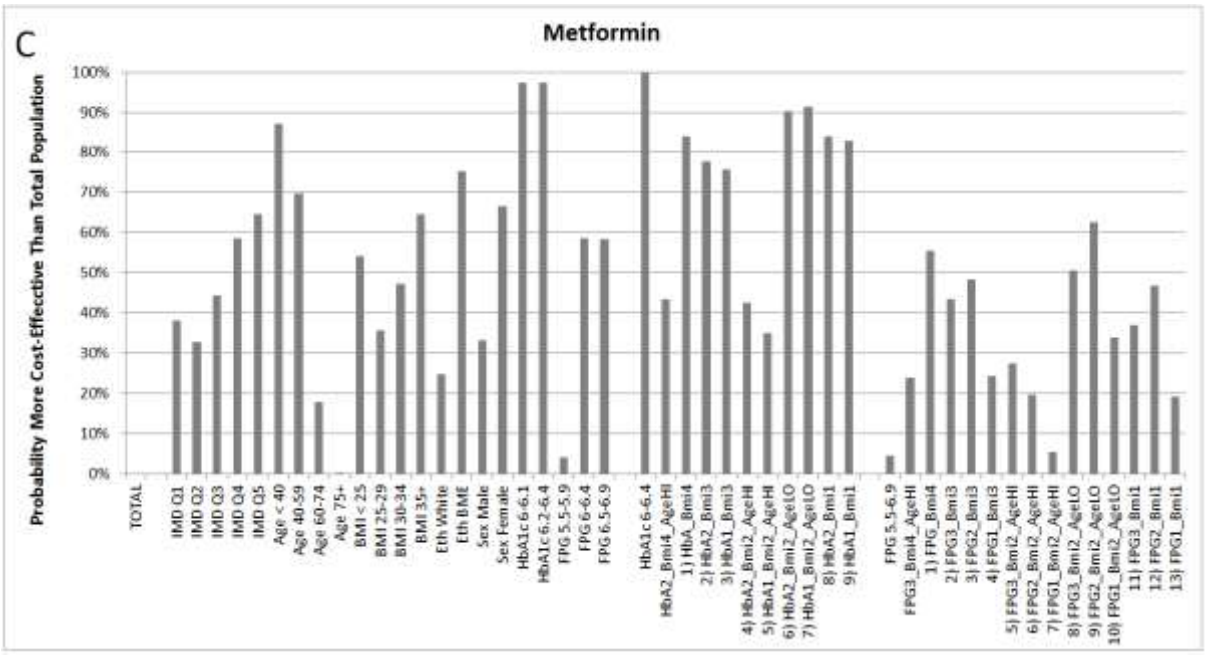
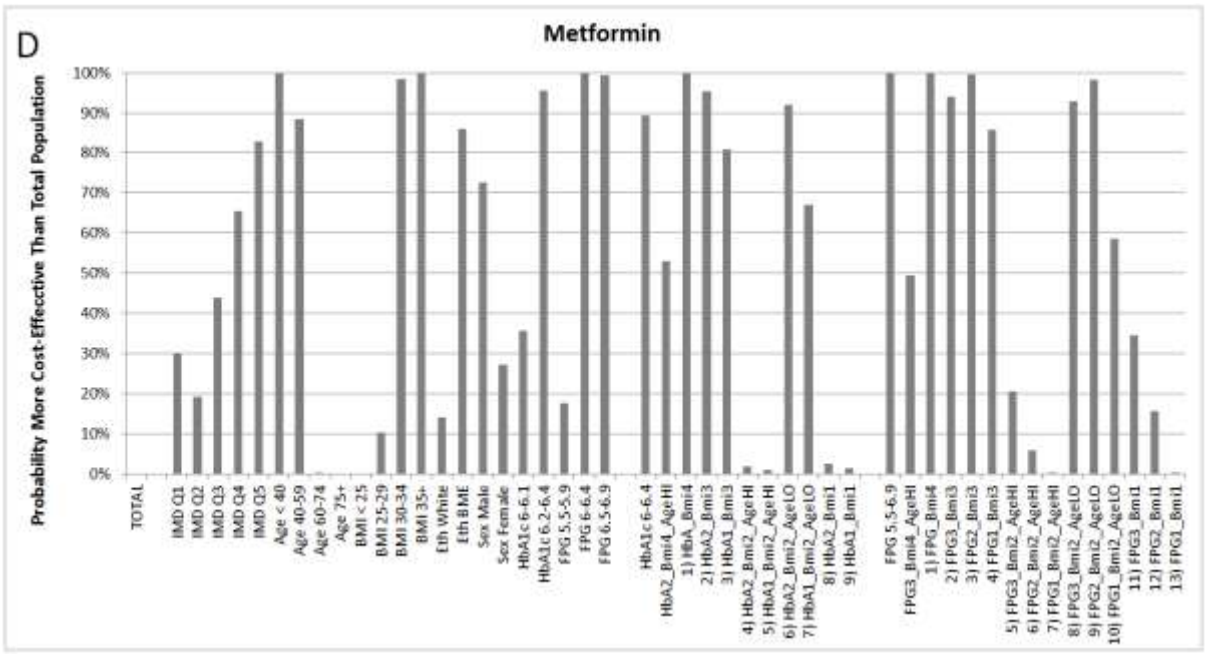


Figure 79: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is stratified and persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



3: Comparison of Intensive Lifestyle Cost-effectiveness with Metformin Cost-effectiveness under Different Scenarios

3A: Comparison of Total Population Results

In order to aid comparison of cost-effectiveness between intensive lifestyle intervention and metformin under the range of scenarios analysed, results for the total population were plotted on the cost-effectiveness plane. Results for each population subgroup were not plotted as this would produce an unmanageable number of graphs.

Figure 80 shows the mean cost-effectiveness results for each of the 12 intensive lifestyle scenarios and the eight metformin scenarios, plotted together on one cost-effectiveness plane. Comparison of incremental net monetary benefit compared to control for all intervention scenarios is shown in Table 46, whilst comparison of the probability that the intervention is cost-effective compared to control is shown in Table 47. Individual PSA results plotted on the cost-effectiveness plane for each scenario can be found in Appendix 4. Key findings are summarised below:

A3.1 The most cost-effective scenario is the optimistic lifestyle intervention assuming that HbA1c effect is persistent but not stratified. This dominates all other scenarios (both gains more QALYs and costs less).

A3.2 The least cost-effective scenario is the conservative metformin intervention assuming that HbA1c is stratified but not persistent.

A3.3 No matter which set of assumptions around HbA1c effect are used, the optimistic lifestyle intervention is more cost-effective over the total population than either the optimistic or conservative metformin interventions.

A3.4 The conservative lifestyle intervention is more cost-effective than either the optimistic or conservative metformin interventions under all sets of assumptions around HbA1c effect apart from the HbA1c persistent and stratified scenario, in which the optimistic metformin intervention is more cost-effective than the conservative lifestyle intervention.

A3.5 The pessimistic lifestyle intervention is more cost-effective than the conservative metformin intervention if it is assumed that HbA1c effect is not stratified, but is less cost-effective than the conservative metformin intervention if it is assumed that HbA1c effects are stratified.

A3.6 There is a correlation between costs saved and QALYs gained, which means that scenarios and interventions which produce more benefits for individuals tend to also produce more savings for the NHS.

Figure 80: Mean cost-effectiveness results for each scenario plotted on the cost-effectiveness plane. The willingness to pay threshold (dotted line) is assumed to be £20,000 per QALY.

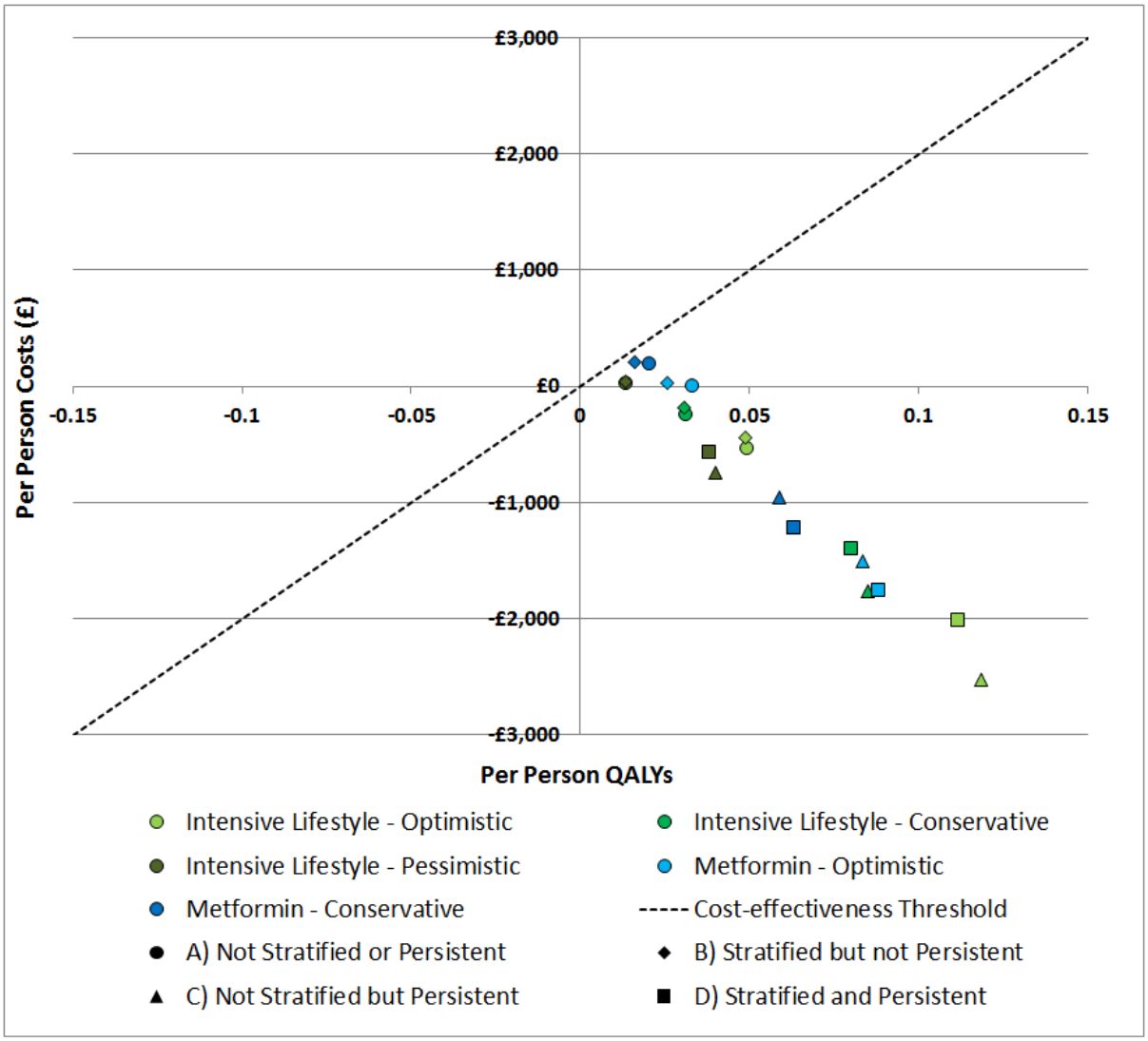


Table 46: Table showing incremental net monetary benefit compared to control in the total population for all scenarios

	A) HbA1c neither stratified nor persistent	B) HbA1c stratified but not persistent	C) HbA1c persistent but not stratified	D) HbA1c persistent and stratified
Optimistic Intensive Lifestyle	£1,520	£1,414	£4,897	£4,247
Conservative Intensive Lifestyle	£863	£805	£3,466	£2,998

Pessimistic Intensive Lifestyle	£244	£223	£1,551	£1,320
Optimistic Metformin	£655	£486	£3,171	£3,517
Conservative Metformin	£202	£116	£2,128	£2,475

Table 47: Table showing the probability cost-effective compared to control in the total population for all scenarios

	A) HbA1c neither stratified nor persistent	B) HbA1c stratified but not persistent	C) HbA1c persistent but not stratified	D) HbA1c persistent and stratified
Optimistic Intensive Lifestyle	100%	100%	100%	100%
Conservative Intensive Lifestyle	97%	97%	94%	95%
Pessimistic Intensive Lifestyle	79%	79%	83%	83%
Optimistic Metformin	99%	96%	100%	100%
Conservative Metformin	81%	68%	100%	100%

3B: Comparison of Subgroup Results

In order to compare subgroup results in a manageable way, the committee were asked to select which scenario they thought was most likely to reflect reality. The committee indicated that stratification but not persistence of the HbA1c effect was most likely to reflect reality, but thought that the uncertainty around intervention effectiveness was too high to decide whether optimistic, conservative or pessimistic effectiveness estimates were more likely to be accurate.

Figure 81 to Figure 83 compare the net monetary benefit of the intensive lifestyle and metformin interventions within the same chart, for each of the population subgroups, when HbA1c effect is assumed to be stratified but not persistent. It is generally recommended in cost-effectiveness analysis to provide estimates of the probability that one intervention is

more cost-effective than another, derived from probabilistic sensitivity analysis. However, this only takes account of parameter uncertainty. In this case, the structural uncertainty around which effectiveness estimates are most likely to best represent reality will have a greater impact on the decision than parameter uncertainty, meaning that estimates of uncertainty produced through PSA will misleadingly underestimate the true decision uncertainty. It was therefore thought inappropriate to provide estimates of the probability that lifestyle intervention is more cost-effective than metformin in different population subgroups. Key points and conclusions from the comparison of cost-effectiveness results are as follows:

B3.1. It was not possible to directly compare intensive lifestyle intervention with metformin as the guidelines committee were unable to decide which effectiveness estimates (i.e. optimistic, conservative or pessimistic) were most likely to reflect reality.

B3.2. The guidelines committee did decide that the most realistic scenario was to assume that the HbA1c effect would be stratified but not persistent. The stratification effect means that individuals of low age, high BMI and high FPG tend to benefit more from metformin, whereas individuals of high age, low BMI and high FPG tend to benefit more from intensive lifestyle intervention ([14] and see Figure 54).

B3.3. In most subgroups, intensive lifestyle intervention is likely to be more cost-effective than metformin, providing that the true effectiveness of intensive lifestyle intervention is no lower than conservative estimates and that the true effectiveness of metformin is no higher than optimistic estimates.

B3.4. In some subgroups, it is possible that metformin could be more cost-effective than intensive lifestyle intervention, particularly if the effectiveness of metformin is closer to optimistic than conservative estimates and the effectiveness of intensive lifestyle intervention is closer to conservative or pessimistic estimates than optimistic estimates. These include the BMI 35+ subgroup (middle of Figure 81), the FPG 6.5-6.9 subgroup (right hand side of Figure 81), the high HbA1c or FPG, and high BMI combinatorial subgroups (Figure 82 and Figure 83), and the high HbA1c or FPG, moderate BMI and low age combinatorial subgroups (Figure 82 and Figure 83).

Figure 81: Comparison of net monetary benefit for intensive lifestyle and metformin interventions in different subgroups defined by a single population

characteristic, when HbA1c effect is assumed to be stratified but not persistent. Discount rate = 3.5%.

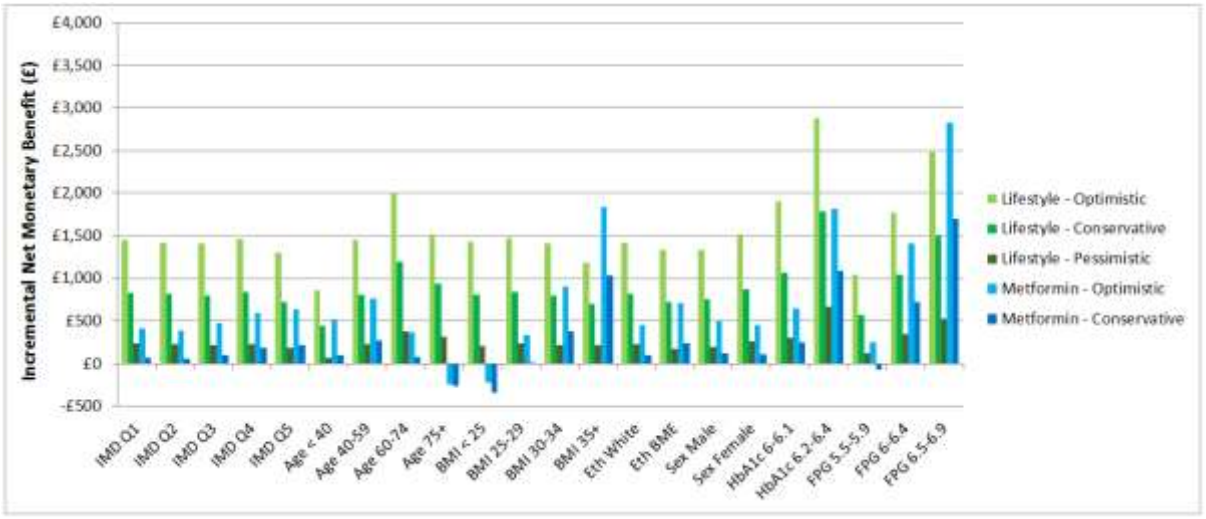


Figure 82: Comparison of net monetary benefit for intensive lifestyle and metformin interventions in different multifactorial subgroups defined through HbA1c criteria, when HbA1c effect is assumed to be stratified but not persistent. Discount rate = 3.5%.

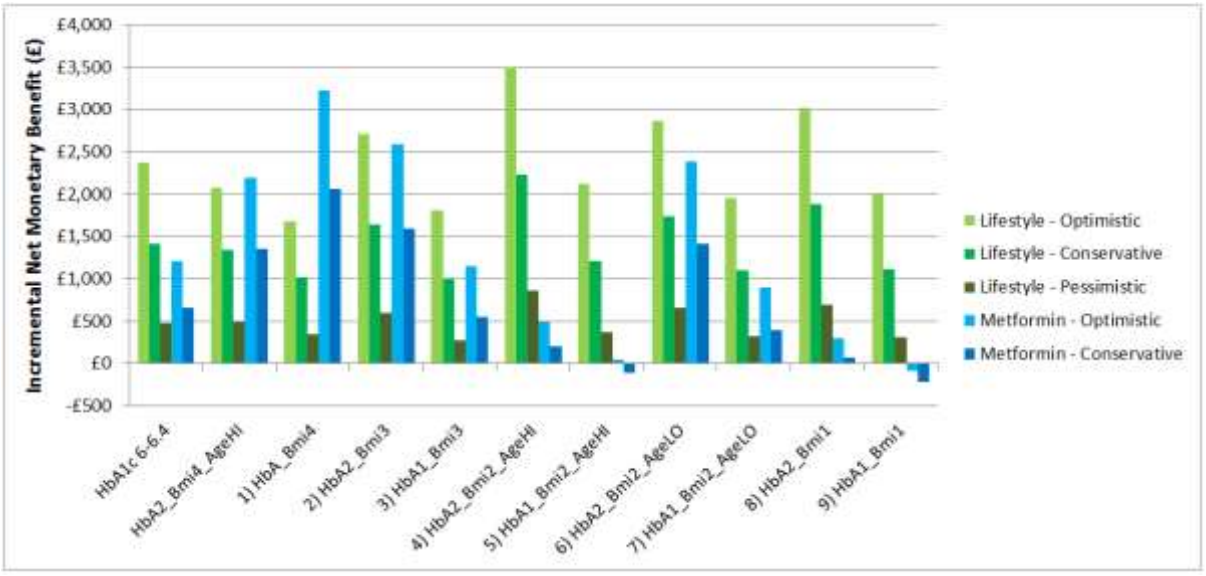
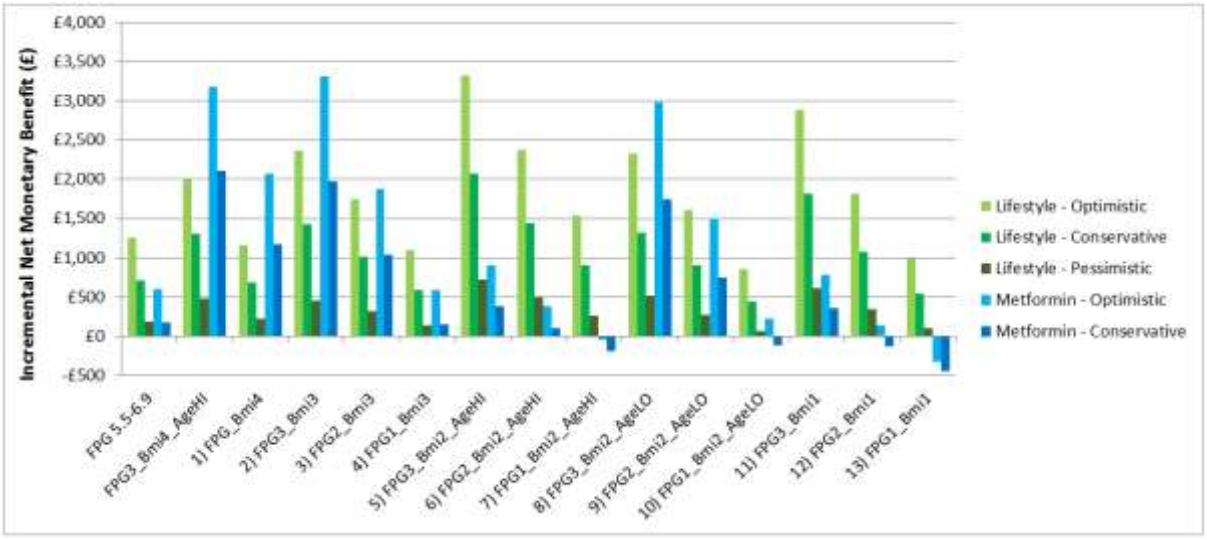


Figure 83: Comparison of net monetary benefit for intensive lifestyle and metformin interventions in different multifactorial subgroups defined through FPG

criteria, when HbA1c effect is assumed to be stratified but not persistent. Discount rate = 3.5%.



4: Long-term Diabetes Incidence Reduction in the Total Population

Ten year and lifetime projections of cumulative diabetes incidence in the total population for each of the 12 intensive lifestyle scenarios and the eight metformin scenarios compared to control are presented in Figure 84 to Figure 87. Key details are summarised below:

A4.1 The model predicts that in the control scenario, about 40% of individuals at high risk of type 2 diabetes will have developed diabetes within ten years. This compares with data from the US DPP and Finnish DPS showing that about 50% of individuals developed diabetes within ten years (see Figure 52 and [50;57]). However, the English high risk population is likely to be healthier than the populations selected for these trials (for example, the average BMI of individuals in the US DPP was 34 kg/m^2, whereas it is only 28.4 kg/m^2 in the HSE 2011).

A4.2 The model predicts that without any intervention to prevent diabetes or lose weight, about 70% of individuals at high risk of type 2 diabetes will develop diabetes over their lifetime.

A4.3 The model predicts that intensive lifestyle intervention can reduce the ten year cumulative incidence of diabetes in participants to as low as 30% (i.e. a 25% reduction in cumulative incidence), and that metformin can reduce the ten year cumulative incidence in participants to as low as 32%, if the most optimistic estimates of effectiveness are applied and if the HbA1c effect is assumed to be persistent.

A4.4 Persistence of HbA1c effect is predicted to be associated with a gradual widening of the gap between cumulative diabetes incidence in control and intervention populations over time, whereas if the HbA1c effect is not assumed to be persistent, the gap is maximal at about five years post intervention implementation and then starts to narrow as individuals succumb to diabetes that had been delayed due to intervention effect. In the US DPP and Finnish DPS, the gap tends to stay the same between five and ten years post-intervention implementation (see Figure 52 and [50;57]), suggesting that there could be partial persistence of HbA1c effect, perhaps depending upon the adherence of different individuals to the interventions.

A4.5 Stratification of HbA1c effect has little impact on cumulative diabetes incidence, affecting mainly whether the conservative lifestyle intervention has a greater or lesser effect than the conservative metformin intervention in reducing diabetes incidence.

Figure 84: Projected diabetes incidence reduction over ten years (left) or over lifetime (right) in the total population assuming neither stratification nor persistence of HbA1c effect.

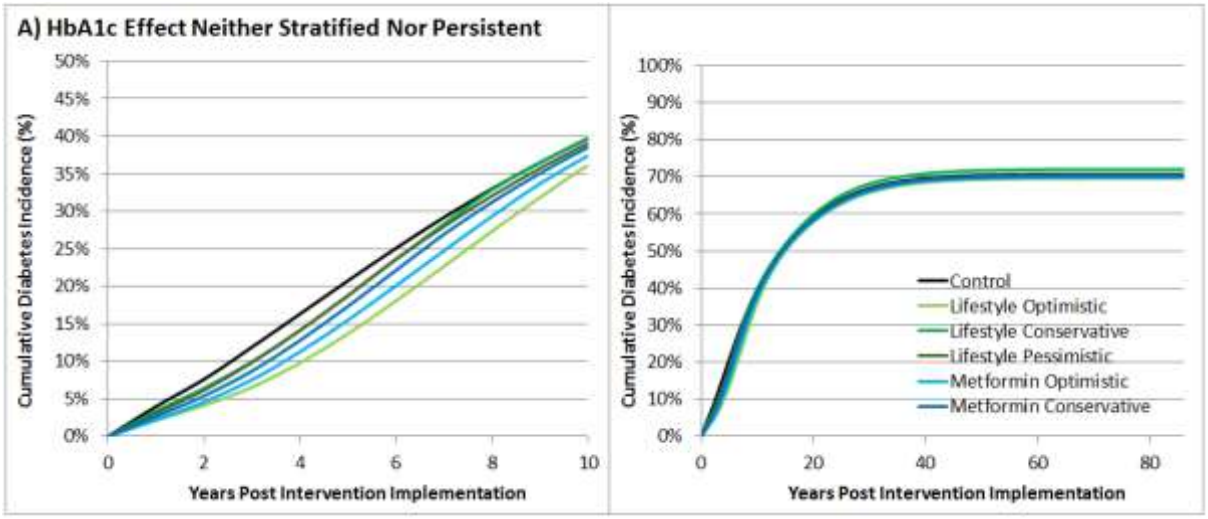


Figure 85: Projected diabetes incidence reduction over ten years (left) or over lifetime (right) in the total population assuming stratification but not persistence of HbA1c effect.

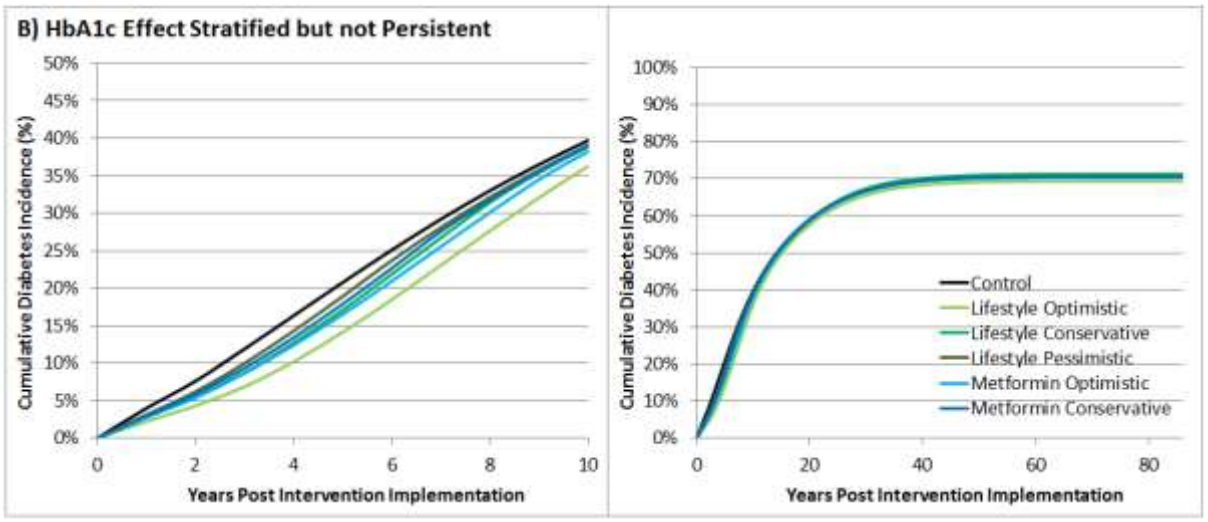


Figure 86: Projected diabetes incidence reduction over ten years (left) or over lifetime (right) in the total population assuming persistence but not stratification of HbA1c effect.

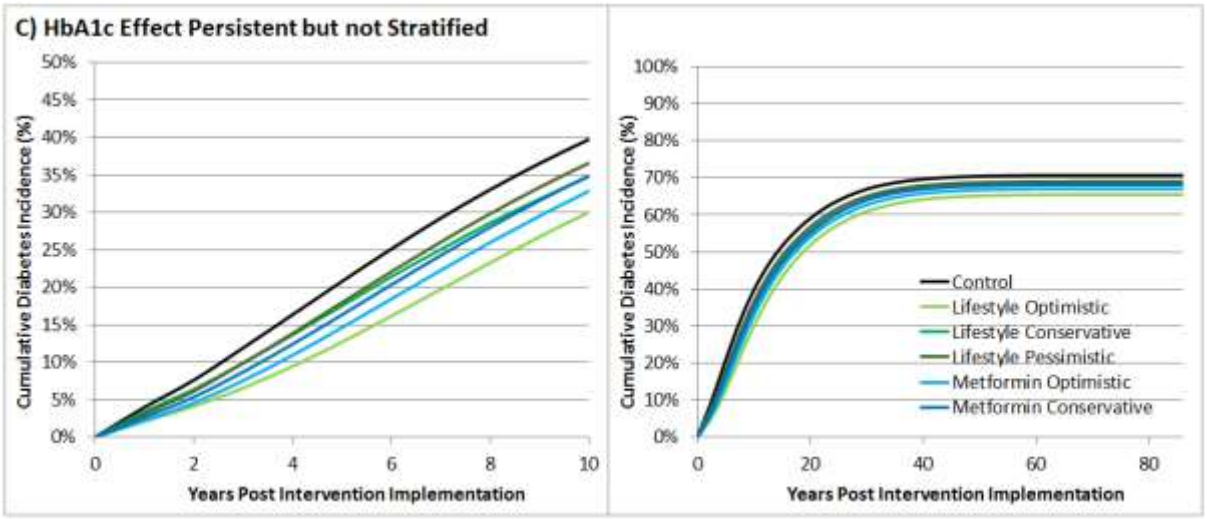
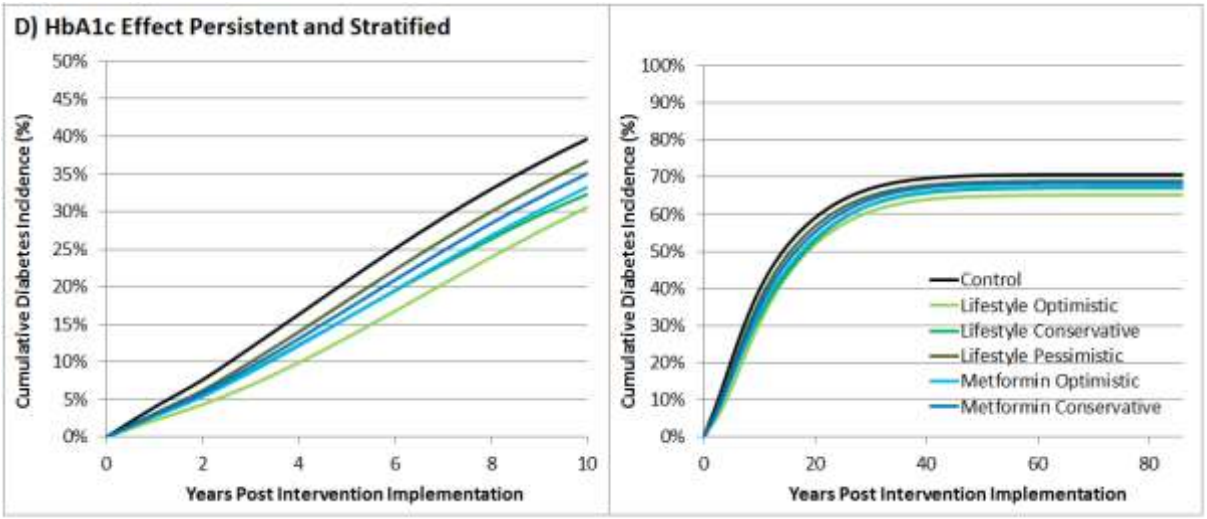


Figure 87: Projected diabetes incidence reduction over ten years (left) or over lifetime (right) in the total population assuming persistence and stratification of HbA1c effect.



5: Budget Impact

Given the large number of scenarios analysed, it was not possible to produce a budget impact for each one. The full incremental budget impact compared to control, of implementing either the conservative intensive lifestyle intervention, or the conservative metformin intervention, assuming stratification but no persistence of HbA1c effect, over the next five years is presented in Table 108 and Table 109 in Appendix 5, whilst bar charts showing an overview of intervention costs, NHS costs and total costs (the sum of intervention and NHS costs) are shown in Figure 88 to Figure 93. Results are cumulative and assume that the intervention is taken up by 100,000 individuals in each subgroup.

It is important to note that there are projected to be fewer than 100,000 individuals in England in some subgroups, and not all of these individuals will take up an offered intervention. The predicted proportions of each subgroup in the high risk population, and the projected numbers of individuals in each subgroup in England can be found in Table 24. Whilst an estimate of 32% was used for uptake of the intensive lifestyle intervention in the PHE analysis [1], there are no useful estimates of uptake for metformin as a diabetes prevention medication, and it is likely that uptake will differ between population subgroups [58;59].

Key details of the budget impact results are summarised below:

A5.1 Cumulative intervention costs are identical in each population subgroup for the intensive lifestyle intervention and stay fixed over time as no costs are incurred beyond year one (Figure 88), whilst metformin intervention costs increase over time and differ between subgroups depending on the differences in mortality and diabetes incidence rates between subgroups (Figure 91). Note that in particular, metformin intervention costs are predicted to be lower in the Age > 75 subgroup in which it is expected that mortality is particularly high, and in the HbA1c 6.2-6.4% subgroup in which it is expected that diabetes incidence is particularly high

A5.2 Cost savings generally start to accrue to the NHS from the first year after intervention implementation and continue to accrue in subsequent years for both interventions (Figure 89 and Figure 92).

A5.3 Cumulative total costs are projected to diminish over time for the intensive lifestyle intervention (Figure 90). This fall is particularly steep for subgroups with higher age, higher BMI and higher HbA1c or FPG. Note that this pattern differs slightly from lifetime cost-effectiveness which is predicted to be higher in the middle aged than the older aged (see A1.6 and Figure 56), indicating that age has differential effects on short-term versus long-term outcomes.

A5.4 For intensive lifestyle intervention, in the HbA1c 6.2-6.4, overweight, aged ≥ 60' subgroup cumulative total costs are projected to fall below zero (i.e. become cost-saving overall) within five years. This subgroup is also the one which produces the greatest lifetime net benefit for this scenario.

A5.5 For metformin, cumulative total costs generally rise over the five year period, although in some subgroups; particularly those with high HbA1c, high FPG or high BMI, they start to diminish either from year three or four (Figure 93). This difference from the intensive lifestyle intervention reflects the ongoing intervention costs accrued due to metformin use.

A5.6 For this metformin scenario, it is not predicted that the intervention will become cost-saving within five years in any subgroup.

Figure 88: Intensive lifestyle intervention: Estimated cumulative incremental intervention costs over years 1-5 in different population subgroups.

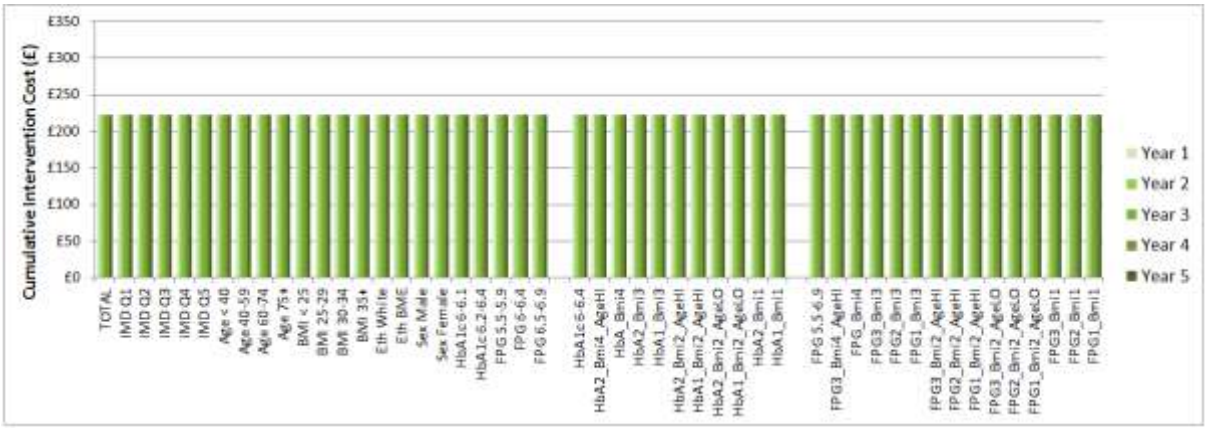


Figure 89: Intensive lifestyle intervention: Estimated cumulative incremental NHS costs over years 1-5 in different population subgroups. Note that these costs are negative and represent cost-savings to the NHS.

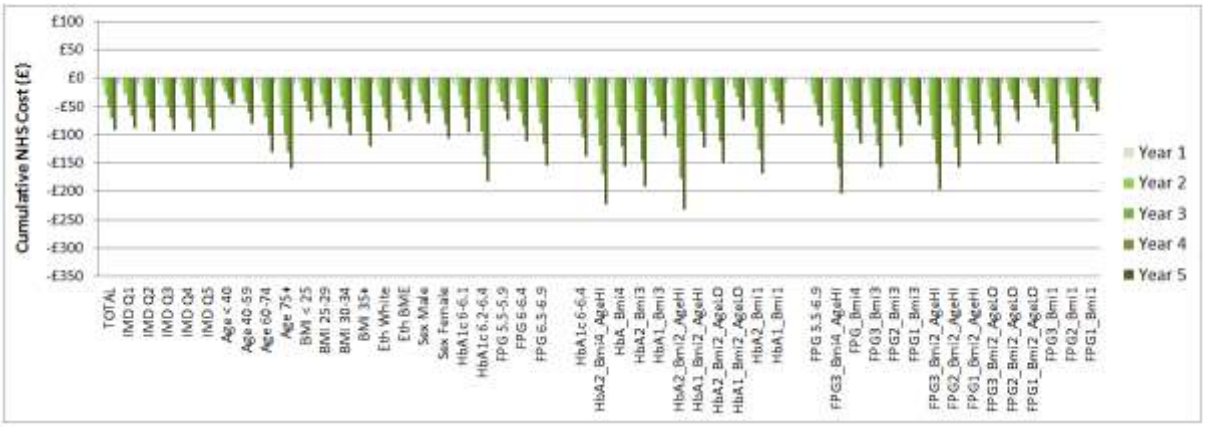


Figure 90: Intensive lifestyle intervention: Estimated cumulative incremental total costs over years 1-5 in different population subgroups. Note that these costs are composed of the NHS costs and intervention costs shown above.

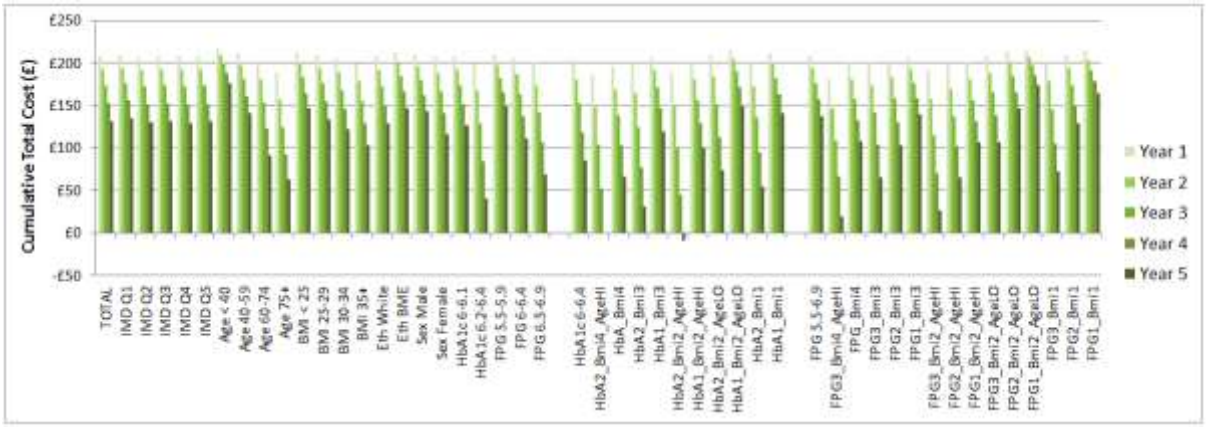


Figure 91: Metformin: Estimated cumulative incremental intervention costs over years 1-5 in different population subgroups.

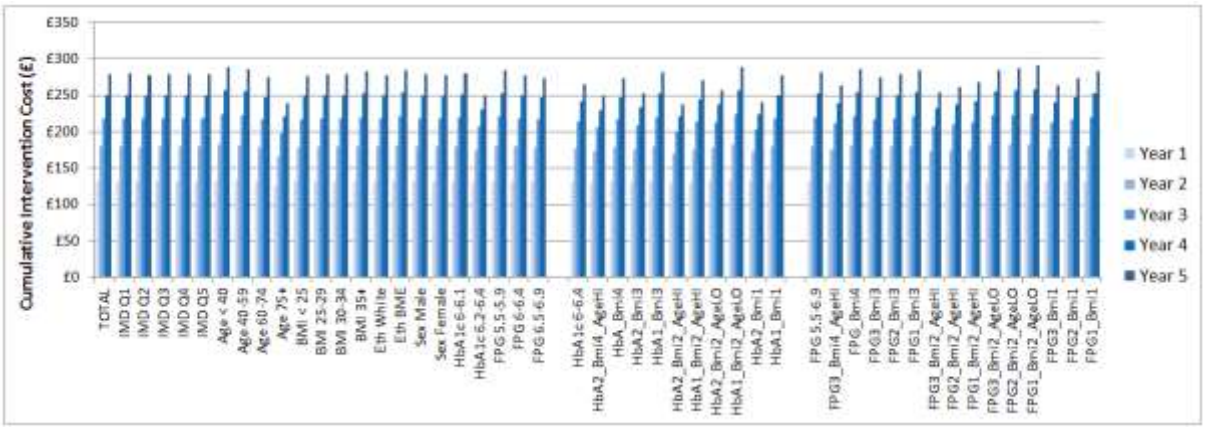


Figure 92: Metformin: Estimated cumulative incremental NHS costs over years 1-5 in different population subgroups. Note that these costs are negative and represent cost-savings to the NHS.

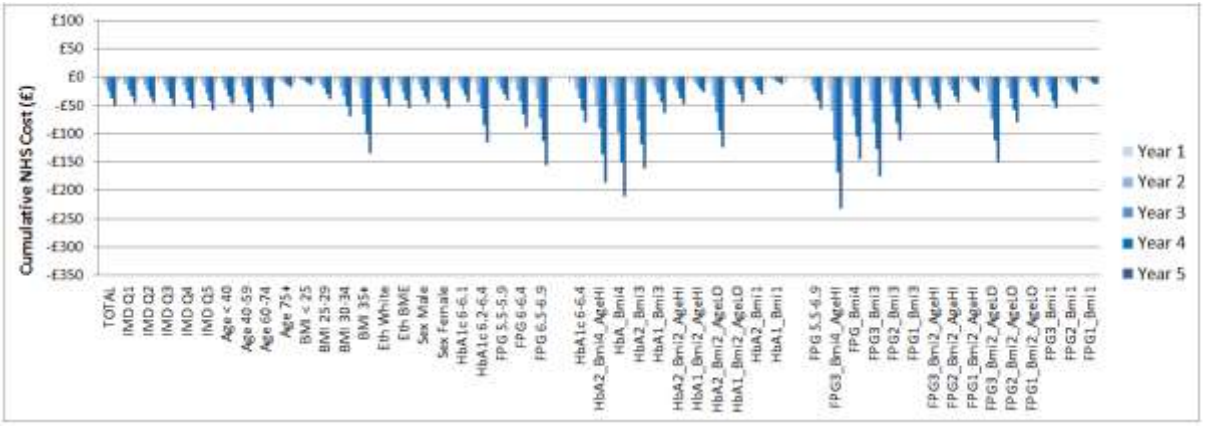
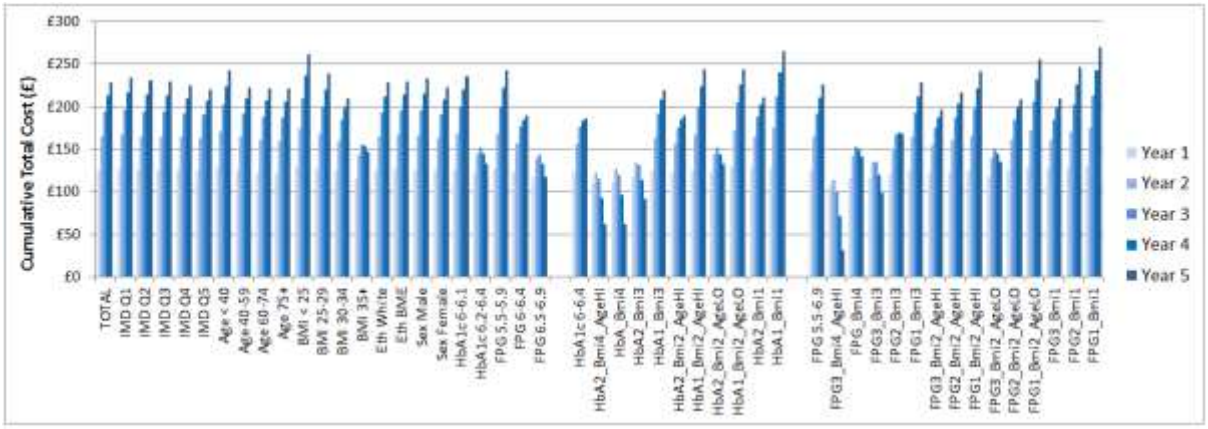


Figure 93: Metformin: Estimated cumulative incremental total costs over years 1-5 in different population subgroups. Note that these costs are composed of the NHS costs and intervention costs shown above.



Discussion

Summary and Interpretation of Key Findings

A summary and interpretation of the key findings concerning the relative cost-effectiveness of the subgroups and scenarios is presented here.

1. The estimated relative cost-effectiveness of giving the intensive lifestyle intervention or metformin to different population subgroups varies substantially depending upon which assumptions around the stratification and persistence of the HbA1c effect are likely to best represent the NHS DPP.
2. The estimated relative cost-effectiveness of the intensive lifestyle intervention or metformin in different population subgroups does not vary by magnitude of intervention effectiveness (i.e. optimistic versus conservative versus pessimistic), nor does it vary substantially when the discount rate is reduced to 1.5%.
3. In most scenarios, prioritising individuals with the highest baseline HbA1c or FPG for intensive lifestyle intervention or for metformin is predicted to have a high probability of yielding more benefits than intervening in those with lower baseline HbA1c or FPG. Given that this appears to be the case even in scenarios where the HbA1c intervention effect is not stratified by baseline FPG, it is likely that it is the higher disease risk in such individuals that is driving these results rather than higher intervention effectiveness.
4. When comparing these results with the previous PHE work [1], it is not quite as clear that prioritising individuals with the highest baseline BMI for intensive lifestyle intervention would yield more benefits than intervening in those with lower baseline BMI. The differences arise due to: a) implementation of a smaller stratification effect on weight by baseline BMI than was used for the previous work (see Table 34); b) the expansion of the population to include FPG-defined individuals, many of whom are at low risk due to low HbA1c even if they have high BMI; c) the addition of new scenarios based on the NICE evidence review in which an HbA1c effect stratification is assumed, and in which the effect goes in the opposite direction (i.e. a larger HbA1c reduction effect is seen in individuals with lower baseline BMI - see Figure 54). It does appear however, that individuals of high BMI are likely to produce more benefit from metformin than individuals of low BMI, particularly if it is assumed that the HbA1c effect is stratified, which for metformin means a larger effect is implemented in individuals with higher baseline BMI.
5. It is unclear from this analysis which age group could benefit most either from an intensive lifestyle intervention or from metformin, as it depends which assumptions around the persistence of HbA1c effect are most likely to be achieved in the NHS

DPP. Whilst middle aged individuals (aged 40-74) are predicted to benefit most if it is assumed that HbA1c effects are not persistent, the young (aged < 40) would benefit most if it is assumed that HbA1c effects are persistent. The old (aged >75) tend to benefit less than other age groups from either intensive lifestyle intervention or metformin in any scenario. It is important to consider that the persistence of the HbA1c effect could be related to the adherence of individuals to each intervention, and therefore could be lower in practice than that achieved in the US DPP [45]. In particular, individuals following an intensive lifestyle intervention in these two studies received regular maintenance sessions in the months and years following intervention implementation [14;44], whereas for the NHS DPP no maintenance beyond nine months is specified other than for the provider to ensure that links are made with local or national activities and services to enable individuals to continue with lifestyle improvements [36].

6. In general, this analysis suggests that the same subgroups that would benefit most from an intensive lifestyle intervention would also benefit most from metformin. However, differences between the two interventions are apparent if the HbA1c effect is assumed to be stratified. This is due to the opposing stratification effects on diabetes incidence reduction by age and BMI observed in the US DPP for metformin versus intensive lifestyle intervention [14], such that metformin appears to reduce diabetes incidence to a greater extend in the young and those with higher BMI, whereas intensive lifestyle intervention appears to reduce diabetes incidence to a greater extent in the old and those with lower BMI (see Figure 54). Given the lack of statistical significance of some of these observations, the lack of subgroup data from other studies, and the different population composition of the US DPP study compared to the population of England, it is unclear whether these subgroup differences would be replicated within the NHS DPP. If so, it could be more cost-effective to give intensive lifestyle intervention to individuals of low baseline BMI and old age, and to give metformin to individuals of high baseline BMI and young age, depending upon which effectiveness scenarios are likely to be achieved in practice.
7. There are no clear benefits to differentially intervening in individuals by socioeconomic background or by ethnicity. Whilst some scenarios imply a slightly higher benefit in those from the most deprived IMD quintile or the BME ethnic subgroup, this is likely to be due to the correlations between low age, BME ethnicity and high socioeconomic deprivation in the HSE 2011 (see Table 25).
8. It is not clear from this analysis whether an intensive lifestyle intervention similar to the NHS DPP would always be more cost-effective than metformin for diabetes prevention, as it depends which assumptions around intervention effectiveness,

stratification and duration of effect are most likely to reflect reality in England. Further research investigating the effectiveness of metformin as a first line prevention intervention in parallel to the NHS DPP would help to answer this question.

Limitations of this Analysis

There are several limitations of this analysis that should be considered as part of the decision-making process

1. There was some concern from the NICE guidelines committee about whether the effectiveness data; taken from clinical trials, could be over-estimating the effectiveness of interventions implemented in the real world where motivation and adherence may be likely to be lower. This analysis has attempted to mitigate this issue by modelling scenarios around the level of effectiveness (i.e. optimistic versus conservative versus pessimistic). In addition, the modelled mean weight loss is actually lower than that stated by the clinical evidence reviews as a consequence of stratification of weight loss (plus SBP reduction and cholesterol reduction) by baseline BMI (see Table 35 and Table 36), because the mean BMI of the high risk population is lower than that in the reviewed studies. However; it is in principle also possible that even the most pessimistic estimates assumed here are more optimistic than may be obtained in practice. This could have an impact upon the relative cost-effectiveness of intensive lifestyle intervention compared with metformin or control. Nevertheless the range of analyses presented here indicate that it is unlikely to impact upon the ordering of subgroup cost-effectiveness.
2. This analysis has incorporated available data about subgroup differences in intervention effectiveness (see Table 34 and Figure 54). However, it must be recognised that such data is limited and generally non-significant according to standard statistical tests. Furthermore, there is no available information about differential adherence to interventions in different population subgroups. Given the large effect of HbA1c persistence on intervention effectiveness, differential adherence could have substantive effects on the relative cost-effectiveness of interventions between subgroups. Subgroup effectiveness data could be improved considerably if efforts were made to facilitate a well-designed future analysis of the NHS DPP.
3. Whilst the subgroup analysis is reasonably robust for large subgroups, there are some subgroups which consist of small numbers of individuals in the HSE 2011 (e.g. the FPG 6.5-6.9 mmol/L combinatorial subgroups, some of which have as few as five individuals represented in HSE 2011). Uncertainty around results produced from these subgroups is extremely high and therefore such results should be treated with

caution. It was not possible to expand the baseline population by using additional years from the HSE, as only certain years focus on cardiovascular disease and diabetes, and so most years do not collect all the disease risk factors required for the model to run. This aspect of the modelling process could be improved by collecting baseline data on a large representative subset of the individuals eligible for the NHS DPP, which would also have the advantage of being more up-to-date and therefore reflecting recent changes in population composition and treatment of cardiovascular risk factors e.g. with statins.

4. In most scenarios, individuals with high HbA1c are predicted to yield more benefits than individuals with high FPG. This could be due to a limitation in the structure of the model and the risk equations underpinning it, which use HbA1c, but not FPG, to diagnose diabetes and confer risk for other diseases. This could imply that the model is under-estimating the net benefit that could be produced by intervening in individuals with high FPG. Furthermore, the lack of FPG measurements in the HSE 2011 means that baseline FPG had to be estimated, which increases the potential for error when determining the cost-effectiveness of different FPG subgroups. A further consideration is that whilst the model currently estimates that interventions are less cost-effective if given to individuals identified at high risk through FPG but with HbA1c < 6%, there is currently a lack of evidence from prevention studies to identify whether interventions are effective in such individuals or not. In practice, individuals are likely to have either HbA1c or FPG measurements, not both and so, in the absence of specific evidence suggesting otherwise, it may not be appropriate to produce differential guidelines for those diagnosed at high risk through the different measures of blood glucose given the limitations discussed above.

Appendix 1: Model Parameters

This appendix contains details of all parameters used in the model and their distributions for PSA.

GP Attendance in the General Population

GP attendance is estimated from statistical analysis of the Yorkshire Health Study [60]. In the PSA, the parameters are sampled from a multivariate normal distribution, using the mean estimates described in Table 48 and covariance matrix in Table 49.

Table 48: GP attendance reported in the Yorkshire Health Study (N= 18,437) [60]

	Mean	Standard error	Uncertainty Distribution
Age	0.0076	0.0005	MULTIVARIATE NORMAL
Male	-0.1495	0.0159	MULTIVARIATE NORMAL
BMI	0.0110	0.0015	MULTIVARIATE NORMAL
Ethnicity (Non-white)	0.2620	0.0375	MULTIVARIATE NORMAL
Heart Disease	0.2533	0.0289	MULTIVARIATE NORMAL
Depression	0.6127	0.0224	MULTIVARIATE NORMAL
Osteoarthritis	0.2641	0.0238	MULTIVARIATE NORMAL
Diabetes	0.2702	0.0278	MULTIVARIATE NORMAL
Stroke	0.1659	0.0474	MULTIVARIATE NORMAL
Cancer	0.2672	0.0414	MULTIVARIATE NORMAL
Intercept	-0.5014	0.0468	MULTIVARIATE NORMAL
Alpha	0.3423	0.0108	MULTIVARIATE NORMAL

Table 49: Variance-covariance matrix for GP attendance regression

	Age	Male	BMI	Ethnicity (Non-white)	Heart Disease	Depression	Osteo-arthritis	Diabetes	Stroke	Cancer	Intercept	Alpha
Age	0.0000											
Male	0.0000	0.0003										
BMI	0.0000	0.0000	0.0000									
Ethnicity (Non-white)	0.0000	0.0000	0.0000	0.0014								
Heart Disease	0.0000	0.0000	0.0000	0.0000	0.0008							
Depression	0.0000	0.0000	0.0000	0.0000	0.0000	0.0005						
Osteoarthritis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0006					
Diabetes	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0000	0.0000	0.0008				
Stroke	0.0000	0.0000	0.0000	0.0000	-0.0002	-0.0001	0.0000	-0.0001	0.0022			
Cancer	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	-0.0001	0.0017		
Intercept	0.0000	0.0000	-0.0001	-0.0002	0.0002	0.0000	0.0002	0.0003	0.0000	0.0001	0.0022	
Alpha	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0010

Whitehall II Statistical Model of Metabolic Trajectories

The metabolic trajectories used in the model are derived from statistical analysis of the longitudinal Whitehall II cohort [23]. The parameters derived from this model are described in the following tables.

Table 50: Coefficient estimates for metabolic risk factor parallel growth models

	Parameter Description	Estimated Mean	Standard error	p-value
BMI Intercept				
α_{10}	Population mean BMI intercept	2.2521	0.045	<0.001
γ_{10}	Age at baseline coefficient for BMI intercept	0.0056	0.001	<0.001
	Sex coefficient for BMI intercept	-0.0311	0.012	0.009
	Family history of CVD coefficient for BMI intercept	-0.0079	0.012	0.515
υ_{10}	Random error term for BMI intercept	0.1165	0.003	<0.001
BMI linear slope				
α_{11}	Population mean BMI linear slope	0.6409	0.042	<0.001
γ_{11}	Age at baseline coefficient for BMI linear slope	-0.0084	0.001	<0.001
	Sex coefficient for BMI linear slope	-0.0285	0.011	0.009
	Family history of CVD coefficient for BMI linear slope	-0.0155	0.010	0.117
υ_{11}	Random error term for BMI linear slope	0.0222	<0.001	<0.001
BMI quadratic slope				
α_{12}	Population mean BMI quadratic slope	-0.2007	0.023	<0.001
γ_{12}	Age at baseline coefficient for quadratic slope	0.0026	<0.001	<0.001
	Sex coefficient for quadratic slope	0.0089	0.006	0.147
	Family history of CVD coefficient for quadratic slope	0.0104	0.006	0.061
ε_1	Random error term for BMI	0.0104	<0.001	<0.001
Glyc Intercept				
α_{20}	Population mean glyc intercept	0	NA	NA
γ_{20}	Smoker coefficient for glyc intercept	-0.1388	0.029	<0.001
τ_{20}	Association between BMI intercept and glyc intercept	0.2620	0.024	<0.001
υ_{20}	Random error term for glyc intercept	0.0851	0.008	<0.001
Glyc linear slope				
α_{21}	Population mean glyc linear slope	-0.4255	0.071	<0.001
γ_{21}	Sex coefficient for glyc linear slope	0.1486	0.045	0.001
	Ethnicity coefficient for glyc linear slope	-0.0218	0.081	0.786
	Family history of T2DM coefficient for glyc linear slope	-0.0512	0.054	0.345

	Smoker coefficient for glyc linear slope	0.1796	0.066	0.007
τ_{21}	Association between BMI intercept and glyc linear slope	0.0821	0.024	0.001
τ_{22}	Association between BMI linear slope and glyc linear slope	0.1984	0.073	0.007
υ_{21}	Random error term for glyc linear slope	0.0222	0.011	0.053
Glyc quadratic slope				
α_{22}	Population mean glyc quadratic slope	0.1094	0.025	<0.001
γ_{22}	Sex coefficient for glyc quadratic slope	-0.0855	0.027	0.002
	Ethnicity coefficient for glyc quadratic slope	0.0899	0.049	0.067
	Family history of T2DM coefficient for glyc quadratic slope	0.0633	0.033	0.052
	Smoker coefficient for glyc quadratic slope	-0.0390	0.040	0.330
υ_{22}	Random error term for glyc quadratic slope	0.0107	0.003	0.002
ε_2	Glyc measurement error	0.0707	0.005	<0.001
SBP Intercept				
α_{30}	Population mean SBP intercept	0.6934	0.021	<0.001
γ_{30}	Age at baseline coefficient for SBP intercept	0.0043	<0.001	<0.001
	Sex coefficient for SBP intercept	0.0380	0.004	<0.001
	Smoking coefficient for SBP intercept	-0.0243	0.006	<0.001
	Ethnicity coefficient for SBP intercept	0.0078	0.007	0.300
	Family history of CVD coefficient for SBP intercept	0.0061	0.004	0.160
τ_{31}	Association between BMI intercept and SBP intercept	0.1080	0.006	<0.001
υ_{30}	Random error term for SBP intercept	0.0085	0.00	<0.001
SBP linear slope				
α_{31}	Population mean SBP linear slope	-0.0227	0.021	0.278
γ_{31}	Age at baseline coefficient for SBP linear slope	0.0024	<0.001	<0.001
	Sex coefficient for SBP linear slope	-0.0004	0.004	0.927
	Smoking coefficient for SBP linear slope	0.0205	0.005	<0.001
	Ethnicity coefficient for SBP linear slope	0.0224	0.007	0.001
	Family history of CVD coefficient for SBP linear slope	-0.0013	0.004	0.748
τ_{31}	Association between BMI intercept and SBP linear slope	-0.0396	0.006	<0.001
	Association between BMI linear slope and SBP linear slope	0.2325	0.019	<0.001
υ_{31}	Random error term for SBP linear slope	0.0024	<0.001	<0.001
ε_3	SBP measurement error variance	0.0093	<0.001	<0.001

TC Intercept				
α_{40}	Population mean TC intercept	2.9956	0.176	<0.001
γ_{40}	Age at baseline coefficient for TC intercept	0.0456	0.003	<0.001
	Sex coefficient for TC intercept	0.0660	0.036	0.070
τ_{40}	Association between BMI intercept and TC intercept	0.4459	0.049	<0.001
υ_{40}	Random error term for TC intercept	0.8960	0.025	<0.001
TC linear slope				
α_{41}	Population mean TC linear slope	2.1216	0.128	<0.001
γ_{41}	Age at baseline coefficient for TC linear slope	-0.0316	0.002	<0.001
	Sex coefficient for TC linear slope	-0.2677	0.026	<0.001
τ_{41}	Association between BMI intercept and TC linear slope	-0.4808	0.035	<0.001
τ_{42}	Association between BMI linear slope and TC linear slope	0.9802	0.108	<0.001
υ_{41}	Random error term for TC linear slope	0.1583	0.011	<0.001
ε_4	TC measurement error variance	0.3426	0.006	<0.001
HDL Intercept				
α_{50}	Population mean HDL intercept	2.4124	0.054	<0.001
γ_{50}	Age at baseline coefficient for HDL intercept	0.0032	0.011	<0.001
	Sex coefficient for HDL intercept	-0.3710	0.001	<0.001
τ_{51}	Association between BMI intercept and HDL intercept	-0.3514	0.015	<0.001
υ_{50}	Random error term for HDL intercept	0.0827	-0.040	<0.001
HDL linear slope				
α_{51}	Population mean HDL linear slope	0.1241	0.034	<0.001
γ_{51}	Age at baseline coefficient for HDL linear slope	0.0020	0.001	<0.001
	Sex coefficient for HDL linear slope	0.0041	0.007	0.558
τ_{51}	Association between BMI intercept and HDL linear slope	-0.0400	0.010	<0.001
υ_{51}	Random error term for HDL linear slope	0.0090	0.001	<0.001
ε_5	HDL measurement error variance	0.0333	0.001	<0.001

Table 51: Coefficient estimates for latent glycaemic measurement model

	Parameter Description	Estimated Mean	Standard error	p-value
μ_0	FPG intercept	4.2903	0.089	<0.001
θ_{01}	Glycaemic factor to FPG	1	NA	NA
θ_{02}	Age to FPG	0.0031	0.001	0.022

θ_{03}	Sex to FPG	0.2129	0.021	<0.001
θ_{04}	Ethnicity to FPG	0.0100	0.037	0.786
θ_{05}	Family history of diabetes to FPG	0.1168	0.025	<0.001
ε_0	FPG measurement error variance	0.1649	0.007	<0.001
μ_1	2-hr Glucose intercept	0.5707	0.223	0.011
θ_{11}	Glycaemic factor to 2-hr glucose	2.4384	0.078	<0.001
θ_{12}	Age to 2-hr glucose	0.0716	0.003	<0.001
θ_{13}	Sex to 2-hr glucose	-0.1411	0.058	0.014
θ_{14}	Ethnicity to 2-hr glucose	0.3047	0.100	0.002
θ_{15}	Family history of diabetes to 2-hr glucose	0.3496	0.068	<0.001
ε_1	2-hr measurement error variance	2.3679	0.054	<0.001
μ_2	HbA1c intercept	4.4769	0.073	<0.001
θ_{21}	Glycaemic factor to HBA1c	0.5074	0.016	<0.001
θ_{22}	Age to HBA1c	0.0101	0.001	<0.001
θ_{23}	Sex to HBA1c	-0.0457	0.001	<0.001
θ_{24}	Ethnicity to HBA1c	0.1854	0.030	<0.001
θ_{25}	Family history of diabetes to HBA1c	0.0563	0.020	0.004
ε_2	HbA1c measurement error variance	0.1166	0.003	<0.001

Table 52: Covariance matrix Ω for individual random error

	υ_{10}	υ_{11}	υ_{20}	υ_{21}	υ_{22}	υ_{30}	υ_{31}	υ_{40}	υ_{41}	υ_{50}	υ_{51}
υ_{10}	0.1165										
υ_{11}	0.0095	0.0131									
υ_{20}	<0.0010	<0.0010	0.0851								
υ_{21}	<0.0010	<0.0010	0.0222	0.0209							
υ_{22}	<0.0010	<0.0010	<0.0010	<0.0010	0.0107						
υ_{30}	<0.0010	<0.0010	0.0080	<0.0010	<0.0010	0.0085					
υ_{31}	<0.0010	<0.0010	<0.0010	0.0018	<0.0010	<0.0017	0.0024				
υ_{40}	<0.0010	<0.0010	0.0324	<0.0010	<0.0010	0.0031	<0.0010	0.8960			
υ_{41}	<0.0010	<0.0010	<0.0010	-<0.0012	<0.0010	<0.0010	0.0066	-0.2229	0.1583		
υ_{50}	<0.0010	<0.0010	-0.0118	<0.0010	<0.0010	0.0010	<0.0010	0.0273	<0.0010	0.0827	
υ_{51}	<0.0010	<0.0010	<0.0010	-0.0059	<0.0010	<0.0010	0.0020	<0.0010	0.0159	0.0061	0.0090

HbA1c trajectory in individuals diagnosed with type 2 diabetes

The input parameters for the initial reduction in HbA1c and long term trend in HbA1c following diagnosis, derived from analysis of the UKPDS outcomes model [25], are reported in Table 53 and Table 54 respectively.

Table 53: Estimated change in HbA1c in first year following diabetes diagnosis

	Distribution	Parameter 1	Parameter 2	Central estimate
Change in HbA1c Intercept	NORMAL	-2.9465	0.0444513	-2.9465
HbA1c at baseline	NORMAL	0.5184	0.4521958	0.5184

Table 54: Estimated change in HbA1c following diabetes diagnosis over long term

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Longitudinal HbA1c for diabetes intercept	NORMAL	-0.024	0.017	-0.024
Longitudinal HbA1c for diabetes log(time since diagnosis)	NORMAL	0.144	0.009	0.144
Longitudinal HbA1c for diabetes Second year	NORMAL	-0.333	0.05	-0.333
Longitudinal HbA1c for diabetes lag HbA1c	NORMAL	0.759	0.004	0.759
Longitudinal HbA1c for diabetes HbA1c at diagnosis	NORMAL	0.085	0.004	0.0896

Systolic blood pressure and cholesterol trajectory following treatment

The changes in systolic blood pressure and total cholesterol following treatment with anti-hypertensives or statins, and statin uptake are reported in Table 55.

Table 55: Treatment effects following treatment

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Simvastatin treatment effects	NORMAL	-1.45	0.11	-1.45	[61]
Anti-hypertensive treatment effect	NORMAL	-8.4	0.638	-8.4	[62]
Statin Uptake	UNIFORM	0.65	(0.4-0.9)	0.65	[29]

Metabolic Risk Factor screening

The distribution for the HbA1c threshold at which opportunistic screening for type 2 Diabetes is initiated even if the individual does not have a history of cardiovascular disease, microvascular disease or identified impaired glucose regulation is reported in Table 56.

Table 56: Threshold for HbA1c opportunistic diagnosis

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
HbA1c at diagnosis	NORMAL	8.1	0.073	8.1	[63]

Comorbid Outcomes and Mortality

Cardiovascular Disease

Cardiovascular risk is estimated using the QRISK2 model [27]. Parameter distributions for men and women are reported in Table 57.

Table 57: Input parameters of the QRISK2 risk model

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
QRISK female ethnicity 2	NORMAL	0.2163	0.0537	0.2163
QRISK female ethnicity 3	NORMAL	0.6905	0.069	0.6905
QRISK female ethnicity 4	NORMAL	0.3423	0.1073	0.3423
QRISK female ethnicity 5	NORMAL	0.0731	0.1071	0.0731
QRISK female ethnicity 6	NORMAL	-0.0989	0.0619	-0.0989
QRISK female ethnicity 7	NORMAL	-0.2352	0.1275	-0.2352
QRISK female ethnicity 8	NORMAL	-0.2956	0.1721	-0.2956
QRISK female ethnicity 9	NORMAL	-0.1010	0.0793	-0.1010
QRISK female smoke 2	NORMAL	0.2033	0.0152	0.2033
QRISK female smoke 3	NORMAL	0.48200	0.0220	0.4820
QRISK female smoke 4	NORMAL	0.6126	0.0178	0.6126
QRISK female smoke 5	NORMAL	0.7481	0.0194	0.7481
QRISK female age 1	NORMAL	5.0373	1.0065	5.0327
QRISK female age 2	NORMAL	-0.0108	0.0022	-0.0108
QRISK female bmi	NORMAL	0.4724	0.0423	0.4724
QRISK female cholesterol	NORMAL	0.6375	0.0143	0.6375
QRISK female sbp	NORMAL	0.0106	0.0045	0.0106

QRISK female townsend	NORMAL	0.060	0.0068	0.060
QRISK female fibrillation	NORMAL	1.3261	0.0310	1.3261
QRISK female RA	NORMAL	0.3626	0.0319	0.3626
QRISK female Renal	NORMAL	0.7636	0.0639	0.7636
QRISK female Hypertension	NORMAL	0.5421	0.0115	0.5421
QRISK female diabetes	NORMAL	0.8940	0.0199	0.8940
QRISK female family history cvd	NORMAL	0.5997	0.0122	0.5997
QRISK female age1 * smoke 1	NORMAL	0.1774	0.0355	0.1774
QRISK female age 1 * smoke 2	NORMAL	-0.3277	0.0655	-0.3277
QRISK age1 * smoke 3	NORMAL	-1.1533	0.2307	-1.1533
QRISK female age 1 * smoke 4	NORMAL	-1.5397	0.3079	-1.5397
QRISK female age 1 * atrial fibrillation	NORMAL	-4.6084	0.922	-4.6084
QRISK female age 1 * renal	NORMAL	-2.6401	0.5280	-2.6401
QRISK female age 1 * hypertension	NORMAL	-2.2480	0.4496	-2.2480
QRISK female age 1 * diabetes	NORMAL	-1.8452	0.3690	-1.8452
QRISK female age 1 * bmi	NORMAL	-3.0851	0.6170	-3.0851
QRISK female age 1 * family history cvd	NORMAL	-0.2481	0.0496	-0.2481
QRISK female age 1 * sbp	NORMAL	-0.0132	0.0026	-0.0132
QRISK female age 1 * town	NORMAL	-0.0369	0.0074	-0.0369
QRISK female age 2 * smoke 1	NORMAL	-0.0053	0..0001	-0.0053
QRISK female age 2 * smoke 2	NORMAL	-0.0005	0.0001	-0.0005
QRISK female age 2 * smoke 3	NORMAL	-0.0105	0.0021	-0.0105
QRISK female age 2 * smoke 4	NORMAL	-0.0155	0.0031	-0.0155
QRISK female age 2 * fibrillation	NORMAL	-0.0507	0.0101	-0.0507
QRISK female age 2 * renal	NORMAL	0.0343	0.0069	0.0343
QRISK female age 2 * hypertension	NORMAL	0.0258	0.0051	0.0258
QRISK female age 2 * diabetes	NORMAL	0.0180	0.0036	0.0180
QRISK female age 2 * bmi	NORMAL	0.0345	0.0069	0.0345
QRISK female age 2 * family history cardiovascular	NORMAL	-0.0062	0.0012	-0.0062
QRISK female age 2 * sbp	NORMAL	-0.000029	0.000006	-0.000029
QRISK female age 2 * townsend	NORMAL	-0.0011	0.0002	-0.0011
QRISK female 1 year survival	CONSTANT	0.9983	NA	NA
QRISK male ethnicity 2	NORMAL	0.3163	0.0425	0.3163
QRISK male ethnicity 3	NORMAL	0.6092	0.0547	0.6092

QRISK male ethnicity 4	NORMAL	0.5958	0.0727	0.5958
QRISK male ethnicity 5	NORMAL	0.1142	0.0845	0.1142
QRISK male ethnicity 6	NORMAL	-0.3489	0.0641	-0.3489
QRISK male ethnicity 7	NORMAL	-0.3604	0.1094	-0.3604
QRISK male ethnicity 8	NORMAL	-0.2666	0.1538	-0.2666
QRISK male ethnicity 9	NORMAL	-0.1208	0.0734	-0.1208
QRISK male SMOKE 2	NORMAL	0.2033	0.0152	0.2033
QRISK male SMOKE 3	NORMAL	0.4820	0.0220	0.4820
QRISK male SMOKE 4	NORMAL	0.6126	0.0178	0.6126
QRISK male SMOKE 5	NORMAL	0.7481	0.0194	0.7481
QRISK male age 1	NORMAL	47.316	9..4630	47.316
QRISK male age 2	NORMAL	-101.236	20.247	-101.236
QRISK male bmi	NORMAL	0.5425	0.0299	0.5425
QRISK male cholesterol	NORMAL	0.14425	0.0022	0.14425
QRISK male sbp	NORMAL	0.0081	0.0046	0.0081
QRISK male townsend	NORMAL	0.0365	0.0048	0.0365
QRISK male fibrillation	NORMAL	0.7547	0.1018	0.7547
QRISK male RA	NORMAL	0.3089	0.0445	0.3089
QRISK male renal	NORMAL	0.7441	0.0702	0.7441
QRISK male hypertension	NORMAL	0.6965	0.011	0.6965
QRISK male age 1 smoke 1	NORMAL	-3.8805	0.7761	-3.8805
QRISK male age 1 smoke 2	NORMAL	-16.703	3.3406	-16.703
QRISK male age 1 smoke 3	NORMAL	-15.3738	3.5291	-15.3738
QRISK male age 1 smoke 4	NORMAL	-17.6453	3.5291	-17.6453
QRISK male age 1 fibrillation	NORMAL	-7.0146	1.4056	-7.0282
QRISK male age 1 renal	NORMAL	-17.015	3.4029	-17.015
QRISK male age 1 hypertension	NORMAL	33.9625	6.7925	33.9625
QRISK male age 1 diabetes	NORMAL	12.7886	2.5577	12.7886
QRISK male age 1 bmi	NORMAL	3.2680	0.6536	3.2680
QRISK male age 1 fxcd	NORMAL	-17.9219	3.5844	-17.9219
QRISK male age 1 sbp	NORMAL	-0.1511	0.030	-0.1511
QRISK male age 1 town	NORMAL	-2.5502	0.5100	-2.5502
QRISK male age 2 SMOKE 1	NORMAL	7.9709	1.5942	7.9709
QRISK male age 2 SMOKE 2	NORMAL	23.6859	4.7372	23.6859
QRISK male age 2 SMOKE 3	NORMAL	23.1371	4.6274	23.1371

QRISK male age 2 SMOKE 4	NORMAL	26.8674	5.3735	26.8674
QRISK male age 2 Fibrillation	NORMAL	14.4518	2.8904	14.4518
QRISK male age 2 renal	NORMAL	28.2702	5.654	28.2702
QRISK male age 2 hypertension	NORMAL	-18.8167	3.7633	-18.8167
QRISK male age 2 diabetes	NORMAL	0.9630	0.1926	0.963
QRISK male age 2 bmi	NORMAL	10.5517	2.1103	10.5517
QRISK male age 2 FXCD	NORMAL	26.6047	5.3209	26.6047
QRISK male age 2 sbp	NORMAL	0.2911	0.0582	0.2911
QRISK male age 2 town	NORMAL	3.007	0.6014	3.007
QRISK2 male 1 year survival	CONSTANT	0.997	NA	NA

The QRISK2 model was modified to allow a linear relationship between HbA1c and the risk of cardiovascular disease for individuals with IGR and type 2 Diabetes (HbA1c>42 mmol/mol). The parameter distributions for these additional inputs are reported in Table 58.

Table 58: Additional parameters for linear relationship between HbA1c and cardiovascular disease

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Female RR of MI due to HbA1c in diabetics	LOGNORMAL	0.078	0.030	1.08	[26]
Male RR of MI due to HbA1c in diabetics	LOGNORMAL	0.108	0.023	1.11	[26]
RR of stroke due to HbA1c in diabetics	LOGNORMAL	0.092	0.026	1.096	[26]
Log(RR) of cvd due to IGR	NORMAL	0.223	0.043	1.25	[28]

Congestive Heart Failure

The parameter distributions for congestive heart failure based on the Framingham Heart Study [64] are reported in Table 59.

Table 59: Input parameters for Congestive Heart Failure Risk model for men and women

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Male Heart failure baseline hazard	NORMAL	-9.2087	0.9209	-9.2087
Male Heart failure Age	NORMAL	0.0412	0.0278	0.0412

Male Heart failure LVH	NORMAL	0.9026	1.0359	0.9026
Male Heart failure Heart rate	NORMAL	0.0166	0.0174	0.0166
Male Heart failure Systolic blood pressure	NORMAL	0.00804	0.0117	0.00804
Male Heart failure CHD	NORMAL	1.6079	0.5336	1.6079
Male Heart failure Valve disease	NORMAL	0.9714	0.6557	0.9714
Male Heart failure Diabetes	NORMAL	0.2244	0.6682	0.2244
Female Heart failure baseline hazard	NORMAL	-10.7988	1.0799	-10.7988
Female Heart failure Age	NORMAL	0.0503	0.0301	0.0503
Female Heart failure LVH	NORMAL	1.3402	0.8298	1.3402
Female Heart failure Heart rate	NORMAL	0.0105	0.0193	0.0105
Female Heart failure Systolic blood pressure	NORMAL	0.00337	0.0109	0.00337
Female Heart failure CHD	NORMAL	1.5549	0.5973	1.5549
Female Heart failure Valve disease	NORMAL	1.3929	0.6707	1.3929
Female Heart failure Diabetes	NORMAL	1.3857	0.7105	1.3857
Female Heart failure BMI	NORMAL	0.0578	0.0555	0.0578
Female Heart failure Valve disease & Diabetes	NORMAL	-0.986	1.4370	-0.986

Microvascular Complications

The parameter distributions for the risk models for foot ulcer, blindness, renal failure, first amputation and second amputation are reported in Table 60. Parameters for renal failure were based on the UKPDS Outcomes Model 1 [25], whereas parameters for other microvascular complications were based on the UKPDS Outcomes Model 2 [26].

Table 60: Input parameters for microvascular complications

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Renal failure baseline hazard	NORMAL	-10.016	0.939	-10.016
Renal failure Weibull shape	NORMAL	1.865	1.4352	1.865
Renal failure systolic blood pressure	NORMAL	0.404	0.106	0.404
Renal failure blindness	NORMAL	2.082	0.551	2.082
Foot ulcer baseline hazard	NORMAL	-11.295	1.13	-11.295
Foot ulcer age at diagnosis	NORMAL	0.043	0.014	0.043
Foot ulcer female	NORMAL	-0.962	0.255	-0.962

Foot ulcer BMI	NORMAL	0.053	0.019	0.053
Foot ulcer HbA1c	NORMAL	0.16	0.056	0.16
Foot ulcer PVD	NORMAL	0.968	0.258	0.968
Amputation baseline hazard	NORMAL	-14.844	1.205	-14.844
Amputation age at diagnosis	NORMAL	0.023	0.011	0.023
Amputation female	NORMAL	-0.445	0.189	-0.445
Amputation atrial fibrillation	NORMAL	1.088	0.398	1.088
Amputation HbA1c	NORMAL	0.248	0.042	0.248
Amputation HDL	NORMAL	-0.059	0.032	-0.059
Amputation heart rate	NORMAL	0.098	0.05	0.098
Amputation MMALB	NORMAL	0.602	0.18	0.602
Amputation peripheral vascular disease	NORMAL	1.01	0.189	1.01
Amputation white blood count	NORMAL	0.04	0.017	0.04
Amputation Stroke	NORMAL	1.299	0.245	1.299
Amputation shape	NORMAL	2.067	0.193	2.067
Amputation with Ulcer lambda	NORMAL	-0.881	0139	-0.881
Amputation with Ulcer age at diagnosis	NORMAL	-0.065	0.027	-0.065
Amputation with Ulcer PVD	NORMAL	1.769	0.449	1.769
Second Amputation baseline hazard	NORMAL	-3.455	0.565	-3.455
Second Amputation HbA1c	NORMAL	0.127	0.06	0.127
Blindness baseline hazard	NORMAL	-10.6774	0.759	-10.6774
Blindness age at diagnosis	NORMAL	0.047	0.009	0.047
Blindness HbA1c	NORMAL	0.171	0.032	0.171
Blindness heart rate	NORMAL	0.08	0.039	0.08
Blindness systolic blood pressure	NORMAL	0.068	0.032	0.068
Blindness white blood cells	NORMAL	0.052	0.019	0.052
Blindness CHF	NORMAL	0.841	0.287	0.841
Blindness IHD	NORMAL	0.61	0.208	0.61

Cancer

The parameter distributions for the incidence and hazard ratios for breast cancer and colorectal cancer are reported in Table 61.

Table 61: Input parameters for breast cancer and colorectal cancer risk models

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Colorectal cancer men	NORMAL	0.0011	0.0001	0.0011	[65]
Colorectal cancer women	NORMAL	0.0005	0.0000	0.0005	[65]
Breast cancer pre-menopause	NORMAL	0.0010	0.0001	0.0010	[66]
Breast cancer post-menopause	NORMAL	0.0028	0.0002	0.0028	[66]
Colorectal cancer BMI relative risk for men	LOGNORMAL	0.1906	0.0111	1.21	[67]
Colorectal cancer BMI relative risk for women	LOGNORMAL	0.0392	0.0151	1.04	[67]
Breast cancer BMI relative risk for pre-menopause	LOGNORMAL	-0.1165	0.0251	0.89	[67]
Breast cancer BMI relative risk for post-menopause	LOGNORMAL	0.0862	0.0205	1.09	[67]

The parameter distributions for breast and colorectal cancer mortality are reported in Table 62.

Table 62: Input parameters for breast cancer and colorectal cancer mortality [(48)]

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Breast cancer 5 year survival	BETA	439.69	2354.44	0.157
Colorectal cancer 5 year survival	BETA	1457.56	1806.35	0.447

Osteoarthritis

The parameter distributions for the incidence and hazard ratios for osteoarthritis are reported below.

Table 63: Input parameters for the osteoarthritis risk model [68]

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Osteoarthritis incidence	NORMAL	0.0053	0.0000004	0.0053
Osteoarthritis RR of diabetes	LOGNORMAL	0.723	0.317	2.06
Osteoarthritis RR of BMI	LOGNORMAL	0.073	0.026	1.076

Depression

The parameter distributions for the incidence and hazard ratios for depression are reported below.

Table 64: Input parameters for the depression risk model

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Odds of depression	BETA	336	8803	0.0397	[69]
Odds ratio for diabetes	LOGNORMAL	0.4187	0.1483	1.52	[69]
Odds ratio for stroke	LOGNORMAL	1.8406	0.5826	6.3	[70]

Utilities

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 65: Utility input parameters

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
Renal/ulcer baseline utility	NORMAL	0.689	0.014	0.689	[71]
Renal dialysis	NORMAL	-0.078	0.026	-0.078	[71]
Foot ulcer	NORMAL	-0.099	0.013	-0.099	[71]
Amputation/heart failure baseline utility	NORMAL	0.807	0.005	0.807	[26]
Heart failure	NORMAL	-0.101	0.032	-0.101	[26]
Amputation	NORMAL	-0.172	0.045	-0.172	[26]
Stable angina multiplicative factor decrement	NORMAL	0.801	0.038	0.801	[29]
Unstable angina multiplicative factor decrement	NORMAL	0.77	0.038	0.77	[29]
MI multiplicative factor decrement	NORMAL	0.76	0.018	0.76	[29]
Stroke multiplicative factor decrement	NORMAL	0.629	0.04	0.629	[29]
Cancer baseline utility	NORMAL	0.8	0.0026	0.8	[72]
Cancer decrement	NORMAL	-0.06	0.008	-0.06	[72]
Osteoarthritis utility	NORMAL	0.69	0.069	0.69	[73]
Depression baseline utility	NORMAL	0.48	0.048	0.48	[74]
Depression remitters	NORMAL	0.31	0.031	0.31	[74]

Depression responders	NORMAL	0.20	0.020	0.20	[74]
Depression non-responders	NORMAL	0.070	0.007	0.070	[74]
Depression drop-outs	NORMAL	0.050	0.005	0.050	[74]
Age utility decrement	NORMAL	-0.004	0.0001	-0.004	[29]

Unit Health Care Costs

The parameter distributions used to estimate health state utilities in the model are reported below.

Table 66: Cost input parameters

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate	Source
DIABETES COSTS					
Insulin (annual cost)	GAMMA	3.367	408.6	£1375.72	[75]
Metformin (annual cost)	CONSTANT	NA	NA	£28.24	[32]
Sitagliptin (annual cost)	CONSTANT	NA	NA	£433.77	[32]
Nurse appointment (Advanced)	GAMMA	100	0.26	£25.52	[32]
Health care assistant appointment	GAMMA	100	0.03	£3.40	[32]
Eye screening	GAMMA	15.3664	1.58219	£24.31	[76]
HbA1c test	GAMMA	100	0.03	£3.00	[54]
Lipids test	GAMMA	100	0.01	£1.00	[54]
LfT test	GAMMA	100	0.03	£3.13	[54]
B12 test	GAMMA	100	0.03	£3.13	[54]
Nicotine replacement therapy	GAMMA	100	1.03	£103.00	[32]
CVD COSTS					
Unstable Angina hospital admission	GAMMA	100	12.75591	£1275.59	[61]
Revascularisation in hospital	GAMMA	100	60.36846	£6036.85	[61]
MI Hospital admission	GAMMA	100	15.54896	£1554.90	[61]
First Outpatient appointment	GAMMA	100	1.653571	£165.36	[61]
Subsequent outpatient appointments	GAMMA	100	1.100574	£110.06	[61]
Fatal CHD	GAMMA	100	7.125001	£712.50	[77]
Fatal Stroke	GAMMA	100	44.42562	£4442.56	[78]
First year stroke	GAMMA	100	126.77	£12676.60	[79]
Subsequent year stroke	GAMMA	100	17.399	£1739.91	[79]
TIA	GAMMA	100	27.226	£2722.65	[79]

Glytrin Spray	CONSTANT	NA	NA	£12.61	[61]
Isosorbide mononitrate	CONSTANT	NA	NA	£13.54	[61]
Verapamil	CONSTANT	NA	NA	£50.57	[61]
Atenolol	CONSTANT	NA	NA	£36.42	[61]
Aspirin	CONSTANT	NA	NA	£8.01	[61]
Ramipril	CONSTANT	NA	NA	£90.45	[61]
ARB	CONSTANT	NA	NA	£253.28	[61]
Clopidogrel	CONSTANT	NA	NA	£554.41	[61]
CHF year 1 inpatient	GAMMA	17.08787	197.607	£3376.68	[80]
CHF year 1 non inpatient	GAMMA	50.13476	20.66365	£1035.97	[80]
CHF subsequent years inpatient	GAMMA	23.46525	66.42644	£1558.71	[80]
CHF subsequent years non inpatient	GAMMA	109.7982	9.377373	£1029.62	[80]
MICROVASCULAR COSTS					
Blindness year 1 inpatient	GAMMA	7.982428	179.6254	£1433.85	[80]
Blindness year 1 non inpatient	GAMMA	14.79887	127.9935	£1894.16	[80]
Blindness subsequent years inpatient	GAMMA	41.39524	11.58007	£479.36	[80]
Blindness subsequent years non inpatient	GAMMA	79.72506	9.795462	£780.94	[80]
Amputation year 1 inpatient	GAMMA	35.73274	282.6952	£10101.48	[80]
Amputation year 1 outpatient	GAMMA	16.81661	169.8352	£2856.05	[80]
Amputation subsequent years inpatient	GAMMA	23.02322	82.36361	£1896.28	[80]
Amputation subsequent years outpatient	GAMMA	57.06248	29.87502	£1704.74	[80]
Renal Haemodialysis	GAMMA	100	420.49	£42049.00	[81]
Renal Automated Peritoneal dialysis	GAMMA	100	272.1714	£27217.14	[81]
Renal Ambulatory peritoneal dialysis	GAMMA	100	197.4225	£19742.25	[81]
Renal transplant	GAMMA	100	236.5973	£23659.73	[82]
Immunosuppressants	GAMMA	100	69.58745	£6958.75	[82]
Foot ulcer not infected	GAMMA	100	1.677526	£167.75	[83]
Foot ulcer with cellulitis	GAMMA	100	4.431003	£443.10	[83]
Foot ulcer with osteomyelitis	GAMMA	100	8.215817	£821.58	[83]
OTHER DISEASE COSTS					
Breast Cancer	GAMMA	100	138.1811	£13818.11	[84]
Colorectal cancer Dukes A	GAMMA	100	100.9135	£10091.35	[85]
Colorectal cancer Dukes B	GAMMA	100	173.1532	£17315.32	[85]
Colorectal cancer Dukes C	GAMMA	100	265.5026	£26550.26	[85]

Colorectal cancer Dukes D	GAMMA	100	166.2553	£16625.53	[85]
Osteoarthritis	GAMMA	100	9.616886	£961.69	[86]
Depression – Practice nurse surgery	GAMMA	100	0.090154	£9.02	[87]
Depression – Practice nurse home	GAMMA	100	0.270463	27.05	[87]
Depression – Practice nurse telephone	GAMMA	100	0.090154	9.02	[87]
Depression – Health visitor	GAMMA	100	0.387834	38.78	[87]
Depression – District nurse	GAMMA	100	0.377628	37.76	[87]
Depression – Other nurse	GAMMA	100	0.090154	9.02	[87]
Depression – HCA phlebotomist	GAMMA	100	0.034021	3.40	[87]
Depression – Other primary care	GAMMA	100	0.255154	25.52	[87]
Depression – Out of Hours	GAMMA	100	0.268661	26.87	[87]
Depression – NHS Direct	GAMMA	100	0.25295	25.30	[87]
Depression – Walk-in Centre	GAMMA	100	0.388316	38.83	[87]
Depression – Prescribed medicines	GAMMA	100	0.096144	9.61	[87]
Depression – Secondary Care	GAMMA	100	0.81	81.00	[87]
DIAGNOSIS AND OTHER COSTS					
GP appointment	GAMMA	100	0.47	£46.95	[32]
Diabetes diagnosis	GAMMA	100	0.12	£14.81	[54]
Hypertension diagnosis	GAMMA	100	0.57	£56.51	[88]
Anti-hypertensives	GAMMA	100	1.96	£195.94	[89]
Simvastatin	CONSTANT	NA	NA	£26.59	[32]

Interventions

The parameter distributions used for each intervention are shown below. Please see economic modelling methods section for details of assumptions and sources.

Table 67: Intervention parameters

Parameter Description	Distribution	Parameter 1	Parameter 2	Central estimate
Intensive Lifestyle Basecase regain period (years)	CONSTANT	NA	NA	8
Intensive Lifestyle Basecase weight loss 12 months	NORMAL	-2.41	0.52403	-2.41
Intensive Lifestyle Basecase HbA1c loss 12 months	NORMAL	-0.07	0.02558	-0.07
Intensive Lifestyle Basecase SBP loss 12 months	NORMAL	-1.33	1.03379	-1.33
Intensive Lifestyle Basecase Chol loss 12 months	NORMAL	-0.04	0.03194	-0.04

Intensive Lifestyle Basecase weight loss 36 months	NORMAL	-1.71	0.74807	-1.71
Intensive Lifestyle Basecase HbA1c loss 36 months	NORMAL	-0.09	0.05960	-0.09
Intensive Lifestyle Basecase SBP loss 36 months	NORMAL	-1.72	2.10699	-1.72
Intensive Lifestyle Basecase Chol loss 36 months	NORMAL	-0.09	0.06819	-0.09
Intensive Lifestyle Pessimistic regain period (years)	CONSTANT	NA	NA	6
Intensive Lifestyle Pessimistic weight loss 12 months	NORMAL	-2.15	0.50765	-2.15
Intensive Lifestyle Pessimistic HbA1c loss 12 months	NORMAL	-0.04	0.01786	-0.04
Intensive Lifestyle Pessimistic SBP loss 12 months	NORMAL	-0.06	0.74745	-0.06
Intensive Lifestyle Pessimistic Chol loss 12 months	NORMAL	-0.06	0.03827	-0.06
Intensive Lifestyle Pessimistic weight loss 36 months	NORMAL	-1.3	0.81378	-1.3
Intensive Lifestyle Pessimistic HbA1c loss 36 months	NORMAL	-0.04	0.04592	-0.04
Intensive Lifestyle Pessimistic SBP loss 36 months	NORMAL	0	1.23469	0
Intensive Lifestyle Pessimistic Chol loss 36 months	NORMAL	-0.02	0.08418	-0.02
Intensive Lifestyle Optimistic regain period (years)	CONSTANT	NA	NA	10
Intensive Lifestyle Optimistic weight loss 12 months	NORMAL	-2.97	0.90816	-2.97
Intensive Lifestyle Optimistic HbA1c loss 12 months	NORMAL	-0.10	0.03827	-0.10
Intensive Lifestyle Optimistic SBP loss 12 months	NORMAL	-1.33	1.03379	-1.33
Intensive Lifestyle Optimistic Chol loss 12 months	NORMAL	-0.04	0.03194	-0.04
Intensive Lifestyle Optimistic weight loss 36 months	NORMAL	-2.29	0.91582	-2.29
Intensive Lifestyle Optimistic HbA1c loss 36 months	NORMAL	-0.13	0.03827	-0.13
Intensive Lifestyle Optimistic SBP loss 36 months	NORMAL	-2.26	1.18367	-2.26
Intensive Lifestyle Optimistic Chol loss 36 months	NORMAL	-0.08	0.04337	-0.08
Mean Intensive Lifestyle study BMI	CONSTANT	NA	NA	32
BMI Modifier (per unit > mean)	CONSTANT	NA	NA	0.049585
Intensive Lifestyle Intervention Cost	CONSTANT	NA	NA	223
Intensive Lifestyle Intervention BMI Modifier	CONSTANT	NA	NA	-0.05
Intensive Lifestyle Intervention Age Modifier	CONSTANT	NA	NA	0.015

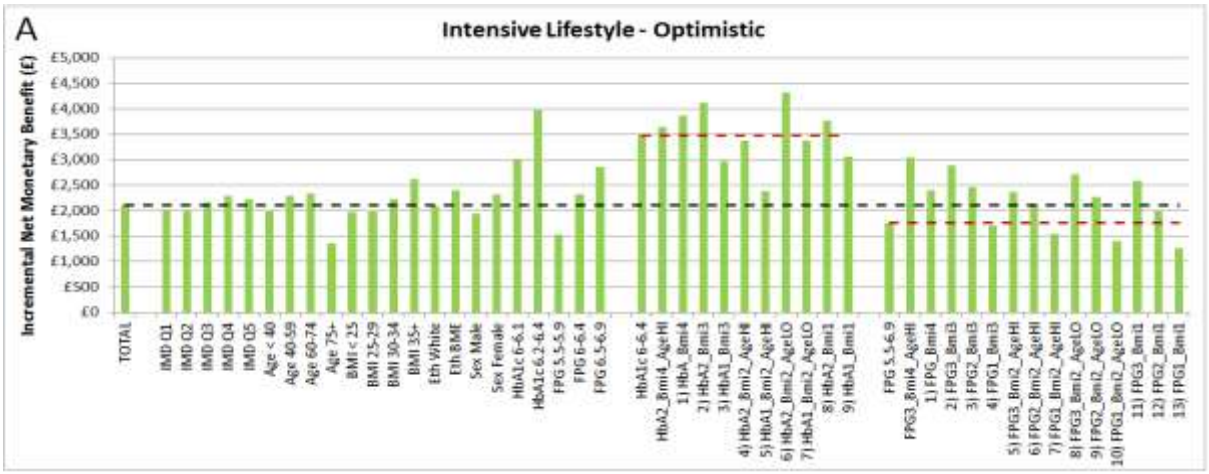
Intensive Lifestyle Intervention FPG Modifier	CONSTANT	NA	NA	0.4
Metformin Basecase regain period (years)	CONSTANT	NA	NA	7
Metformin Basecase weight loss 12 months	NORMAL	-1.84	0.0581	-1.84
Metformin Basecase HbA1c loss 12 months	NORMAL	-0.06	0.0095	-0.06
Metformin Basecase weight loss 36 months	NORMAL	-1.27	0.2597	-1.27
Metformin Basecase HbA1c loss 36 months	NORMAL	-0.06	0.0095	-0.06
Metformin Optimistic regain period (years)	CONSTANT	NA	NA	9
Metformin Optimistic weight loss 12 months	NORMAL	-2.27	0.20807	-2.27
Metformin Optimistic HbA1c loss 12 months	NORMAL	-0.09	0.01419	-0.09
Metformin Optimistic weight loss 36 months	NORMAL	-1.7	0.21363	-1.7
Metformin Optimistic HbA1c loss 36 months	NORMAL	-0.09	0.01419	-0.09
Mean Metformin study BMI	CONSTANT	NA	NA	34
Metformin Costs Annual	GAMMA	100	0.601	60.01006
Metformin Costs Additional Year 1	GAMMA	100	0.78348	78.34834
Metformin BMI Modifier	CONSTANT	NA	NA	0.12
Metformin Age Modifier	CONSTANT	NA	NA	-0.038
Metformin FPG Modifier	CONSTANT	NA	NA	1.5

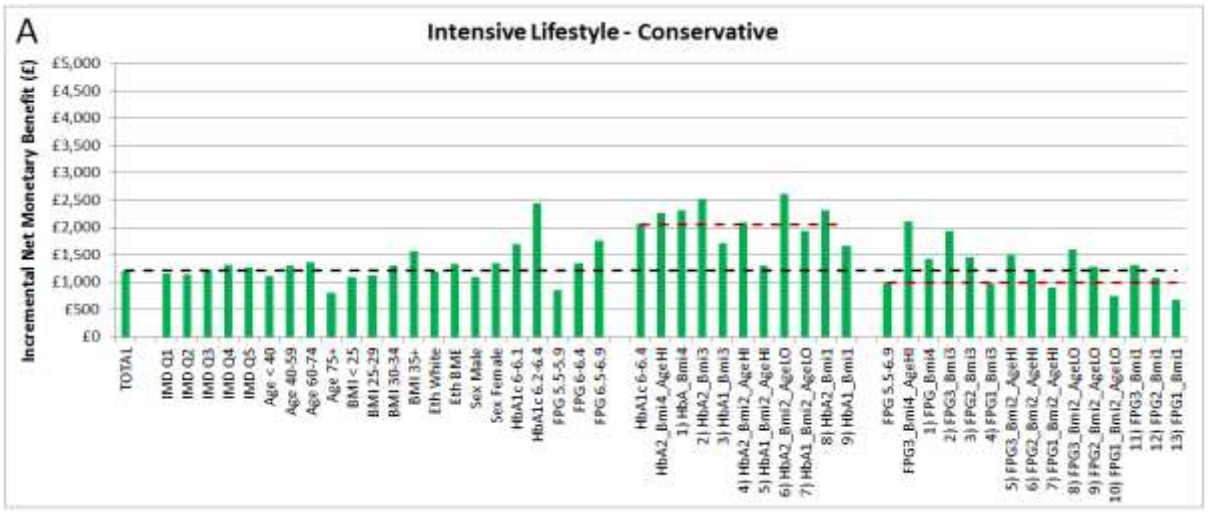
Appendix 2: Results Charts using a Discount Rate of 1.5%

1A: Investigating the Impact of Study Effectiveness on Lifestyle Intervention

Figure 94: Mean incremental NBM per person of intensive lifestyle compared to control in different population subgroups under optimistic, conservative or pessimistic estimates of intervention effectiveness, assuming that HbA1c effect is neither stratified nor persistent. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI

23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.





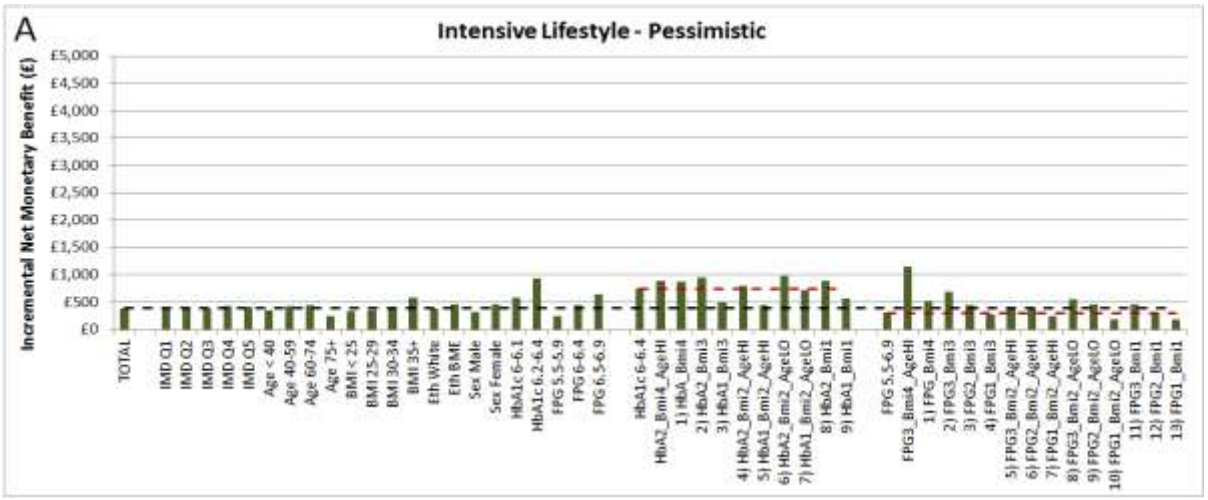


Figure 95: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is neither stratified nor persistent. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 =

BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

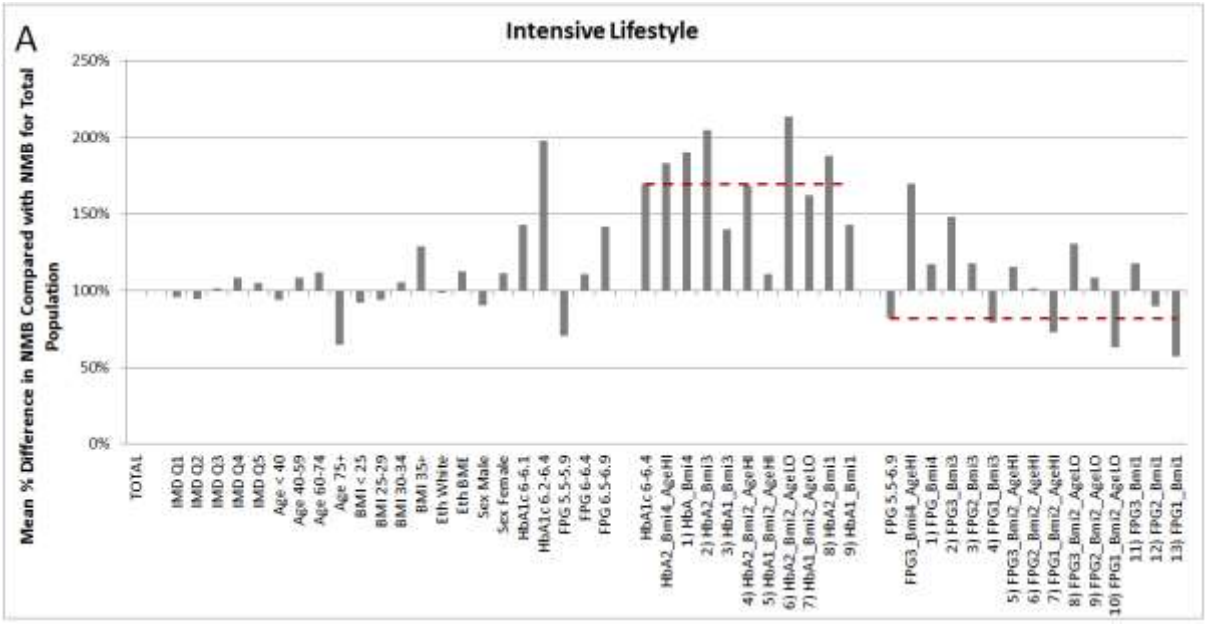
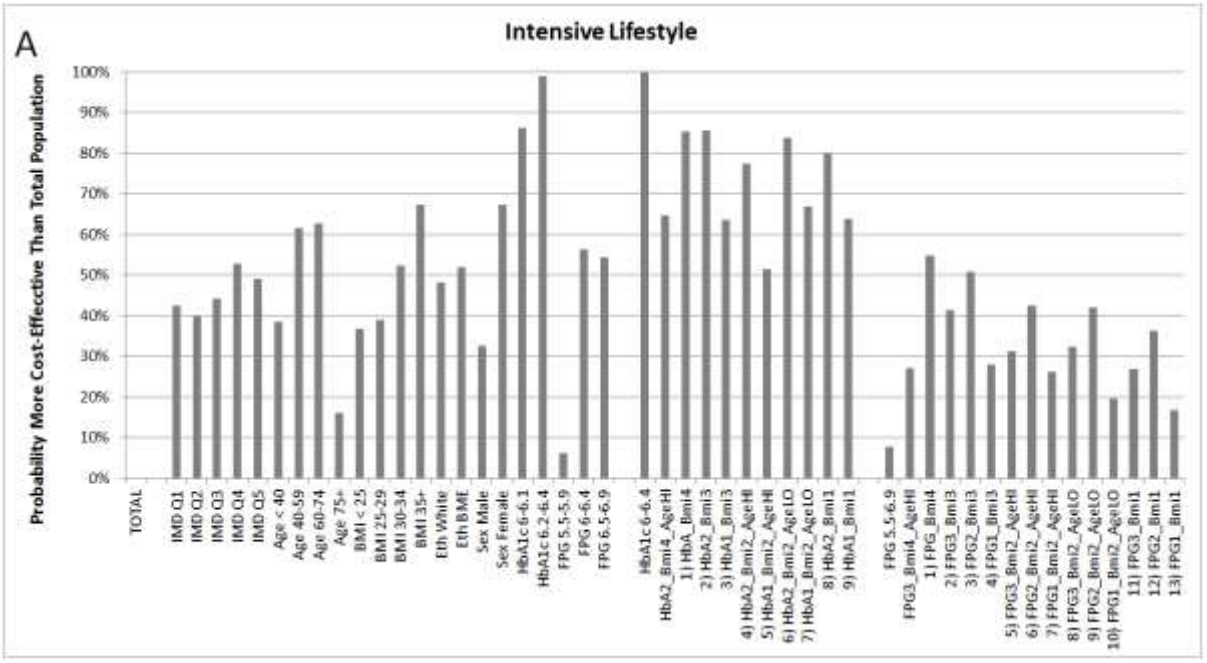
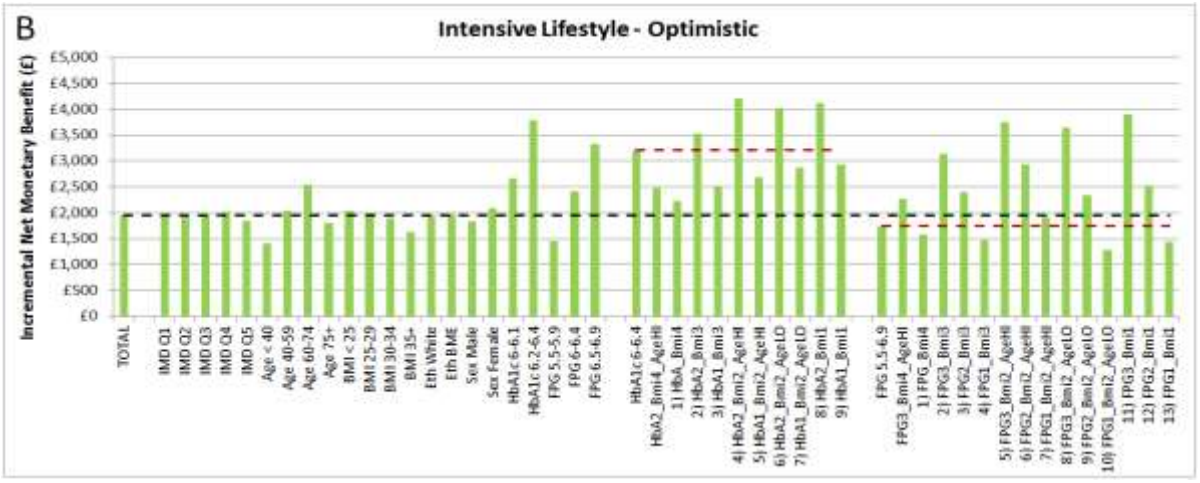


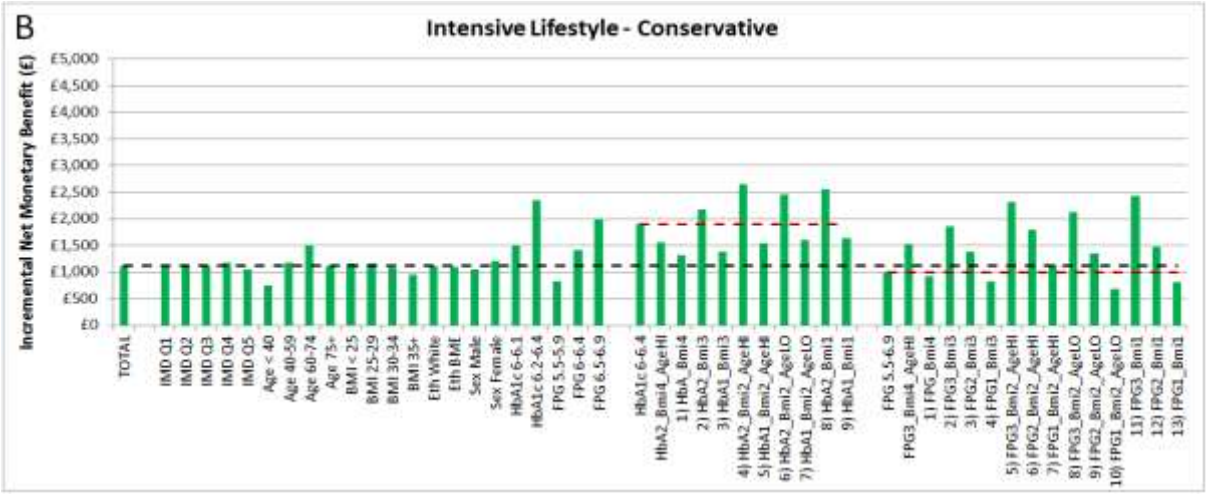
Figure 96: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is neither stratified nor persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



1B: Investigating the Impact of HbA1c Stratification (by age, BMI and FPG) on Intensive Lifestyle Intervention

Figure 97: Mean incremental NBM per person of intensive lifestyle compared to control in different population subgroups under optimistic, conservative or pessimistic estimates of intervention effectiveness, assuming that HbA1c effect is stratified but not persistent. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.





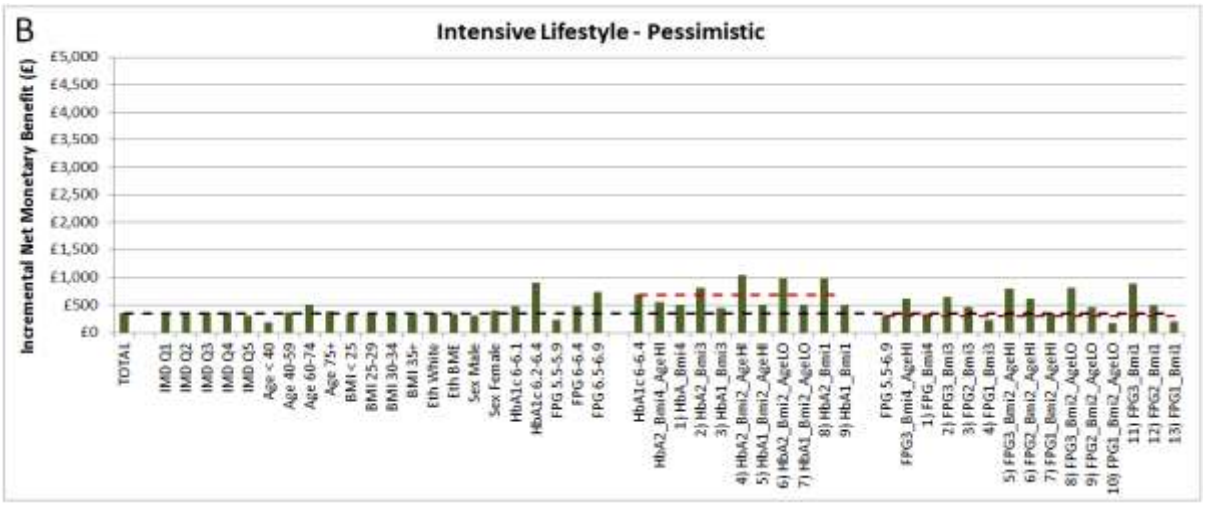


Figure 98: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is stratified but not persistent. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

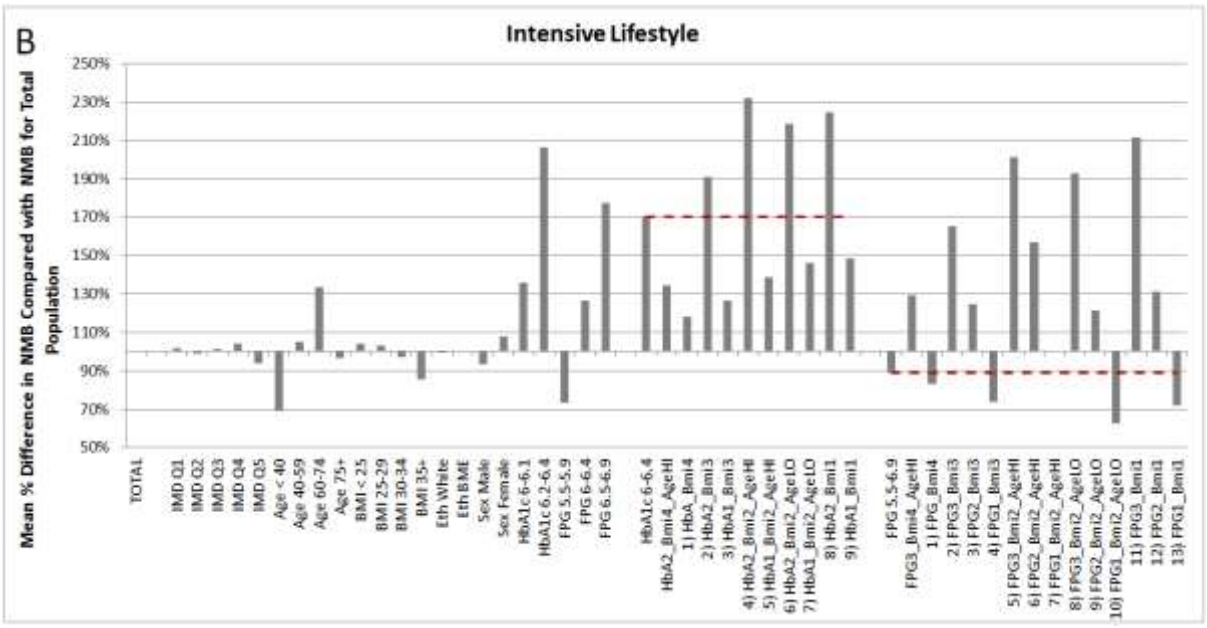
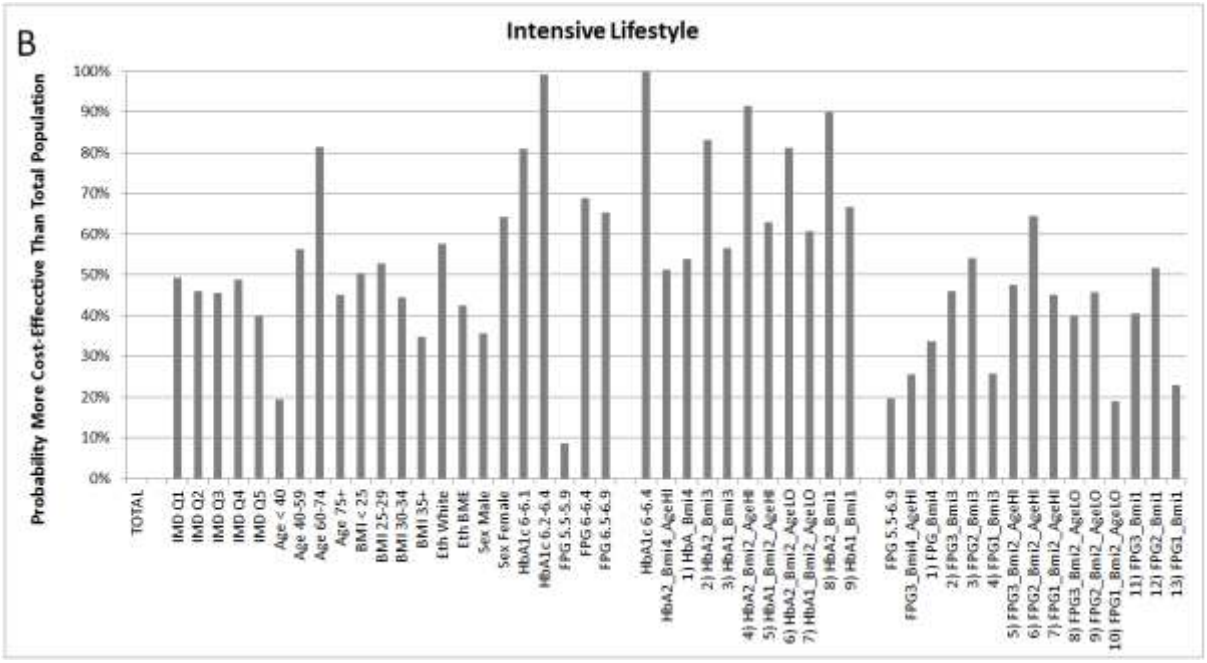


Figure 99: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is stratified but not persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME);

BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



1C: Investigating the Impact of Assumptions regarding Persistence of HbA1c Effect on Lifestyle Intervention

Figure 100: Mean incremental NBM per person of intensive lifestyle compared to control in different population subgroups under optimistic, conservative or pessimistic estimates of intervention effectiveness, assuming that HbA1c effect is persistent but not stratified. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI

23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

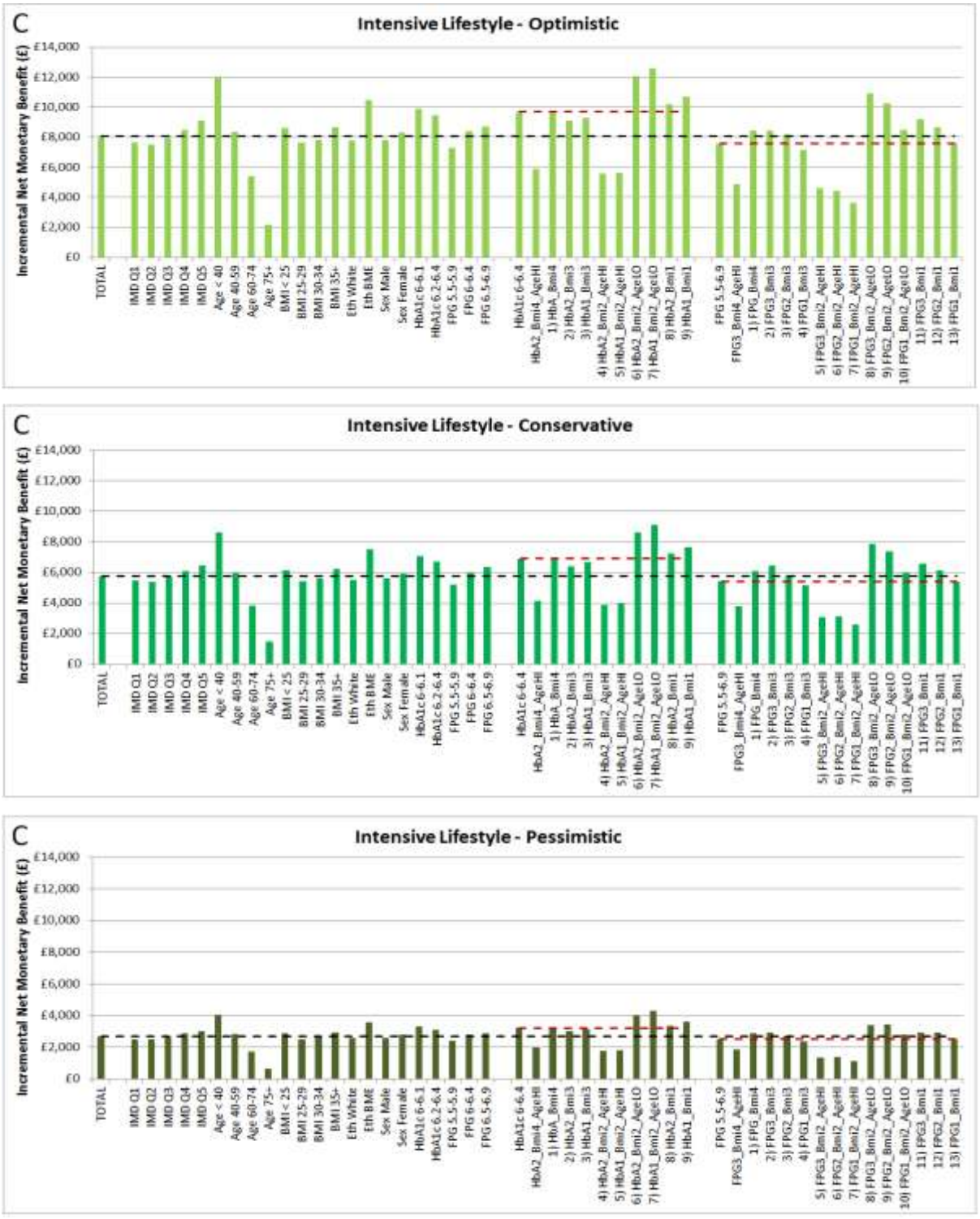
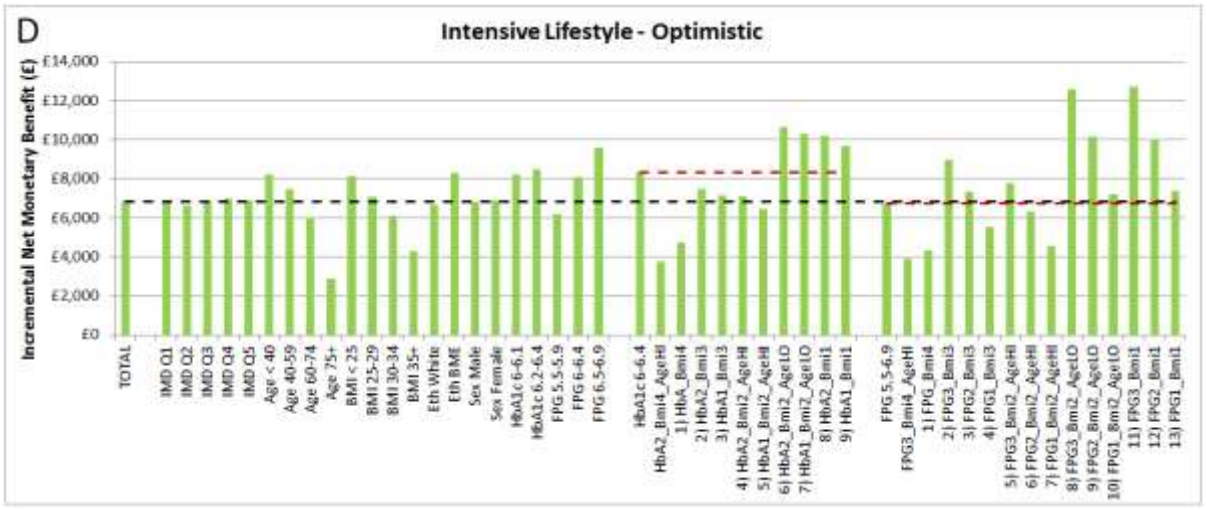
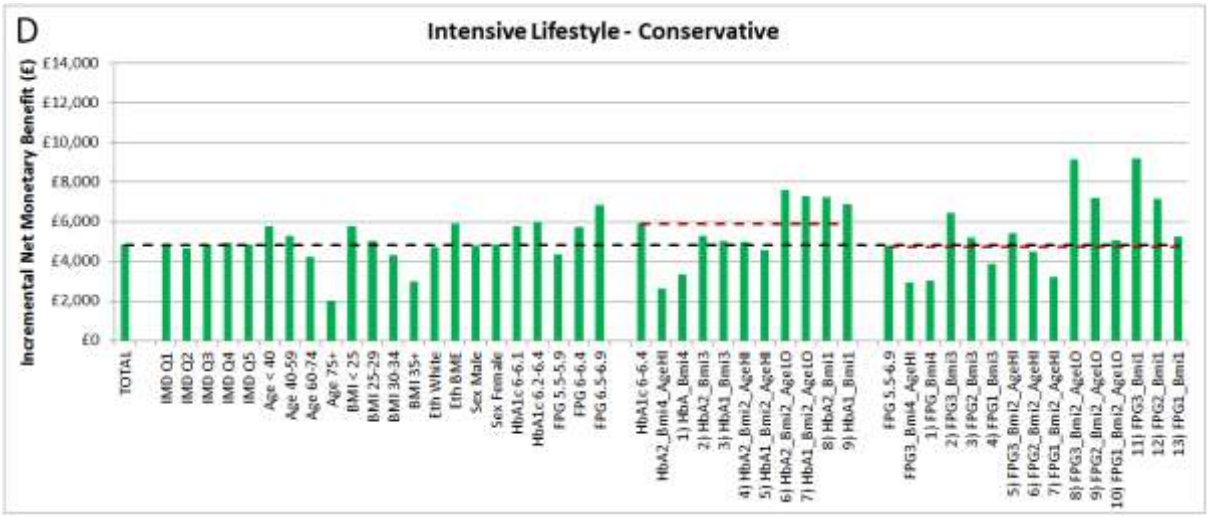


Figure 101: Mean incremental NBM per person of intensive lifestyle compared to control in different population subgroups under optimistic, conservative or pessimistic estimates of intervention effectiveness, assuming that HbA1c effect is persistent and stratified. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 =

HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.





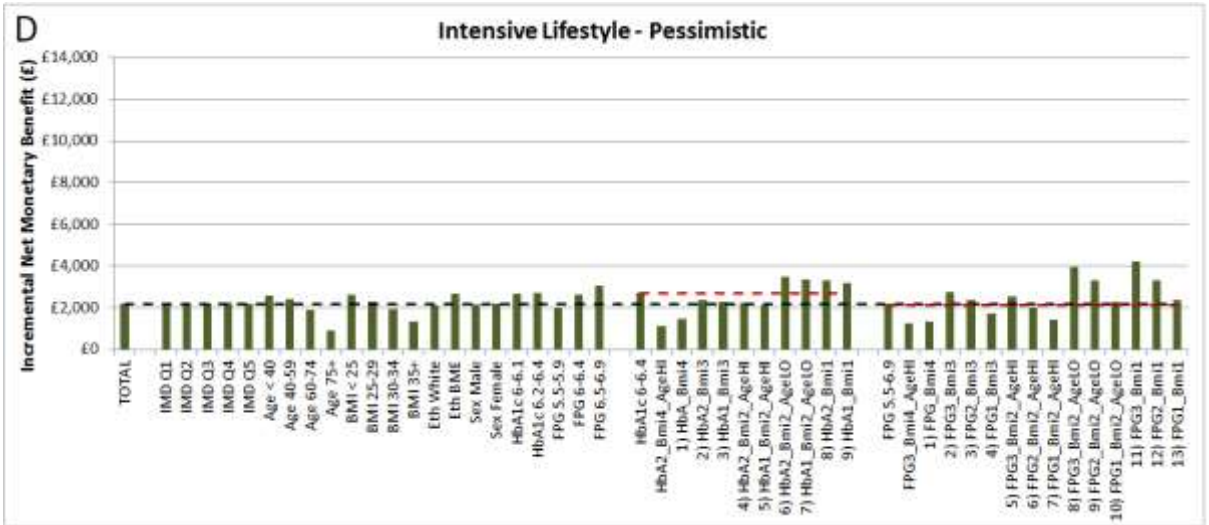


Figure 102: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is persistent but not stratified. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

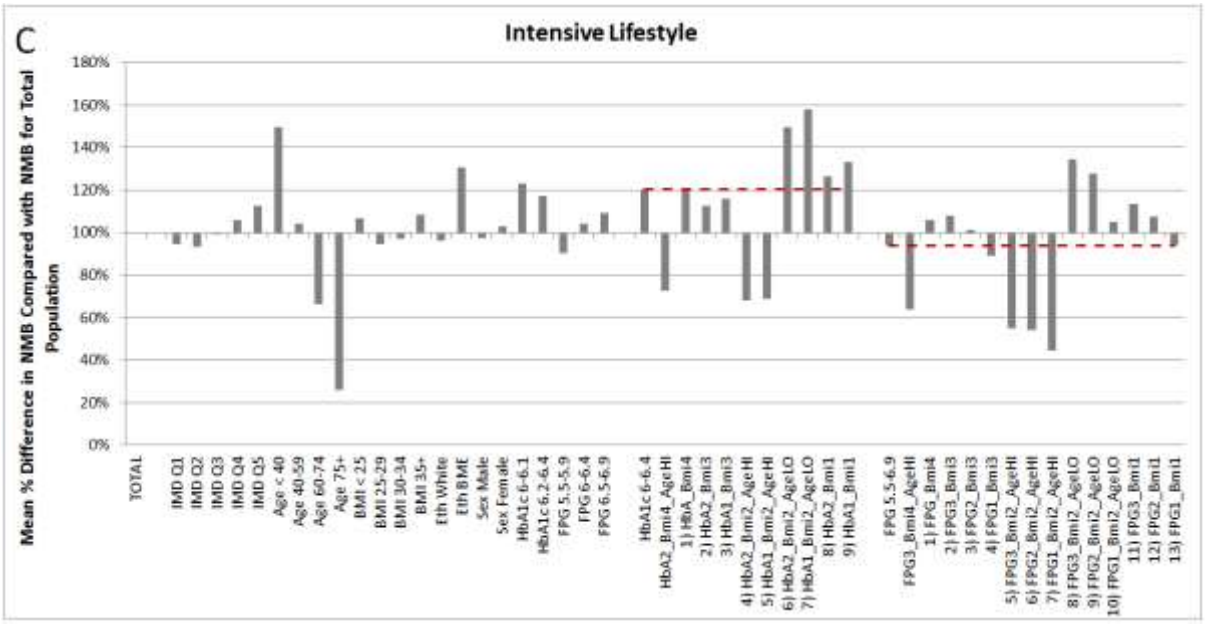


Figure 103: The mean proportional difference in incremental NBM of each subgroup compared to the total population assuming that HbA1c effect is persistent and stratified. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI

25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

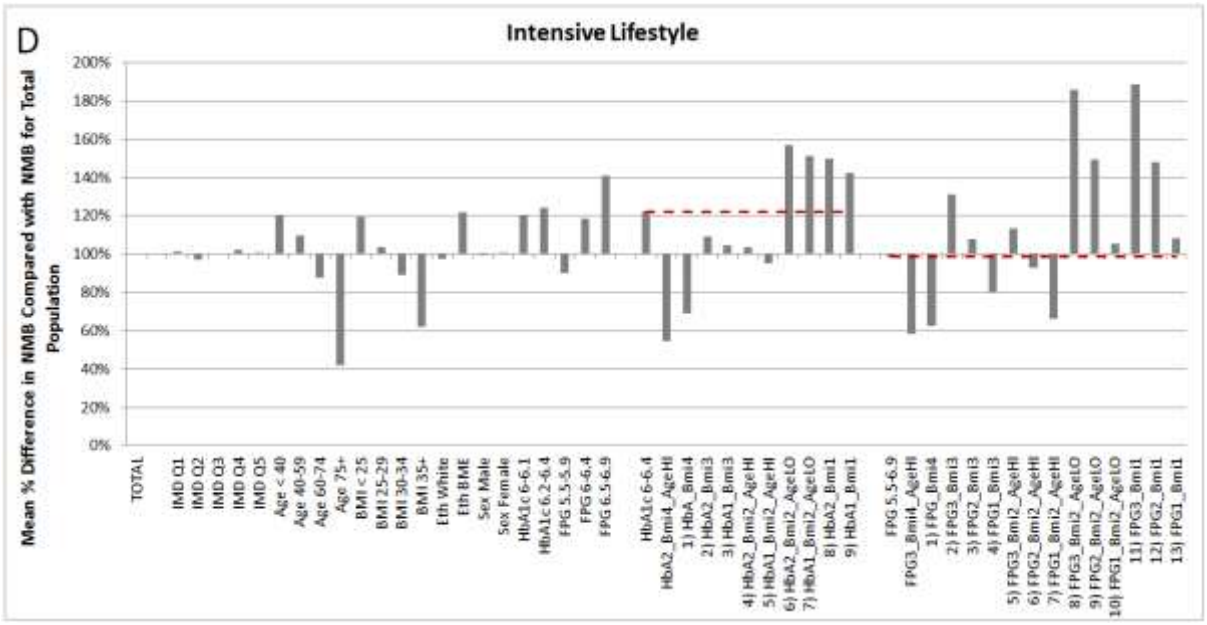


Figure 104: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is persistent but not stratified. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

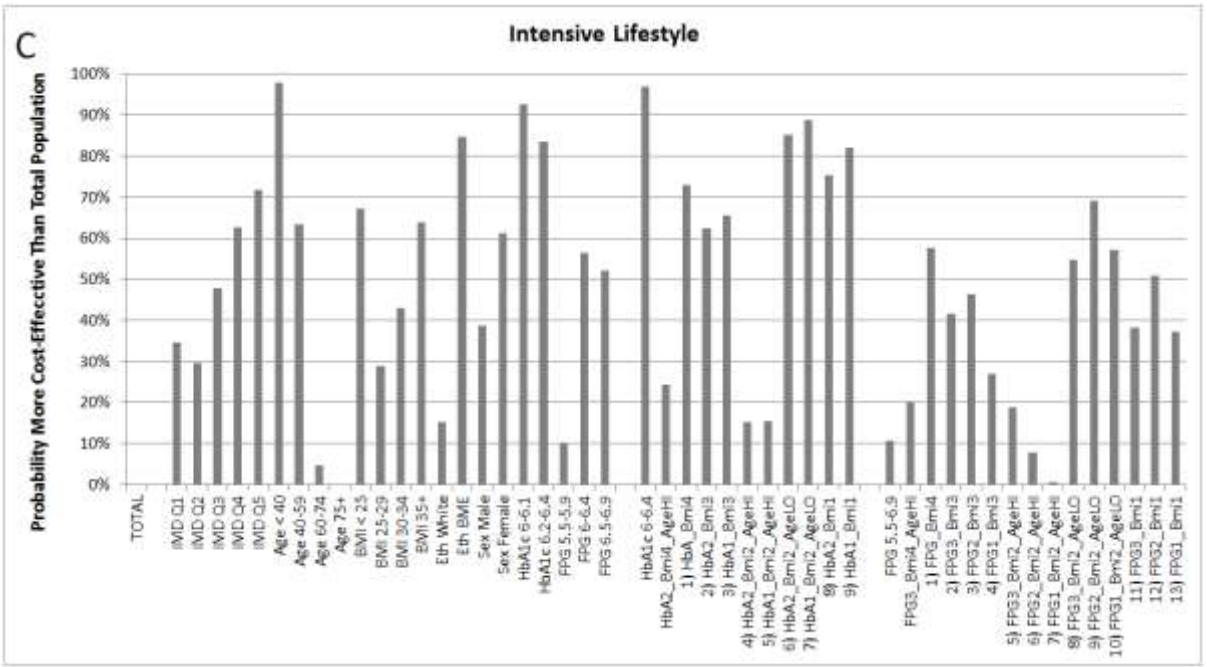
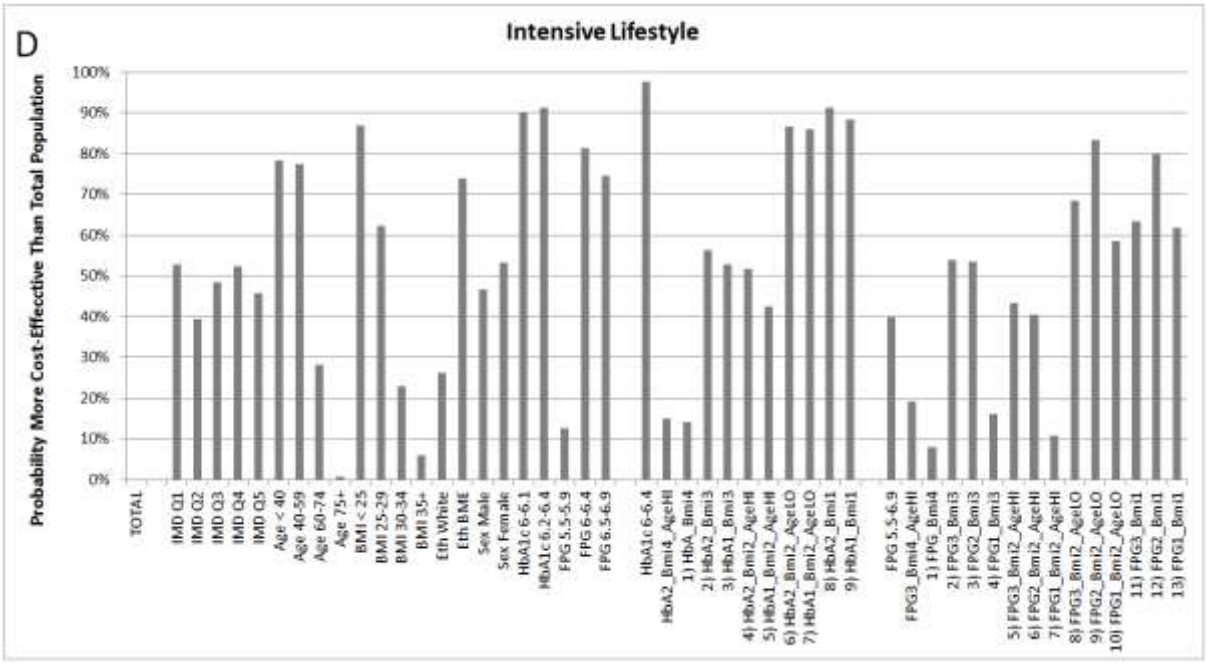
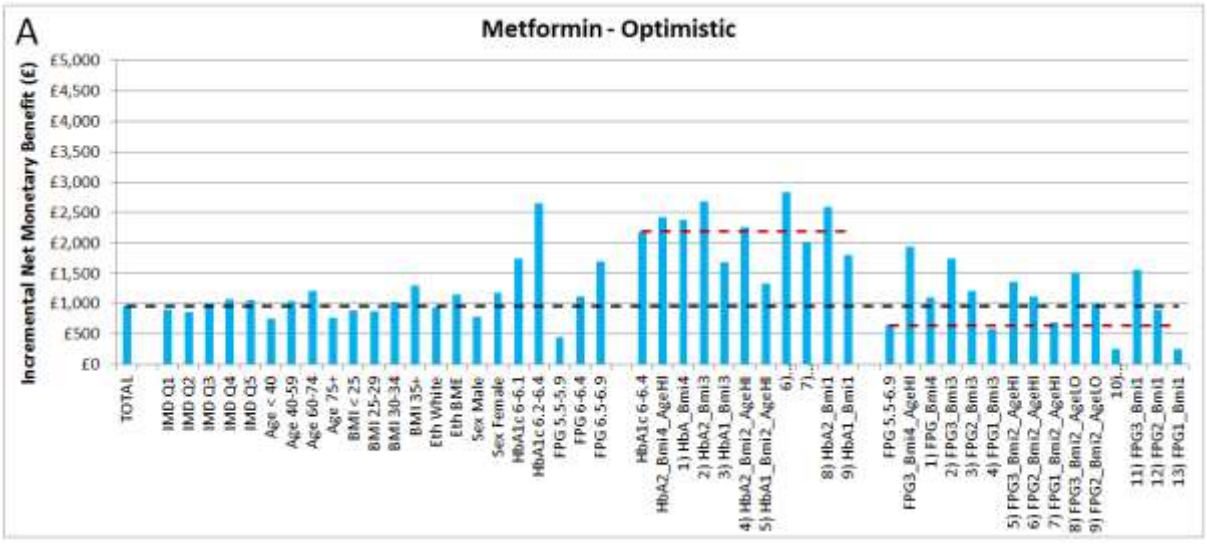


Figure 105: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is persistent and stratified. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



2A: Investigating the Impact of Study Effectiveness on Metformin

Figure 106: Mean incremental NMB per person of metformin compared to control in different population subgroups under optimistic or conservative estimates of intervention effectiveness, assuming that HbA1c is neither stratified nor persistent. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



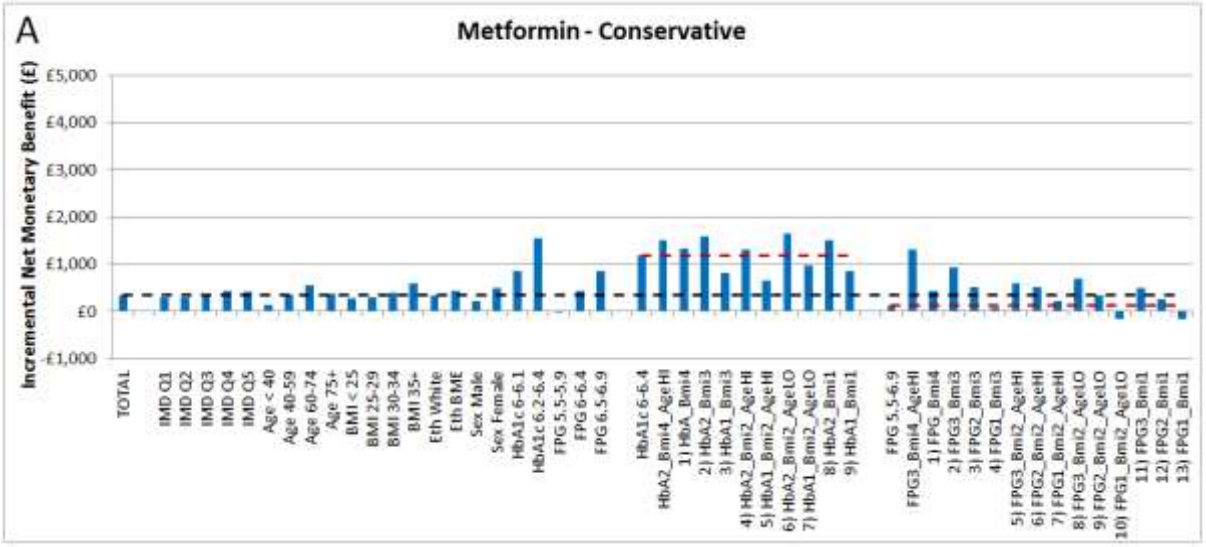


Figure 107: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is neither stratified nor persistent. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG

6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

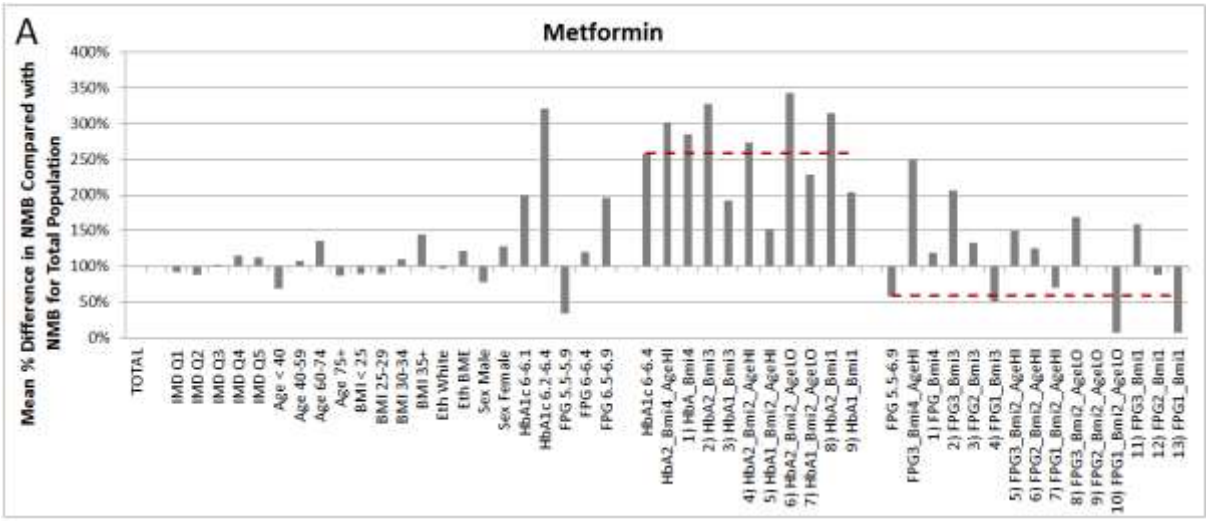
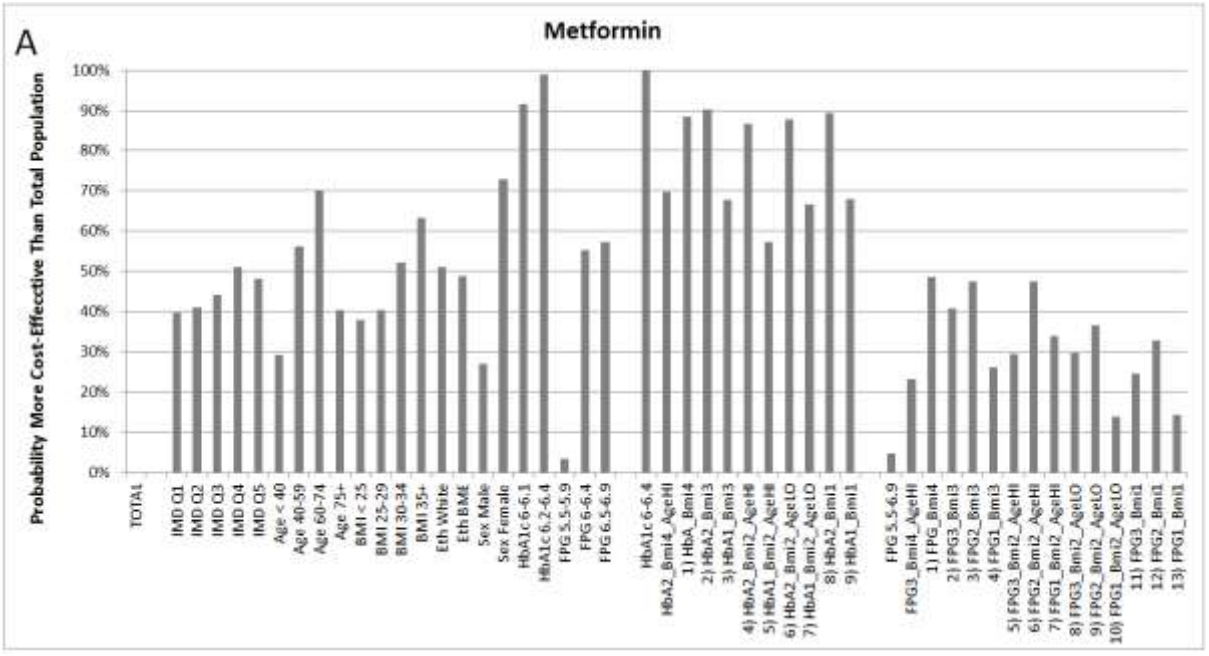
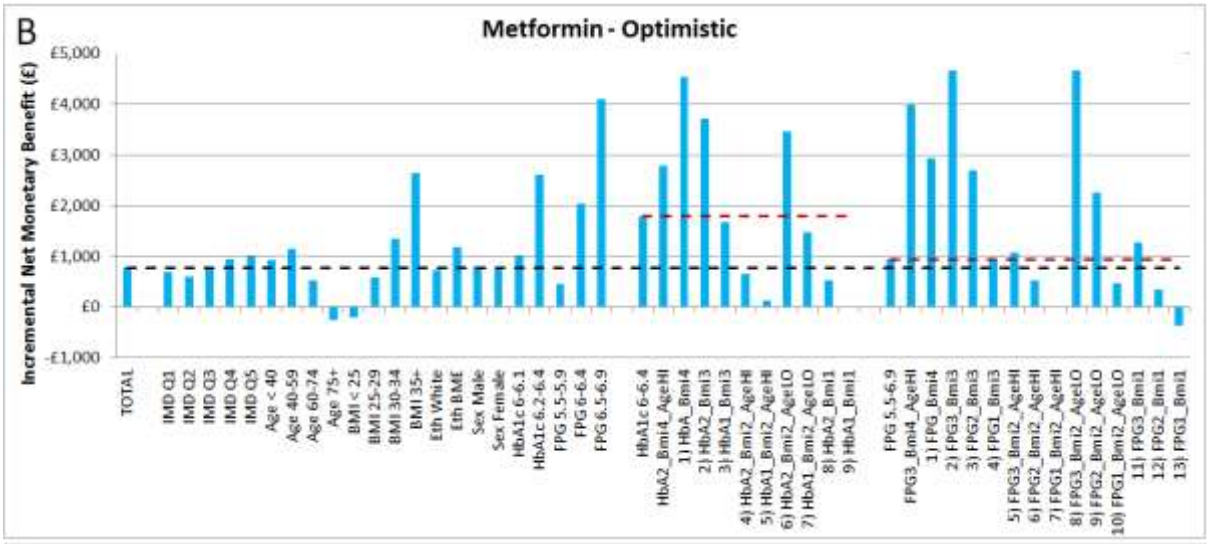


Figure 108: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is neither stratified nor persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



2B: Investigating the Impact of HbA1c Stratification (by age, BMI and FPG) on Metformin

Figure 109: Mean incremental NBM per person of metformin compared to control in different population subgroups under optimistic or conservative estimates of intervention effectiveness, assuming that HbA1c effect is stratified but not persistent. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



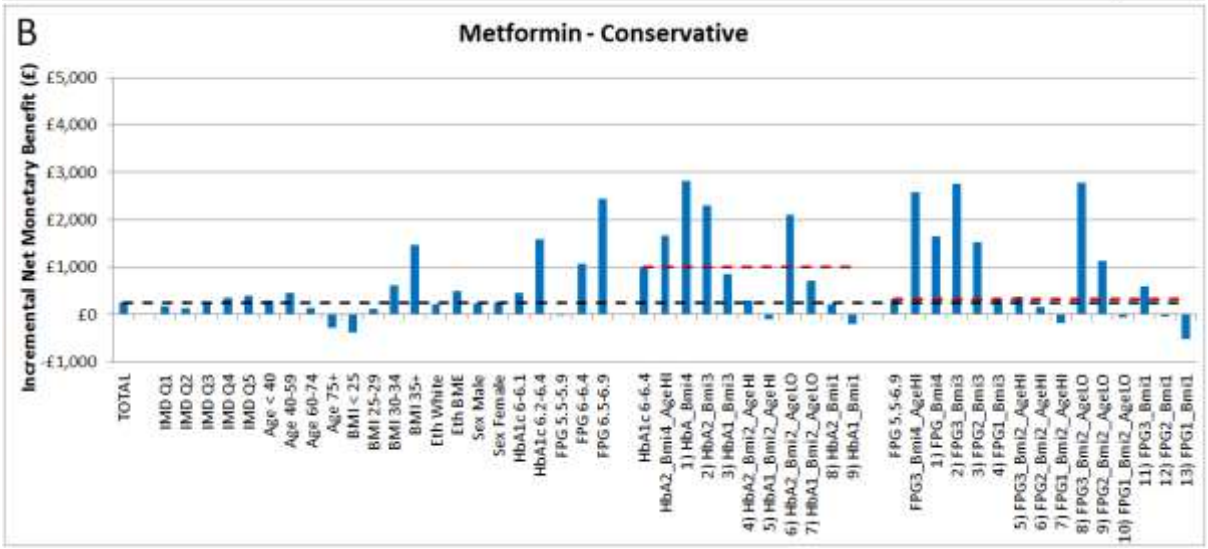


Figure 110: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is stratified but not persistent. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

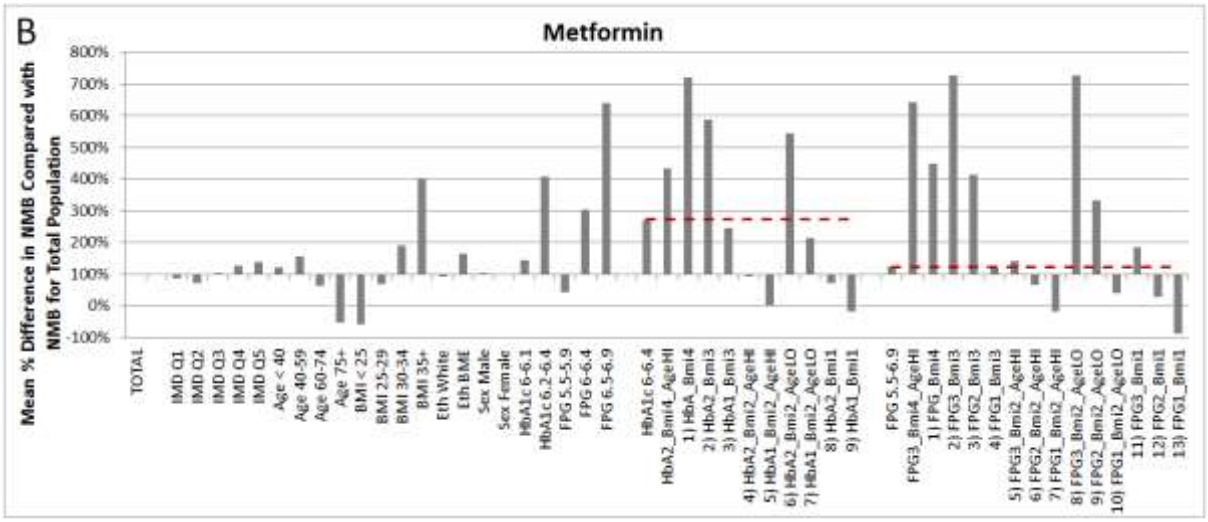
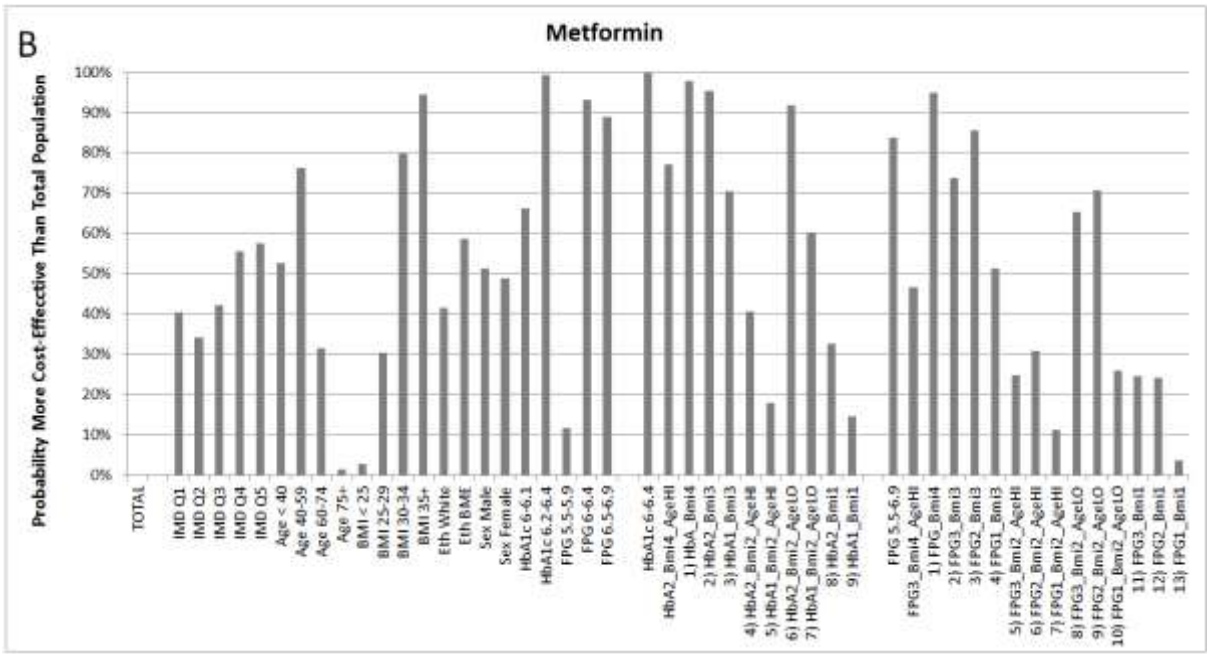


Figure 111: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is stratified but not persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



2C: Investigating the Impact of Assumptions regarding Persistence of HbA1c Effect on Metformin

Figure 112: Mean incremental NBM per person of metformin compared to control in different population subgroups under optimistic or conservative estimates of intervention effectiveness, assuming that HbA1c effect is persistent but not stratified. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

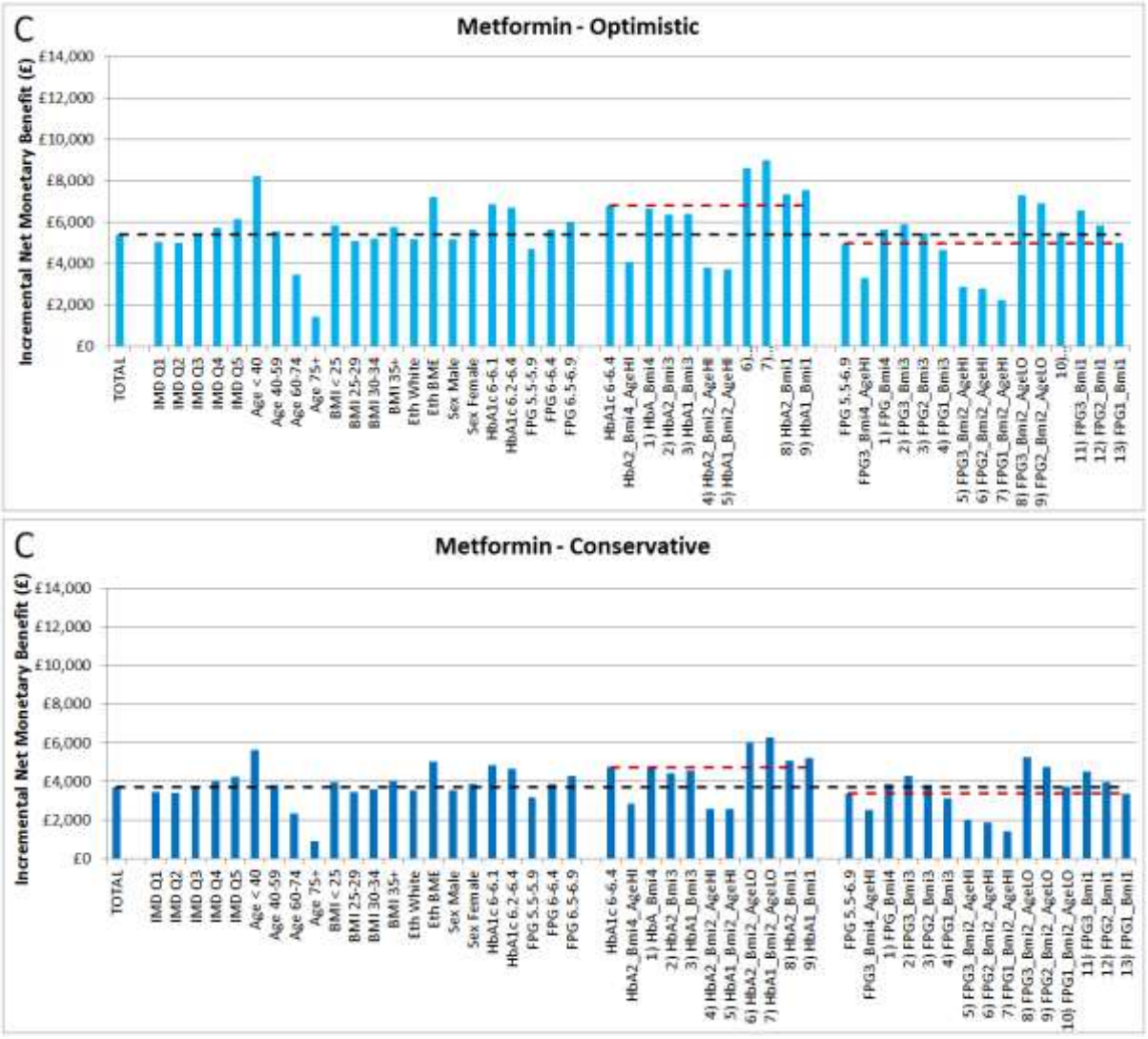


Figure 113: Mean incremental NBM per person of metformin compared to control in different population subgroups under optimistic or conservative estimates of intervention effectiveness, assuming that HbA1c effect is persistent and stratified. The black dotted line represents the total population mean net benefit, whilst the red dotted lines represent the mean net benefit in the HbA1c-defined or FPG-defined populations. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

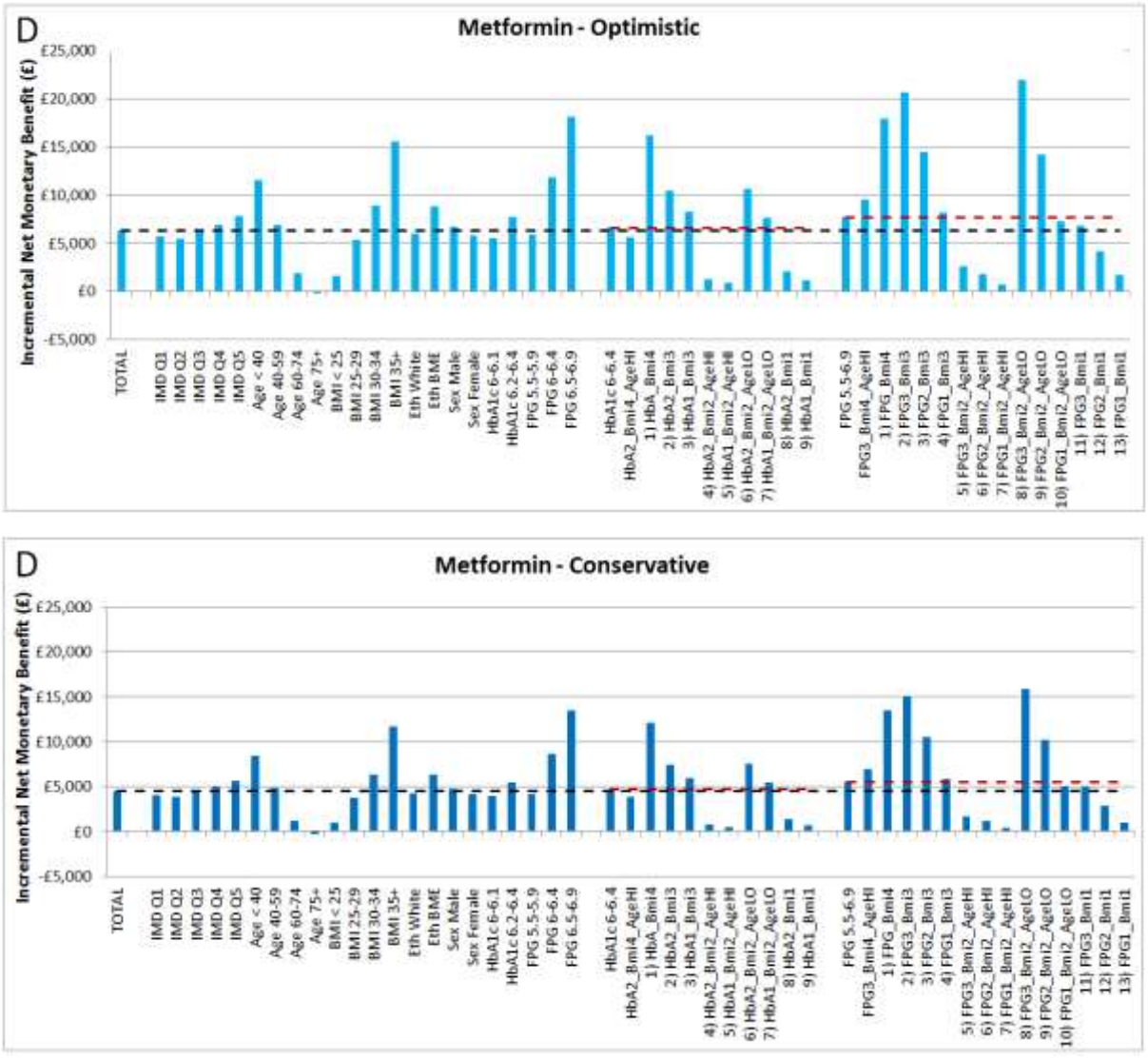


Figure 114: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is persistent but not stratified. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 =

BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

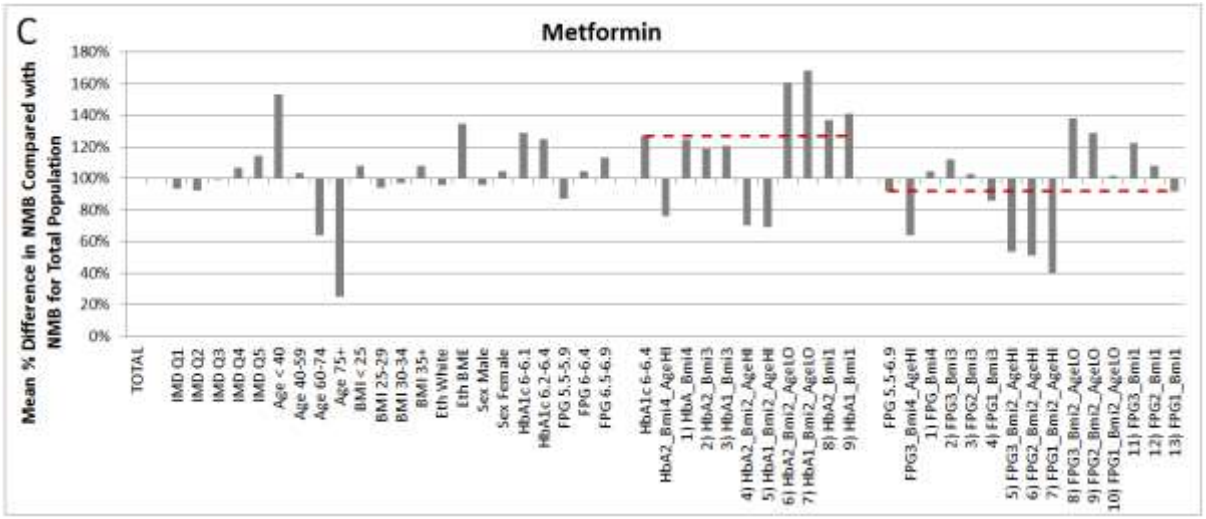


Figure 115: The mean proportional difference in incremental NMB of each subgroup compared to the total population, assuming that HbA1c effect is persistent and stratified. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

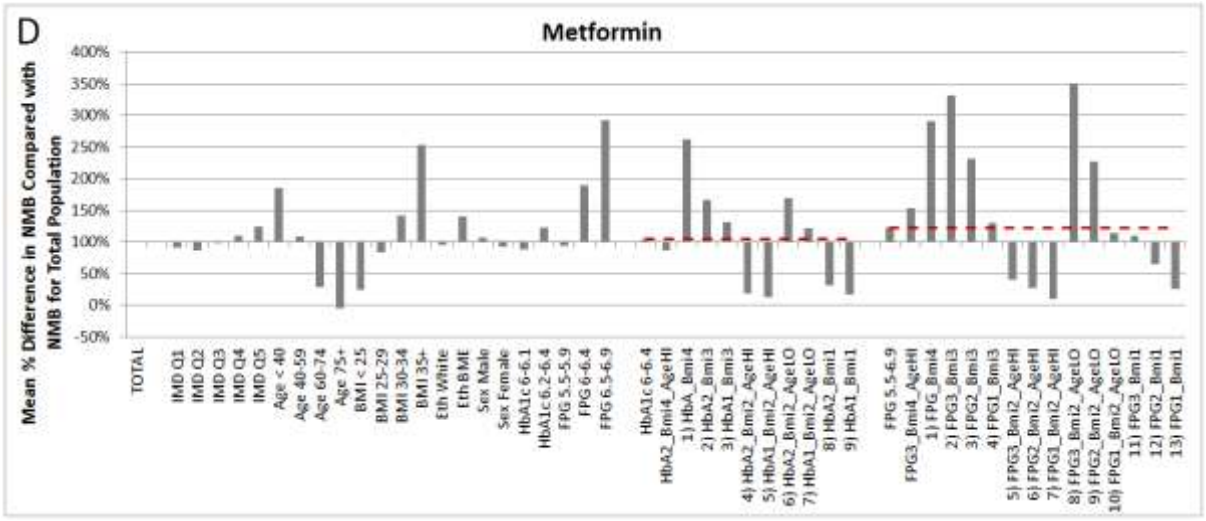


Figure 116: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is persistent but not stratified. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME);

BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

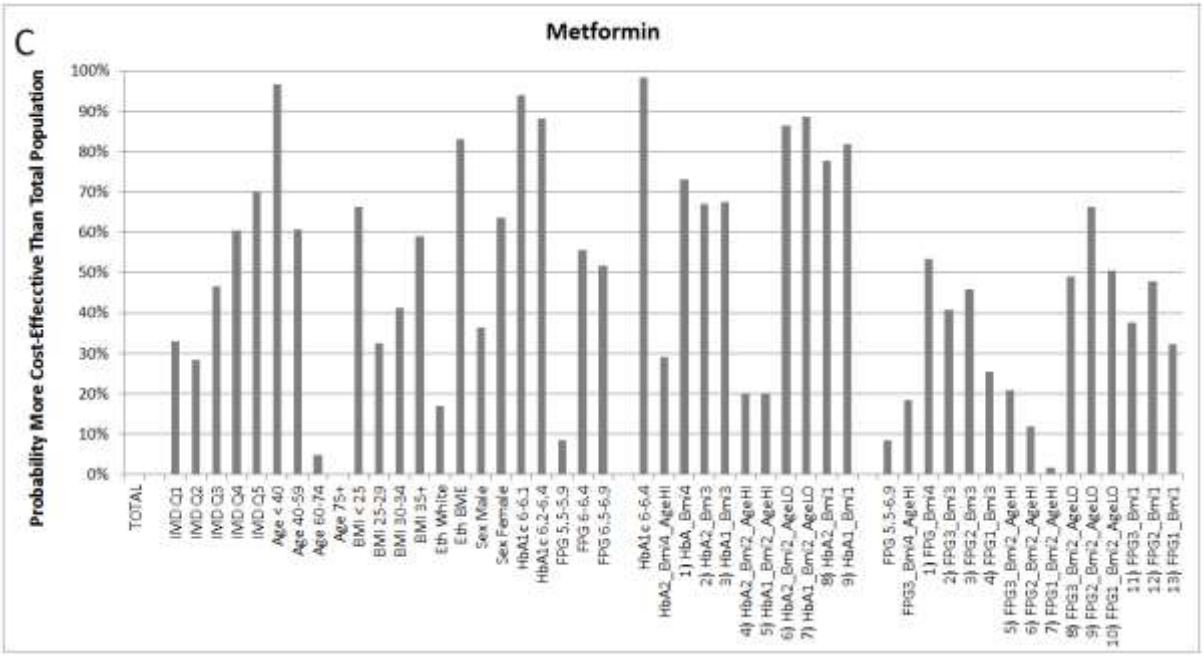
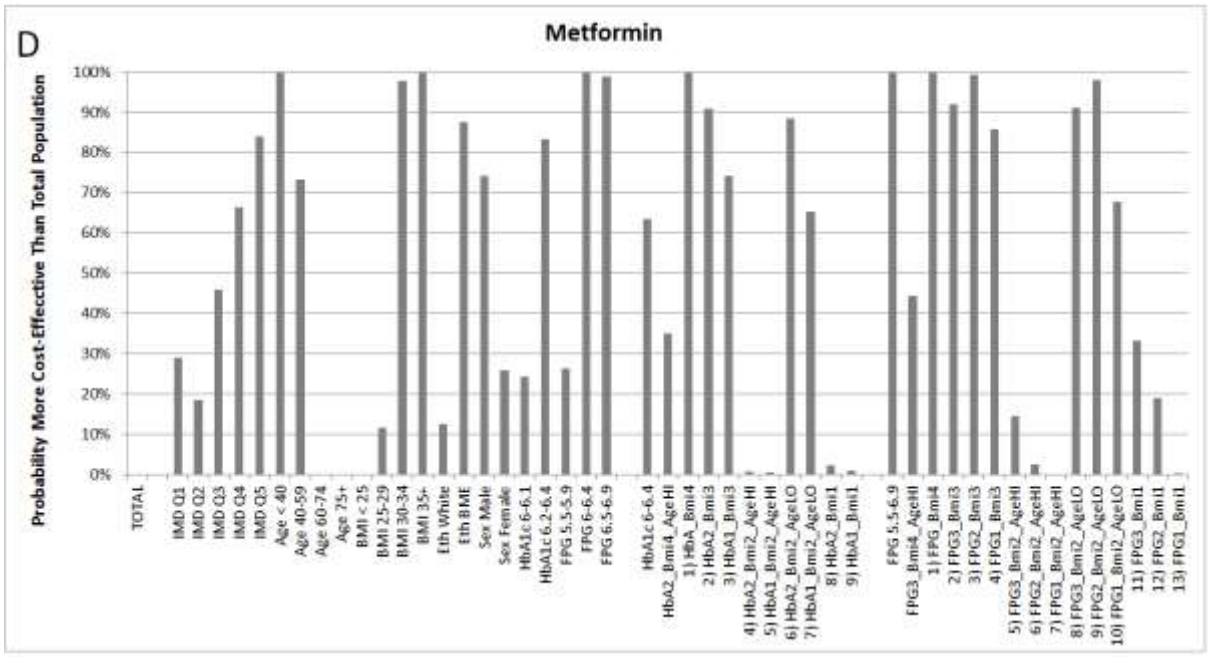


Figure 117: The probability that it is more cost-effective to give each subgroup the intervention than the total population, assuming that HbA1c effect is stratified and persistent. Note that the probability estimates are affected by both parameter uncertainty and subgroup size, with uncertainty being higher (probability closer to 50%) in small subgroups. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.



Appendix 3: Full Cost-effectiveness Results for each Scenario

Full Results: Discount Rate of 3.5%

Table 68: Optimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB	ICER (£/QALY)
TOTAL	**-£533**	**0.049**	**£1,520**	**-£10,816**
Single Subgroups				
IMD 1 (least deprived)	-£483	0.050	£1,474	-£9,744
IMD 2	-£469	0.050	£1,467	-£9,405
IMD 3	-£524	0.049	£1,500	-£10,749
IMD 4	-£602	0.051	£1,615	-£11,875
IMD 5 (most deprived)	-£644	0.047	£1,581	-£13,759
Age < 40	-£589	0.034	£1,271	-£17,247
Age 40-59	-£661	0.048	£1,626	-£13,698
Age 60-74	-£489	0.068	£1,844	-£7,221
Age >= 75	-£74	0.055	£1,165	-£1,360
BMI < 25 (White) OR BMI < 23 (BME)	-£474	0.044	£1,356	-£10,740
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£468	0.049	£1,445	-£9,585
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£580	0.052	£1,623	-£11,115
BMI >= 35 (White OR BME)	-£816	0.058	£1,972	-£14,108
Ethnicity White	-£514	0.050	£1,511	-£10,305
Ethnicity BME	-£694	0.045	£1,589	-£15,505
Sex Male	-£441	0.048	£1,407	-£9,126
Sex Female	-£646	0.051	£1,657	-£12,781
HbA1c 6-6.1	-£810	0.068	£2,170	-£11,901
HbA1c 6.2-6.4	-£1,241	0.087	£2,987	-£14,216
FPG 5.5-5.9	-£334	0.038	£1,094	-£8,785

FPG 6-6.4	-£592	0.054	£1,681	-£10,883
FPG 6.5-6.9	-£818	0.066	£2,132	-£12,459
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,019**	**0.077**	**£2,566**	**-£13,168**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,134*	*0.094*	*£3,018*	*-£12,044*
1) HbA1c 6-6.4, BMI >=35	-£1,356	0.081	£2,982	-£16,674
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,260	0.088	£3,029	-£14,255
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£849	0.069	£2,223	-£12,357
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£700	0.104	£2,780	-£6,730
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£337	0.076	£1,866	-£4,411
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,561	0.079	£3,143	-£19,735
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,036	0.064	£2,318	-£16,157
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,148	0.079	£2,727	-£14,543
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£762	0.066	£2,073	-£11,621
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£409**	**0.043**	**£1,263**	**-£9,589**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£894*	*0.079*	*£2,472*	*-£11,336*
1) FPG 5.5-6.9, BMI >=35	-£719	0.054	£1,807	-£13,233
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£866	0.062	£2,105	-£13,979
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£632	0.058	£1,784	-£10,962
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£400	0.042	£1,242	-£9,488
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£495	0.079	£2,080	-£6,250
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£332	0.066	£1,656	-£5,023

7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£181	0.052	£1,226	-£3,462
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£742	0.056	£1,853	-£13,341
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£641	0.045	£1,546	-£14,147
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£333	0.030	£941	-£10,924
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£661	0.063	£1,921	-£10,504
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£440	0.046	£1,359	-£9,593
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£249	0.031	£868	-£8,039

Table 69: Conservative Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£244**	**0.031**	**£863**	**-£7,866**
Single Subgroups				
IMD 1 (least deprived)	-£212	0.031	£830	-£6,860
IMD 2	-£205	0.031	£830	-£6,566
IMD 3	-£244	0.031	£858	-£7,940
IMD 4	-£287	0.032	£927	-£8,974
IMD 5 (most deprived)	-£306	0.030	£896	-£10,349
Age < 40	-£269	0.021	£689	-£12,837
Age 40-59	-£320	0.030	£920	-£10,682
Age 60-74	-£220	0.043	£1,078	-£5,129
Age >= 75	£21	0.036	£691	£581
BMI < 25 (White) OR BMI < 23 (BME)	-£198	0.028	£749	-£7,207
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£201	0.031	£814	-£6,566

BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£277	0.032	£925	-£8,537
BMI >= 35 (White OR BME)	-£436	0.037	£1,185	-£11,656
Ethnicity White	-£231	0.031	£860	-£7,350
Ethnicity BME	-£346	0.027	£885	-£12,843
Sex Male	-£180	0.030	£785	-£5,944
Sex Female	-£321	0.032	£957	-£10,099
HbA1c 6-6.1	-£399	0.041	£1,218	-£9,757
HbA1c 6.2-6.4	-£709	0.057	£1,846	-£12,483
FPG 5.5-5.9	-£119	0.024	£596	-£5,009
FPG 6-6.4	-£283	0.035	£973	-£8,188
FPG 6.5-6.9	-£431	0.042	£1,278	-£10,168
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£549**	**0.049**	**£1,522**	**-£11,299**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£660*	*0.063*	*£1,914*	*-£10,522*
1) HbA1c 6-6.4, BMI >=35	-£783	0.053	£1,841	-£14,821
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£722	0.056	£1,848	-£12,829
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£437	0.041	£1,253	-£10,728
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£360	0.068	£1,714	-£5,322
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£115	0.046	£1,043	-£2,482
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£910	0.052	£1,944	-£17,602
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£526	0.038	£1,294	-£13,688
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£643	0.052	£1,680	-£12,396
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£356	0.039	£1,136	-£9,142
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£167**	**0.027**	**£705**	**-£6,224**

FPG 6.5-6.9, BMI >=35, Age >= 60	*-£426*	*0.055*	*£1,526*	*-£7,752*
1) FPG 5.5-6.9, BMI >=35	-£376	0.035	£1,084	-£10,608
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£476	0.040	£1,266	-£12,045
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£308	0.036	£1,028	-£8,546
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£160	0.026	£679	-£6,177
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£199	0.053	£1,254	-£3,775
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£126	0.042	£958	-£3,029
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£27	0.033	£689	-£824
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£398	0.035	£1,102	-£11,292
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£299	0.028	£866	-£10,569
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£115	0.019	£493	-£6,115
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£302	0.042	£1,137	-£7,219
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£176	0.029	£763	-£5,982
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£66	0.020	£456	-£3,357

Table 70: Pessimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**£24**	**0.013**	**£244**	**£1,802**
Single Subgroups				
IMD 1 (least deprived)	£38	0.014	£233	£2,778
IMD 2	£38	0.014	£241	£2,711

IMD 3	£26	0.013	£235	£2,025
IMD 4	£10	0.014	£261	£772
IMD 5 (most deprived)	-£4	0.012	£253	-£359
Age < 40	£18	0.009	£165	£1,933
Age 40-59	-£7	0.013	£269	-£528
Age 60-74	£30	0.018	£329	£1,694
Age >= 75	£128	0.016	£201	£7,774
BMI < 25 (White) OR BMI < 23 (BME)	£45	0.011	£183	£3,972
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£44	0.013	£223	£3,267
BMI 30–34 (White) OR BMI 27.5-34 (BME)	£16	0.014	£268	£1,095
BMI >= 35 (White OR BME)	-£79	0.017	£423	-£4,571
Ethnicity White	£29	0.014	£245	£2,115
Ethnicity BME	-£15	0.011	£241	-£1,315
Sex Male	£57	0.013	£204	£4,401
Sex Female	-£16	0.014	£294	-£1,167
HbA1c 6-6.1	-£26	0.017	£363	-£1,555
HbA1c 6.2-6.4	-£186	0.025	£690	-£7,402
FPG 5.5-5.9	£76	0.010	£131	£7,300
FPG 6-6.4	£4	0.015	£305	£236
FPG 6.5-6.9	-£59	0.019	£430	-£3,204
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£104**	**0.021**	**£521**	**-£4,970**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£198*	*0.028*	*£766*	*-£6,967*
1) HbA1c 6-6.4, BMI >=35	-£229	0.023	£695	-£9,813
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£196	0.025	£689	-£7,962
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£18	0.017	£360	-£1,076
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£20	0.030	£626	-£665

5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£82	0.019	£306	£4,239
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£270	0.023	£732	-£11,671
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£82	0.016	£409	-£5,022
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£158	0.022	£607	-£7,043
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£10	0.015	£312	-£638
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£55**	**0.012**	**£181**	**£4,638**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£80*	*0.027*	*£628*	*-£2,931*
1) FPG 5.5-6.9, BMI >=35	-£53	0.016	£380	-£3,243
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£67	0.017	£411	-£3,870
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£5	0.016	£310	£333
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£58	0.011	£170	£5,085
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£63	0.022	£374	£2,905
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£70	0.018	£284	£3,954
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£119	0.014	£165	£8,401
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£91	0.017	£426	-£5,425
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£0	0.014	£272	-£10
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£78	0.008	£88	£9,431
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	£24	0.016	£289	£1,535
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£52	0.012	£190	£4,292
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£101	0.008	£62	£12,371

Table 71: Optimistic Metformin Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**£4**	**0.033**	**£655**	**£127**
Single Subgroups				
IMD 1 (least deprived)	£51	0.033	£618	£1,529
IMD 2	£52	0.033	£615	£1,546
IMD 3	£12	0.033	£644	£373
IMD 4	-£55	0.034	£730	-£1,634
IMD 5 (most deprived)	-£82	0.031	£704	-£2,633
Age < 40	£59	0.023	£392	£2,602
Age 40-59	-£56	0.032	£692	-£1,764
Age 60-74	-£30	0.045	£932	-£662
Age >= 75	£123	0.039	£660	£3,136
BMI < 25 (White) OR BMI < 23 (BME)	£43	0.031	£567	£1,416
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£55	0.033	£604	£1,682
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£34	0.034	£710	-£991
BMI >= 35 (White OR BME)	-£196	0.037	£944	-£5,246
Ethnicity White	£16	0.033	£653	£471
Ethnicity BME	-£91	0.029	£681	-£3,091
Sex Male	£91	0.032	£546	£2,848
Sex Female	-£101	0.034	£789	-£2,937
HbA1c 6-6.1	-£292	0.046	£1,204	-£6,397
HbA1c 6.2-6.4	-£740	0.062	£1,978	-£11,965
FPG 5.5-5.9	£219	0.025	£276	£8,851
FPG 6-6.4	-£63	0.036	£792	-£1,736
FPG 6.5-6.9	-£298	0.046	£1,224	-£6,420

Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£509**	**0.053**	**£1,578**	**-£9,515**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£642*	*0.066*	*£1,953*	*-£9,805*
1) HbA1c 6-6.4, BMI >=35	-£730	0.054	£1,816	-£13,446
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£750	0.060	£1,956	-£12,441
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£303	0.045	£1,207	-£6,713
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£351	0.075	£1,859	-£4,660
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£32	0.052	£1,000	£611
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£961	0.056	£2,091	-£17,019
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£441	0.043	£1,305	-£10,212
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£701	0.058	£1,857	-£12,119
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£277	0.045	£1,173	-£6,173
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£137**	**0.028**	**£426**	**£4,868**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£355*	*0.055*	*£1,464*	*-£6,408*
1) FPG 5.5-6.9, BMI >=35	-£98	0.035	£797	-£2,816
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£332	0.042	£1,174	-£7,881
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£100	0.037	£843	-£2,699
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£159	0.027	£375	£5,964
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£81	0.059	£1,254	-£1,383
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£27	0.045	£881	£590
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£185	0.035	£514	£5,289

8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£243	0.041	£1,061	-£5,933
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£22	0.031	£635	-£731
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£286	0.020	£107	£14,567
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£233	0.047	£1,171	-£4,954
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£40	0.032	£606	£1,249
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£297	0.021	£120	£14,256

Table 72: Conservative Metformin Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**£203**	**0.020**	**£202**	**£10,024**
Single Subgroups				
IMD 1 (least deprived)	£236	0.020	£172	£11,587
IMD 2	£228	0.021	£186	£11,021
IMD 3	£212	0.020	£183	£10,744
IMD 4	£164	0.021	£249	£7,943
IMD 5 (most deprived)	£148	0.019	£232	£7,794
Age < 40	£280	0.013	-£12	£20,908
Age 40-59	£177	0.019	£210	£9,137
Age 60-74	£151	0.028	£406	£5,416
Age >= 75	£187	0.025	£314	£7,455
BMI < 25 (White) OR BMI < 23 (BME)	£237	0.018	£127	£13,005
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£234	0.020	£171	£11,548
BMI 30–34 (White) OR BMI 27.5-34 (BME)	£175	0.021	£243	£8,380

BMI >= 35 (White OR BME)	£64	0.024	£408	£2,700
Ethnicity White	£208	0.021	£202	£10,141
Ethnicity BME	£158	0.018	£197	£8,916
Sex Male	£264	0.019	£126	£13,525
Sex Female	£128	0.021	£294	£6,087
HbA1c 6-6.1	-£9	0.027	£551	-£331
HbA1c 6.2-6.4	-£360	0.039	£1,146	-£9,148
FPG 5.5-5.9	£360	0.015	-£59	£23,931
FPG 6-6.4	£150	0.023	£303	£6,613
FPG 6.5-6.9	-£35	0.030	£627	-£1,165
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£179**	**0.033**	**£839**	**-£5,418**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£331*	*0.043*	*£1,182*	*-£7,787*
1) HbA1c 6-6.4, BMI >=35	-£331	0.034	£1,018	-£9,628
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£371	0.039	£1,146	-£9,571
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£10	0.027	£556	-£374
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£104	0.048	£1,064	-£2,170
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£166	0.031	£459	£5,308
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£500	0.036	£1,216	-£13,963
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£97	0.025	£606	-£3,808
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£328	0.036	£1,048	-£9,134
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	£9	0.026	£510	£362
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£298**	**0.017**	**£47**	**£17,282**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£141*	*0.036*	*£864*	*-£3,905*
1) FPG 5.5-6.9, BMI >=35	£137	0.022	£300	£6,273

2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£44	0.027	£592	-£1,614
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£121	0.023	£337	£5,295
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£315	0.016	£10	£19,379
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£77	0.037	£671	£2,048
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£159	0.028	£400	£5,684
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£285	0.022	£151	£13,055
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£24	0.025	£517	-£953
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£203	0.019	£183	£10,525
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£426	0.012	-£189	£35,973
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	£74	0.029	£507	£2,536
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£230	0.020	£172	£11,455
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£420	0.012	-£174	£34,227

Table 73: Optimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£442**	**0.049**	**£1,414**	**-£9,084**
Single Subgroups				
IMD 1 (least deprived)	-£428	0.051	£1,448	-£8,388
IMD 2	-£409	0.051	£1,422	-£8,062
IMD 3	-£445	0.048	£1,414	-£9,184
IMD 4	-£483	0.049	£1,463	-£9,846

IMD 5 (most deprived)	-£472	0.042	£1,302	-£11,354
Age < 40	-£354	0.026	£864	-£13,870
Age 40-59	-£563	0.044	£1,452	-£12,663
Age 60-74	-£523	0.074	£2,006	-£7,056
Age >= 75	-£118	0.070	£1,516	-£1,688
BMI < 25 (White) OR BMI < 23 (BME)	-£451	0.049	£1,432	-£9,208
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£436	0.052	£1,470	-£8,439
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£456	0.048	£1,408	-£9,592
BMI >= 35 (White OR BME)	-£407	0.039	£1,186	-£10,461
Ethnicity White	-£431	0.050	£1,424	-£8,672
Ethnicity BME	-£532	0.040	£1,332	-£13,315
Sex Male	-£368	0.048	£1,333	-£7,642
Sex Female	-£531	0.049	£1,513	-£10,809
HbA1c 6-6.1	-£641	0.063	£1,908	-£10,121
HbA1c 6.2-6.4	-£1,089	0.090	£2,879	-£12,164
FPG 5.5-5.9	-£281	0.038	£1,046	-£7,337
FPG 6-6.4	-£577	0.060	£1,778	-£9,614
FPG 6.5-6.9	-£894	0.080	£2,487	-£11,220
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£858**	**0.076**	**£2,378**	**-£11,288**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£742*	*0.067*	*£2,077*	*-£11,118*
1) HbA1c 6-6.4, BMI >=35	-£669	0.050	£1,678	-£13,253
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,050	0.083	£2,714	-£12,615
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£635	0.059	£1,816	-£10,757
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£865	0.132	£3,506	-£6,554
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£397	0.086	£2,124	-£4,598

6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,381	0.074	£2,870	-£18,556
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£837	0.056	£1,960	-£14,903
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,156	0.094	£3,027	-£12,348
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£678	0.067	£2,020	-£10,095
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£369**	**0.045**	**£1,262**	**-£8,272**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£654*	*0.067*	*£1,995*	*-£9,756*
1) FPG 5.5-6.9, BMI >=35	-£385	0.039	£1,155	-£9,996
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£912	0.073	£2,366	-£12,543
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£586	0.058	£1,749	-£10,084
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£316	0.039	£1,095	-£8,106
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£759	0.128	£3,321	-£5,929
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£510	0.093	£2,372	-£5,480
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£249	0.064	£1,533	-£3,883
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,024	0.065	£2,332	-£15,648
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£648	0.048	£1,615	-£13,395
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£278	0.029	£853	-£9,686
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£983	0.095	£2,890	-£10,312
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£565	0.063	£1,818	-£9,015
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£261	0.036	£988	-£7,186

Table 74: Conservative Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£188**	**0.031**	**£805**	**-£6,112**
Single Subgroups				
IMD 1 (least deprived)	-£183	0.032	£825	-£5,696
IMD 2	-£169	0.032	£816	-£5,238
IMD 3	-£188	0.030	£796	-£6,193
IMD 4	-£218	0.031	£844	-£6,972
IMD 5 (most deprived)	-£197	0.026	£723	-£7,489
Age < 40	-£128	0.016	£443	-£8,166
Age 40-59	-£256	0.028	£811	-£9,211
Age 60-74	-£248	0.047	£1,194	-£5,237
Age >= 75	-£10	0.046	£937	-£224
BMI < 25 (White) OR BMI < 23 (BME)	-£186	0.031	£805	-£6,009
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£185	0.033	£840	-£5,627
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£199	0.030	£795	-£6,694
BMI >= 35 (White OR BME)	-£187	0.026	£704	-£7,241
Ethnicity White	-£183	0.032	£816	-£5,789
Ethnicity BME	-£233	0.024	£720	-£9,582
Sex Male	-£140	0.031	£751	-£4,573
Sex Female	-£248	0.031	£872	-£7,952
HbA1c 6-6.1	-£296	0.039	£1,069	-£7,653
HbA1c 6.2-6.4	-£613	0.059	£1,786	-£10,451
FPG 5.5-5.9	-£88	0.024	£571	-£3,644
FPG 6-6.4	-£278	0.038	£1,045	-£7,260
FPG 6.5-6.9	-£474	0.052	£1,511	-£9,142
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£449**	**0.048**	**£1,416**	**-£9,299**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£423*	*0.046*	*£1,338*	*-£9,247*
1) HbA1c 6-6.4, BMI >=35	-£351	0.034	£1,021	-£10,466
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£586	0.053	£1,649	-£11,042
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£306	0.035	£1,014	-£8,635
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£481	0.087	£2,227	-£5,516
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£152	0.053	£1,215	-£2,851
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£783	0.048	£1,737	-£16,423
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£411	0.034	£1,100	-£11,941
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£648	0.062	£1,887	-£10,466
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£304	0.041	£1,119	-£7,449
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£145**	**0.028**	**£711**	**-£5,109**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£335*	*0.048*	*£1,300*	*-£6,932*
1) FPG 5.5-6.9, BMI >=35	-£175	0.025	£685	-£6,850
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£498	0.046	£1,424	-£10,752
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£284	0.037	£1,018	-£7,749
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£106	0.024	£585	-£4,412
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£397	0.083	£2,066	-£4,763
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£246	0.060	£1,442	-£4,104
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£75	0.041	£902	-£1,805
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£499	0.041	£1,318	-£12,179
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£305	0.030	£903	-£10,230

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£85	0.018	£445	-£4,744
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£501	0.066	£1,821	-£7,599
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£257	0.041	£1,069	-£6,323
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£74	0.023	£535	-£3,234

Table 75: Pessimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**£45**	**0.013**	**£223**	**£3,367**
Single Subgroups				
IMD 1 (least deprived)	£47	0.014	£234	£3,370
IMD 2	£54	0.014	£231	£3,761
IMD 3	£42	0.013	£221	£3,204
IMD 4	£33	0.013	£234	£2,466
IMD 5 (most deprived)	£43	0.011	£183	£3,774
Age < 40	£74	0.007	£66	£10,617
Age 40-59	£17	0.012	£226	£1,435
Age 60-74	£19	0.020	£375	£950
Age >= 75	£110	0.021	£311	£5,223
BMI < 25 (White) OR BMI < 23 (BME)	£49	0.013	£210	£3,764
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£50	0.014	£234	£3,518
BMI 30–34 (White) OR BMI 27.5-34 (BME)	£44	0.013	£219	£3,319
BMI >= 35 (White OR BME)	£22	0.012	£222	£1,804
Ethnicity White	£48	0.014	£228	£3,490
Ethnicity BME	£19	0.010	£180	£1,929

Sex Male	£72	0.013	£192	£5,475
Sex Female	£12	0.014	£260	£889
HbA1c 6-6.1	£9	0.016	£306	£552
HbA1c 6.2-6.4	-£144	0.026	£667	-£5,502
FPG 5.5-5.9	£87	0.011	£123	£8,266
FPG 6-6.4	£2	0.017	£342	£98
FPG 6.5-6.9	-£84	0.022	£524	-£3,833
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£65**	**0.021**	**£481**	**-£3,137**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£80*	*0.020*	*£487*	*-£3,939*
1) HbA1c 6-6.4, BMI >=35	-£49	0.015	£347	-£3,268
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£130	0.023	£598	-£5,568
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£19	0.015	£278	£1,255
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£79	0.039	£866	-£2,010
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£64	0.022	£376	£2,926
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£217	0.022	£656	-£9,885
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£35	0.014	£318	-£2,457
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£159	0.027	£698	-£5,900
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	£7	0.016	£307	£452
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£62**	**0.012**	**£187**	**£4,968**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£31*	*0.022*	*£476*	*-£1,415*
1) FPG 5.5-6.9, BMI >=35	£26	0.012	£217	£2,139
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£80	0.019	£456	-£4,246
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£3	0.016	£322	£154

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£81	0.011	£133	£7,583
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£45	0.034	£717	-£1,352
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£14	0.026	£506	£545
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£97	0.018	£255	£5,516
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£129	0.019	£510	-£6,763
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£4	0.014	£277	£274
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£91	0.008	£67	£11,557
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£68	0.027	£609	-£2,495
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£9	0.017	£340	£514
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£95	0.010	£97	£9,885

Table 76: Optimistic Metformin Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**£27**	**0.026**	**£486**	**£1,040**
Single Subgroups				
IMD 1 (least deprived)	£79	0.025	£416	£3,196
IMD 2	£90	0.024	£389	£3,755
IMD 3	£34	0.026	£479	£1,307
IMD 4	-£42	0.027	£590	-£1,525
IMD 5 (most deprived)	-£84	0.028	£638	-£3,042
Age < 40	-£6	0.026	£521	-£216
Age 40-59	-£92	0.033	£761	-£2,750

Age 60-74	£136	0.025	£370	£5,365
Age >= 75	£263	0.001	-£245	£284,402
BMI < 25 (White) OR BMI < 23 (BME)	£374	0.008	-£221	£49,031
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£112	0.022	£338	£4,957
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£183	0.036	£908	-£5,064
BMI >= 35 (White OR BME)	-£678	0.058	£1,844	-£11,632
Ethnicity White	£44	0.025	£459	£1,755
Ethnicity BME	-£118	0.030	£712	-£3,962
Sex Male	£55	0.028	£509	£1,938
Sex Female	-£7	0.023	£458	-£328
HbA1c 6-6.1	-£107	0.027	£651	-£3,920
HbA1c 6.2-6.4	-£799	0.051	£1,815	-£15,737
FPG 5.5-5.9	£182	0.022	£250	£8,421
FPG 6-6.4	-£428	0.049	£1,404	-£8,761
FPG 6.5-6.9	-£1,200	0.081	£2,828	-£14,738
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£442**	**0.039**	**£1,215**	**-£11,436**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	-£864	0.067	£2,197	-£12,958
1) HbA1c 6-6.4, BMI >=35	-£1,523	0.085	£3,231	-£17,826
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,202	0.069	£2,589	-£17,338
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£345	0.041	£1,155	-£8,501
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£10	0.024	£488	-£423
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£253	0.015	£46	£16,937
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,141	0.062	£2,385	-£18,342
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£240	0.033	£902	-£7,271

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£33	0.014	£303	-£2,412
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	£250	0.008	-£86	£30,405
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£4**	**0.030**	**£601**	**-£149**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,166*	*0.101*	*£3,185*	*-£11,547*
1) FPG 5.5-6.9, BMI >=35	-£771	0.065	£2,068	-£11,896
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,442	0.093	£3,311	-£15,436
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£664	0.061	£1,882	-£10,901
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£6	0.030	£592	£202
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£91	0.041	£905	-£2,248
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£116	0.025	£379	£4,694
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£308	0.013	-£45	£23,386
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,249	0.087	£2,983	-£14,402
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£479	0.051	£1,504	-£9,346
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£219	0.022	£220	£9,992
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£186	0.030	£784	-£6,224
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£199	0.017	£142	£11,657
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£469	0.007	-£324	£64,621

Table 77: Conservative Metformin Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**£207**	**0.016**	**£116**	**£12,835**
Single Subgroups				
IMD 1 (least deprived)	£243	0.015	£67	£15,667
IMD 2	£249	0.015	£53	£16,467
IMD 3	£214	0.016	£104	£13,458
IMD 4	£155	0.017	£191	£8,977
IMD 5 (most deprived)	£137	0.018	£214	£7,810
Age < 40	£222	0.016	£105	£13,570
Age 40-59	£146	0.021	£271	£7,018
Age 60-74	£247	0.016	£73	£15,436
Age >= 75	£277	0.001	-£262	£386,374
BMI < 25 (White) OR BMI < 23 (BME)	£436	0.005	-£345	£95,926
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£265	0.014	£14	£19,025
BMI 30–34 (White) OR BMI 27.5-34 (BME)	£68	0.023	£384	£3,007
BMI >= 35 (White OR BME)	-£268	0.038	£1,037	-£6,963
Ethnicity White	£217	0.016	£100	£13,669
Ethnicity BME	£126	0.018	£242	£6,855
Sex Male	£235	0.018	£119	£13,279
Sex Female	£173	0.014	£112	£12,155
HbA1c 6-6.1	£85	0.017	£254	£5,019
HbA1c 6.2-6.4	-£420	0.033	£1,083	-£12,677
FPG 5.5-5.9	£336	0.013	-£70	£25,278
FPG 6-6.4	-£96	0.031	£725	-£3,049
FPG 6.5-6.9	-£648	0.052	£1,694	-£12,393
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£159**	**0.025**	**£655**	**-£6,434**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£440*	*0.046*	*£1,355*	*-£9,612*
1) HbA1c 6-6.4, BMI >=35	-£901	0.058	£2,058	-£15,564
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£692	0.045	£1,599	-£15,269
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£58	0.025	£554	-£2,317
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£98	0.015	£203	£6,481
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£299	0.009	-£113	£32,220
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£618	0.040	£1,413	-£15,560
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£11	0.020	£393	£523
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	£92	0.008	£70	£11,340
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	£315	0.005	-£214	£62,135
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£204**	**0.019**	**£171**	**£10,872**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£634*	*0.074*	*£2,114*	*-£8,571*
1) FPG 5.5-6.9, BMI >=35	-£314	0.043	£1,166	-£7,357
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£791	0.059	£1,973	-£13,378
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£264	0.039	£1,042	-£6,799
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£219	0.018	£144	£12,077
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£100	0.024	£386	£4,122
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£220	0.016	£97	£13,879
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£357	0.008	-£193	£43,506
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£616	0.056	£1,738	-£10,994
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£95	0.032	£742	-£2,927

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£387	0.013	-£120	£29,007
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	£12	0.018	£353	£633
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£336	0.011	-£125	£31,799
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£530	0.004	-£443	£122,522

Table 78: Optimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£2,524**	**0.119**	**£4,897**	**-£21,279**
Single Subgroups				
IMD 1 (least deprived)	-£2,274	0.122	£4,721	-£18,584
IMD 2	-£2,258	0.119	£4,634	-£19,007
IMD 3	-£2,432	0.119	£4,806	-£20,489
IMD 4	-£2,739	0.120	£5,140	-£22,816
IMD 5 (most deprived)	-£3,148	0.112	£5,383	-£28,163
Age < 40	-£4,203	0.107	£6,338	-£39,367
Age 40-59	-£2,714	0.129	£5,288	-£21,078
Age 60-74	-£1,238	0.136	£3,963	-£9,086
Age >= 75	-£170	0.081	£1,793	-£2,089
BMI < 25 (White) OR BMI < 23 (BME)	-£2,742	0.112	£4,974	-£24,570
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£2,300	0.119	£4,683	-£19,308
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£2,450	0.122	£4,881	-£20,161
BMI >= 35 (White OR BME)	-£2,953	0.128	£5,510	-£23,097
Ethnicity White	-£2,395	0.118	£4,762	-£20,232
Ethnicity BME	-£3,592	0.121	£6,006	-£29,758

Sex Male	-£2,349	0.120	£4,743	-£19,623
Sex Female	-£2,737	0.117	£5,083	-£23,339
HbA1c 6-6.1	-£3,276	0.152	£6,322	-£21,518
HbA1c 6.2-6.4	-£3,622	0.133	£6,284	-£27,220
FPG 5.5-5.9	-£2,124	0.107	£4,269	-£19,817
FPG 6-6.4	-£2,586	0.126	£5,107	-£20,520
FPG 6.5-6.9	-£3,009	0.135	£5,710	-£22,278
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£3,444**	**0.143**	**£6,304**	**-£24,087**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£2,036*	*0.132*	*£4,686*	*-£15,374*
1) HbA1c 6-6.4, BMI >=35	-£3,779	0.142	£6,615	-£26,645
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,436	0.132	£6,085	-£25,940
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,071	0.152	£6,118	-£20,160
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,400	0.149	£4,389	-£9,365
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£970	0.158	£4,122	-£6,156
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,063	0.129	£7,639	-£39,318
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,618	0.158	£7,772	-£29,293
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£3,946	0.124	£6,425	-£31,829
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£3,576	0.148	£6,527	-£24,230
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£2,260**	**0.112**	**£4,509**	**-£20,106**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,695*	*0.115*	*£4,002*	*-£14,702*
1) FPG 5.5-6.9, BMI >=35	-£2,780	0.126	£5,303	-£22,030
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,892	0.130	£5,501	-£22,181
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,539	0.127	£5,084	-£19,948

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,123	0.111	£4,353	-£19,048
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,008	0.138	£3,764	-£7,316
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£820	0.121	£3,233	-£6,795
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£583	0.104	£2,658	-£5,613
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,009	0.140	£6,809	-£28,639
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,328	0.130	£5,929	-£25,598
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,566	0.109	£4,737	-£23,631
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£3,112	0.126	£5,623	-£24,795
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,705	0.115	£4,998	-£23,589
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,238	0.099	£4,212	-£22,683

Table 79: Conservative Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£1,770**	**0.085**	**£3,466**	**-£20,862**
Single Subgroups				
IMD 1 (least deprived)	-£1,585	0.087	£3,331	-£18,153
IMD 2	-£1,571	0.085	£3,269	-£18,501
IMD 3	-£1,714	0.085	£3,412	-£20,190
IMD 4	-£1,944	0.086	£3,662	-£22,633
IMD 5 (most deprived)	-£2,210	0.080	£3,813	-£27,576
Age < 40	-£2,998	0.076	£4,511	-£39,633
Age 40-59	-£1,908	0.092	£3,748	-£20,746

Age 60-74	-£818	0.098	£2,783	-£8,330
Age >= 75	-£63	0.058	£1,232	-£1,081
BMI < 25 (White) OR BMI < 23 (BME)	-£1,927	0.080	£3,520	-£24,207
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£1,609	0.085	£3,308	-£18,929
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£1,718	0.087	£3,457	-£19,761
BMI >= 35 (White OR BME)	-£2,074	0.093	£3,924	-£22,415
Ethnicity White	-£1,674	0.085	£3,368	-£19,779
Ethnicity BME	-£2,556	0.086	£4,279	-£29,653
Sex Male	-£1,637	0.086	£3,352	-£19,081
Sex Female	-£1,932	0.084	£3,605	-£23,086
HbA1c 6-6.1	-£2,325	0.109	£4,505	-£21,321
HbA1c 6.2-6.4	-£2,560	0.094	£4,444	-£27,173
FPG 5.5-5.9	-£1,480	0.077	£3,013	-£19,309
FPG 6-6.4	-£1,816	0.090	£3,622	-£20,110
FPG 6.5-6.9	-£2,112	0.099	£4,083	-£21,427
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£2,439**	**0.102**	**£4,476**	**-£23,942**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,376*	*0.096*	*£3,291*	*-£14,375*
1) HbA1c 6-6.4, BMI >=35	-£2,685	0.102	£4,728	-£26,267
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,410	0.093	£4,266	-£25,956
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,189	0.108	£4,354	-£20,230
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£930	0.106	£3,053	-£8,763
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£640	0.113	£2,903	-£5,653
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,619	0.091	£5,436	-£39,853
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,309	0.114	£5,581	-£29,133

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,809	0.088	£4,572	-£31,870
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£2,520	0.105	£4,625	-£23,934
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£1,578**	**0.080**	**£3,188**	**-£19,612**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,038*	*0.087*	*£2,783*	*-£11,899*
1) FPG 5.5-6.9, BMI >=35	-£1,949	0.092	£3,782	-£21,265
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,031	0.096	£3,948	-£21,192
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,771	0.091	£3,595	-£19,417
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,482	0.079	£3,070	-£18,677
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£622	0.097	£2,558	-£6,421
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£525	0.086	£2,247	-£6,090
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£355	0.075	£1,849	-£4,754
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,845	0.102	£4,883	-£27,922
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,372	0.094	£4,245	-£25,338
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,802	0.077	£3,336	-£23,475
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,207	0.094	£4,097	-£23,364
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,908	0.081	£3,529	-£23,546
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,564	0.071	£2,981	-£22,065

Table 80: Pessimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£749**	**0.040**	**£1,551**	**-£18,687**
Single Subgroups				
IMD 1 (least deprived)	-£662	0.042	£1,493	-£15,955
IMD 2	-£646	0.041	£1,457	-£15,903
IMD 3	-£718	0.040	£1,518	-£17,924
IMD 4	-£831	0.040	£1,637	-£20,640
IMD 5 (most deprived)	-£975	0.037	£1,718	-£26,253
Age < 40	-£1,345	0.035	£2,047	-£38,374
Age 40-59	-£815	0.044	£1,690	-£18,655
Age 60-74	-£286	0.046	£1,211	-£6,193
Age >= 75	£76	0.029	£503	£2,634
BMI < 25 (White) OR BMI < 23 (BME)	-£825	0.037	£1,568	-£22,243
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£671	0.040	£1,478	-£16,600
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£720	0.041	£1,546	-£17,426
BMI >= 35 (White OR BME)	-£906	0.044	£1,779	-£20,751
Ethnicity White	-£702	0.040	£1,504	-£17,498
Ethnicity BME	-£1,136	0.040	£1,932	-£28,590
Sex Male	-£682	0.040	£1,491	-£16,860
Sex Female	-£830	0.040	£1,623	-£20,957
HbA1c 6-6.1	-£1,008	0.051	£2,034	-£19,657
HbA1c 6.2-6.4	-£1,143	0.044	£2,030	-£25,811
FPG 5.5-5.9	-£608	0.036	£1,331	-£16,824
FPG 6-6.4	-£778	0.043	£1,641	-£18,019
FPG 6.5-6.9	-£924	0.046	£1,847	-£20,019
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,074**	**0.048**	**£2,032**	**-£22,414**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£605*	*0.046*	*£1,519*	*-£13,260*
1) HbA1c 6-6.4, BMI >=35	-£1,202	0.047	£2,146	-£25,462
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,085	0.043	£1,945	-£25,243
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£929	0.053	£1,984	-£17,624
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£330	0.051	£1,348	-£6,489
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£201	0.054	£1,276	-£3,730
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,669	0.043	£2,533	-£38,671
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,486	0.053	£2,538	-£28,242
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,252	0.041	£2,075	-£30,398
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£1,109	0.049	£2,086	-£22,706
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£658**	**0.038**	**£1,419**	**-£17,275**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£413*	*0.041*	*£1,236*	*-£10,049*
1) FPG 5.5-6.9, BMI >=35	-£845	0.043	£1,711	-£19,504
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£891	0.046	£1,820	-£19,201
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£743	0.043	£1,610	-£17,141
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£606	0.037	£1,352	-£16,249
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£173	0.046	£1,091	-£3,770
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£145	0.041	£967	-£3,524
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£54	0.036	£770	-£1,515
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,320	0.046	£2,250	-£28,390
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,050	0.044	£1,935	-£23,736

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£769	0.037	£1,505	-£20,882
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£882	0.043	£1,732	-£20,736
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£828	0.040	£1,622	-£20,879
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£649	0.033	£1,301	-£19,919

Table 81: Optimistic Metformin Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£1,504**	**0.083**	**£3,171**	**-£18,045**
Single Subgroups				
IMD 1 (least deprived)	-£1,303	0.087	£3,034	-£15,050
IMD 2	-£1,301	0.084	£2,974	-£15,554
IMD 3	-£1,436	0.084	£3,118	-£17,088
IMD 4	-£1,678	0.084	£3,348	-£20,085
IMD 5 (most deprived)	-£1,980	0.078	£3,537	-£25,427
Age < 40	-£2,680	0.075	£4,174	-£35,900
Age 40-59	-£1,613	0.090	£3,414	-£17,906
Age 60-74	-£589	0.095	£2,497	-£6,179
Age >= 75	£43	0.060	£1,153	£720
BMI < 25 (White) OR BMI < 23 (BME)	-£1,671	0.079	£3,260	-£21,042
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£1,337	0.084	£3,018	-£15,915
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£1,452	0.085	£3,146	-£17,141
BMI >= 35 (White OR BME)	-£1,805	0.088	£3,559	-£20,573
Ethnicity White	-£1,407	0.083	£3,072	-£16,907
Ethnicity BME	-£2,302	0.084	£3,986	-£27,344

Sex Male	-£1,354	0.084	£3,031	-£16,150
Sex Female	-£1,686	0.083	£3,340	-£20,385
HbA1c 6-6.1	-£2,170	0.107	£4,315	-£20,234
HbA1c 6.2-6.4	-£2,555	0.093	£4,423	-£27,344
FPG 5.5-5.9	-£1,134	0.075	£2,638	-£15,075
FPG 6-6.4	-£1,581	0.089	£3,352	-£17,847
FPG 6.5-6.9	-£1,944	0.096	£3,854	-£20,347
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£2,356**	**0.101**	**£4,368**	**-£23,432**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,321*	*0.092*	*£3,166*	*-£14,324*
1) HbA1c 6-6.4, BMI >=35	-£2,564	0.097	£4,499	-£26,487
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,410	0.091	£4,226	-£26,546
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,008	0.107	£4,144	-£18,790
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£874	0.107	£3,009	-£8,190
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£449	0.112	£2,684	-£4,019
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,644	0.091	£5,461	-£40,108
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,178	0.111	£5,396	-£28,663
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,824	0.089	£4,598	-£31,825
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£2,410	0.105	£4,513	-£22,913
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£1,264**	**0.079**	**£2,842**	**-£16,011**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£971*	*0.084*	*£2,657*	*-£11,528*
1) FPG 5.5-6.9, BMI >=35	-£1,651	0.087	£3,387	-£19,023
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,872	0.092	£3,707	-£20,400
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,550	0.089	£3,327	-£17,448

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,144	0.078	£2,698	-£14,729
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£496	0.098	£2,463	-£5,049
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£328	0.086	£2,047	-£3,816
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£121	0.073	£1,587	-£1,645
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,645	0.097	£4,587	-£27,233
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,096	0.092	£3,932	-£22,828
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,404	0.076	£2,926	-£18,443
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,056	0.093	£3,925	-£22,004
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,669	0.082	£3,304	-£20,402
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,204	0.070	£2,606	-£17,162

Table 82: Conservative Metformin Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£953**	**0.059**	**£2,128**	**-£16,212**
Single Subgroups				
IMD 1 (least deprived)	-£808	0.061	£2,027	-£13,244
IMD 2	-£801	0.059	£1,985	-£13,522
IMD 3	-£904	0.059	£2,085	-£15,302
IMD 4	-£1,094	0.059	£2,270	-£18,606
IMD 5 (most deprived)	-£1,289	0.055	£2,386	-£23,504
Age < 40	-£1,773	0.052	£2,816	-£34,012
Age 40-59	-£1,032	0.063	£2,299	-£16,299

Age 60-74	-£305	0.068	£1,664	-£4,490
Age >= 75	£117	0.043	£733	£2,748
BMI < 25 (White) OR BMI < 23 (BME)	-£1,065	0.056	£2,178	-£19,125
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£834	0.059	£2,018	-£14,105
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£920	0.060	£2,122	-£15,313
BMI >= 35 (White OR BME)	-£1,172	0.062	£2,415	-£18,853
Ethnicity White	-£884	0.059	£2,057	-£15,057
Ethnicity BME	-£1,522	0.059	£2,710	-£25,623
Sex Male	-£841	0.059	£2,018	-£14,290
Sex Female	-£1,088	0.059	£2,261	-£18,560
HbA1c 6-6.1	-£1,462	0.076	£2,976	-£19,320
HbA1c 6.2-6.4	-£1,764	0.064	£3,052	-£27,396
FPG 5.5-5.9	-£668	0.053	£1,727	-£12,615
FPG 6-6.4	-£1,012	0.062	£2,261	-£16,197
FPG 6.5-6.9	-£1,315	0.069	£2,686	-£19,172
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,609**	**0.070**	**£3,014**	**-£22,909**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£867*	*0.065*	*£2,162*	*-£13,394*
1) HbA1c 6-6.4, BMI >=35	-£1,756	0.068	£3,118	-£25,776
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,667	0.063	£2,926	-£26,469
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,349	0.077	£2,884	-£17,571
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£546	0.074	£2,024	-£7,394
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£232	0.080	£1,828	-£2,912
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,565	0.063	£3,819	-£40,920
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,194	0.077	£3,724	-£28,675

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,945	0.060	£3,152	-£32,215
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£1,625	0.074	£3,098	-£22,050
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£769**	**0.056**	**£1,881**	**-£13,818**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£612*	*0.060*	*£1,814*	*-£10,184*
1) FPG 5.5-6.9, BMI >=35	-£1,051	0.061	£2,280	-£17,092
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,253	0.064	£2,534	-£19,580
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£989	0.063	£2,248	-£15,715
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£679	0.055	£1,776	-£12,397
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£284	0.074	£1,765	-£3,842
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£139	0.061	£1,358	-£2,282
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£33	0.052	£1,003	£633
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,839	0.068	£3,196	-£27,084
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,365	0.065	£2,661	-£21,069
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£851	0.053	£1,921	-£15,916
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,339	0.069	£2,728	-£19,277
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,070	0.057	£2,209	-£18,799
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£713	0.049	£1,695	-£14,520

Table 83: Optimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£2,015**	**0.112**	**£4,247**	**-£18,061**
Single Subgroups				
IMD 1 (least deprived)	-£1,919	0.121	£4,336	-£15,877
IMD 2	-£1,854	0.116	£4,169	-£16,024
IMD 3	-£1,974	0.113	£4,225	-£17,529
IMD 4	-£2,144	0.110	£4,340	-£19,523
IMD 5 (most deprived)	-£2,311	0.093	£4,177	-£24,773
Age < 40	-£2,836	0.074	£4,311	-£38,452
Age 40-59	-£2,357	0.118	£4,710	-£20,038
Age 60-74	-£1,309	0.153	£4,372	-£8,544
Age >= 75	-£229	0.106	£2,343	-£2,170
BMI < 25 (White) OR BMI < 23 (BME)	-£2,441	0.120	£4,840	-£20,344
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£2,018	0.122	£4,451	-£16,594
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£1,843	0.104	£3,918	-£17,759
BMI >= 35 (White OR BME)	-£1,334	0.072	£2,768	-£18,588
Ethnicity White	-£1,922	0.113	£4,175	-£17,061
Ethnicity BME	-£2,787	0.103	£4,842	-£27,129
Sex Male	-£1,913	0.113	£4,176	-£16,900
Sex Female	-£2,140	0.110	£4,332	-£19,523
HbA1c 6-6.1	-£2,522	0.139	£5,311	-£18,081
HbA1c 6.2-6.4	-£3,058	0.136	£5,773	-£22,520
FPG 5.5-5.9	-£1,703	0.100	£3,707	-£16,992
FPG 6-6.4	-£2,378	0.135	£5,078	-£17,613
FPG 6.5-6.9	-£3,042	0.165	£6,340	-£18,448
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£2,782**	**0.138**	**£5,535**	**-£20,203**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,241*	*0.088*	*£3,010*	*-£14,035*
1) HbA1c 6-6.4, BMI >=35	-£1,707	0.078	£3,273	-£21,788
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,767	0.121	£5,193	-£22,819
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,249	0.126	£4,775	-£17,809
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,703	0.197	£5,634	-£8,666
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,093	0.185	£4,790	-£5,910
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,388	0.120	£6,781	-£36,683
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,685	0.135	£6,395	-£27,201
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£3,704	0.148	£6,662	-£25,033
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£3,001	0.151	£6,026	-£19,840
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£1,903**	**0.110**	**£4,110**	**-£17,246**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,182*	*0.096*	*£3,104*	*-£12,307*
1) FPG 5.5-6.9, BMI >=35	-£1,318	0.073	£2,787	-£17,956
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,922	0.151	£5,936	-£19,385
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,224	0.124	£4,708	-£17,915
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,568	0.094	£3,442	-£16,725
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,569	0.236	£6,287	-£6,649
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,160	0.178	£4,712	-£6,531
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£727	0.130	£3,327	-£5,596
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,408	0.169	£7,793	-£26,052
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,255	0.136	£5,972	-£23,967

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,144	0.097	£4,084	-£22,093
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£3,914	0.200	£7,919	-£19,540
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,963	0.152	£5,999	-£19,525
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,067	0.108	£4,226	-£19,154

Table 84: Conservative Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£1,396**	**0.080**	**£2,998**	**-£17,439**
Single Subgroups				
IMD 1 (least deprived)	-£1,330	0.087	£3,070	-£15,285
IMD 2	-£1,280	0.083	£2,945	-£15,378
IMD 3	-£1,363	0.080	£2,971	-£16,952
IMD 4	-£1,502	0.078	£3,071	-£19,155
IMD 5 (most deprived)	-£1,593	0.067	£2,930	-£23,833
Age < 40	-£1,988	0.052	£3,033	-£38,037
Age 40-59	-£1,646	0.084	£3,329	-£19,563
Age 60-74	-£880	0.111	£3,093	-£7,957
Age >= 75	-£110	0.077	£1,651	-£1,423
BMI < 25 (White) OR BMI < 23 (BME)	-£1,704	0.087	£3,435	-£19,685
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£1,404	0.087	£3,146	-£16,119
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£1,264	0.074	£2,747	-£17,049
BMI >= 35 (White OR BME)	-£898	0.052	£1,929	-£17,423
Ethnicity White	-£1,327	0.081	£2,944	-£16,412
Ethnicity BME	-£1,966	0.073	£3,434	-£26,772

Sex Male	-£1,318	0.081	£2,946	-£16,181
Sex Female	-£1,492	0.078	£3,060	-£19,034
HbA1c 6-6.1	-£1,763	0.100	£3,771	-£17,565
HbA1c 6.2-6.4	-£2,155	0.096	£4,081	-£22,368
FPG 5.5-5.9	-£1,168	0.072	£2,604	-£16,270
FPG 6-6.4	-£1,668	0.097	£3,606	-£17,212
FPG 6.5-6.9	-£2,148	0.120	£4,541	-£17,956
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,953**	**0.098**	**£3,921**	**-£19,844**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£831*	*0.065*	*£2,123*	*-£12,853*
1) HbA1c 6-6.4, BMI >=35	-£1,164	0.056	£2,287	-£20,707
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,912	0.085	£3,616	-£22,424
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,565	0.090	£3,364	-£17,403
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,176	0.140	£3,981	-£8,381
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£730	0.133	£3,392	-£5,488
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,138	0.083	£4,806	-£37,638
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,614	0.097	£4,564	-£26,820
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,631	0.106	£4,747	-£24,872
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£2,108	0.110	£4,305	-£19,200
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£1,316**	**0.079**	**£2,899**	**-£16,628**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£794*	*0.073*	*£2,262*	*-£10,812*
1) FPG 5.5-6.9, BMI >=35	-£888	0.053	£1,938	-£16,900
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,054	0.108	£4,207	-£19,081
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,544	0.090	£3,336	-£17,237

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,065	0.066	£2,391	-£16,064
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,050	0.170	£4,441	-£6,194
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£783	0.128	£3,336	-£6,134
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£466	0.094	£2,339	-£4,975
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,205	0.123	£5,670	-£25,998
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,326	0.098	£4,281	-£23,801
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,488	0.069	£2,873	-£21,489
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,779	0.148	£5,739	-£18,778
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,086	0.108	£4,250	-£19,284
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,435	0.078	£2,998	-£18,357

Table 85: Pessimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£563**	**0.038**	**£1,320**	**-£14,859**
Single Subgroups				
IMD 1 (least deprived)	-£536	0.041	£1,362	-£12,976
IMD 2	-£501	0.040	£1,298	-£12,590
IMD 3	-£549	0.038	£1,306	-£14,522
IMD 4	-£610	0.037	£1,352	-£16,456
IMD 5 (most deprived)	-£662	0.031	£1,278	-£21,473
Age < 40	-£833	0.024	£1,316	-£34,418
Age 40-59	-£687	0.040	£1,482	-£17,282

Age 60-74	-£322	0.052	£1,365	-£6,182
Age >= 75	£47	0.038	£720	£1,222
BMI < 25 (White) OR BMI < 23 (BME)	-£714	0.041	£1,525	-£17,611
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£567	0.041	£1,395	-£13,707
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£492	0.035	£1,191	-£14,090
BMI >= 35 (White OR BME)	-£326	0.025	£825	-£13,064
Ethnicity White	-£530	0.038	£1,297	-£13,826
Ethnicity BME	-£831	0.034	£1,508	-£24,529
Sex Male	-£522	0.038	£1,290	-£13,603
Sex Female	-£612	0.037	£1,357	-£16,435
HbA1c 6-6.1	-£740	0.047	£1,681	-£15,721
HbA1c 6.2-6.4	-£932	0.045	£1,841	-£20,507
FPG 5.5-5.9	-£454	0.034	£1,131	-£13,434
FPG 6-6.4	-£699	0.047	£1,630	-£15,021
FPG 6.5-6.9	-£939	0.056	£2,053	-£16,851
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£833**	**0.046**	**£1,758**	**-£18,002**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£327*	*0.031*	*£942*	*-£10,620*
1) HbA1c 6-6.4, BMI >=35	-£456	0.026	£985	-£17,220
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£816	0.039	£1,598	-£20,890
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£635	0.043	£1,491	-£14,857
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£457	0.067	£1,801	-£6,794
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£261	0.064	£1,531	-£4,107
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,413	0.040	£2,219	-£35,027
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,143	0.044	£2,033	-£25,698

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,152	0.049	£2,142	-£23,283
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£911	0.051	£1,935	-£17,793
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£527**	**0.037**	**£1,276**	**-£14,067**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£257*	*0.034*	*£940*	*-£7,515*
1) FPG 5.5-6.9, BMI >=35	-£323	0.026	£835	-£12,619
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£872	0.050	£1,868	-£17,511
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£626	0.043	£1,478	-£14,692
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£395	0.031	£1,016	-£12,739
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£438	0.080	£2,033	-£5,488
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£290	0.061	£1,516	-£4,730
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£116	0.045	£1,016	-£2,589
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,433	0.057	£2,576	-£25,072
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,015	0.046	£1,931	-£22,172
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£608	0.033	£1,267	-£18,470
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,216	0.068	£2,582	-£17,810
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£911	0.053	£1,975	-£17,133
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£588	0.036	£1,308	-£16,314

Table 86: Optimistic Metformin Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£1,757**	**0.088**	**£3,517**	**-£19,971**
Single Subgroups				
IMD 1 (least deprived)	-£1,505	0.086	£3,231	-£17,432
IMD 2	-£1,447	0.081	£3,067	-£17,870
IMD 3	-£1,661	0.089	£3,448	-£18,600
IMD 4	-£2,026	0.092	£3,872	-£21,957
IMD 5 (most deprived)	-£2,405	0.097	£4,343	-£24,816
Age < 40	-£3,521	0.117	£5,867	-£30,006
Age 40-59	-£1,932	0.113	£4,187	-£17,136
Age 60-74	-£221	0.054	£1,304	-£4,082
Age >= 75	£258	0.002	-£222	£141,811
BMI < 25 (White) OR BMI < 23 (BME)	-£247	0.025	£737	-£10,085
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£1,428	0.075	£2,931	-£19,014
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£2,620	0.124	£5,098	-£21,150
BMI >= 35 (White OR BME)	-£4,786	0.213	£9,042	-£22,490
Ethnicity White	-£1,641	0.086	£3,356	-£19,127
Ethnicity BME	-£2,722	0.106	£4,848	-£25,606
Sex Male	-£1,786	0.099	£3,765	-£18,051
Sex Female	-£1,722	0.075	£3,214	-£23,075
HbA1c 6-6.1	-£1,720	0.078	£3,278	-£22,084
HbA1c 6.2-6.4	-£2,922	0.095	£4,826	-£30,705
FPG 5.5-5.9	-£1,562	0.083	£3,218	-£18,858
FPG 6-6.4	-£3,553	0.163	£6,806	-£21,843
FPG 6.5-6.9	-£5,868	0.250	£10,862	-£23,499
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£2,302**	**0.086**	**£4,027**	**-£26,691**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,940*	*0.115*	*£4,234*	*-£16,906*
1) HbA1c 6-6.4, BMI >=35	-£5,868	0.214	£10,143	-£27,452
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,066	0.129	£6,644	-£31,544
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,637	0.118	£4,997	-£22,356
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£249	0.035	£941	-£7,209
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£86	0.032	£550	£2,700
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,223	0.113	£6,476	-£37,499
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,569	0.096	£4,484	-£26,823
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£730	0.022	£1,161	-£33,826
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£208	0.018	£573	-£11,437
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£2,164**	**0.107**	**£4,298**	**-£20,278**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£2,917*	*0.204*	*£6,991*	*-£14,316*
1) FPG 5.5-6.9, BMI >=35	-£5,472	0.245	£10,365	-£22,362
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£6,765	0.286	£12,483	-£23,661
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,466	0.201	£8,485	-£22,226
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,319	0.115	£4,618	-£20,175
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£538	0.079	£2,110	-£6,842
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£181	0.053	£1,239	-£3,430
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£151	0.029	£435	£5,153
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£7,260	0.272	£12,707	-£26,657
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,393	0.180	£7,995	-£24,395

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,959	0.092	£3,805	-£21,224
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,222	0.076	£3,745	-£29,174
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,108	0.052	£2,143	-£21,408
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£214	0.027	£750	-£7,961

Table 87: Conservative Metformin Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 3.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£1,214**	**0.063**	**£2,475**	**-£19,245**
Single Subgroups				
IMD 1 (least deprived)	-£1,014	0.061	£2,241	-£16,517
IMD 2	-£971	0.058	£2,133	-£16,727
IMD 3	-£1,138	0.064	£2,410	-£17,903
IMD 4	-£1,421	0.067	£2,755	-£21,312
IMD 5 (most deprived)	-£1,728	0.070	£3,123	-£24,750
Age < 40	-£2,573	0.084	£4,260	-£30,494
Age 40-59	-£1,321	0.081	£2,936	-£16,353
Age 60-74	-£40	0.039	£810	-£1,033
Age >= 75	£271	0.001	-£244	£203,192
BMI < 25 (White) OR BMI < 23 (BME)	-£39	0.017	£377	-£2,289
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£941	0.053	£1,999	-£17,771
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£1,870	0.089	£3,645	-£21,085
BMI >= 35 (White OR BME)	-£3,663	0.158	£6,816	-£23,242
Ethnicity White	-£1,127	0.062	£2,359	-£18,305
Ethnicity BME	-£1,929	0.075	£3,435	-£25,621

Sex Male	-£1,231	0.071	£2,651	-£17,347
Sex Female	-£1,192	0.053	£2,261	-£22,319
HbA1c 6-6.1	-£1,199	0.056	£2,316	-£21,480
HbA1c 6.2-6.4	-£2,125	0.066	£3,442	-£32,270
FPG 5.5-5.9	-£1,034	0.059	£2,213	-£17,540
FPG 6-6.4	-£2,623	0.118	£4,983	-£22,241
FPG 6.5-6.9	-£4,544	0.182	£8,182	-£24,984
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,648**	**0.061**	**£2,861**	**-£27,151**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,332*	*0.081*	*£2,953*	*-£16,431*
1) HbA1c 6-6.4, BMI >=35	-£4,481	0.155	£7,590	-£28,834
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,962	0.088	£4,730	-£33,512
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,898	0.085	£3,600	-£22,320
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£97	0.024	£580	-£4,024
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£165	0.023	£293	£7,213
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,072	0.075	£4,581	-£40,707
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,806	0.067	£3,147	-£26,925
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£449	0.014	£729	-£32,065
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£35	0.013	£288	-£2,730
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£1,518**	**0.077**	**£3,050**	**-£19,808**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£2,186*	*0.148*	*£5,152*	*-£14,744*
1) FPG 5.5-6.9, BMI >=35	-£4,205	0.182	£7,838	-£23,151
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£5,143	0.205	£9,245	-£25,078
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,268	0.145	£6,168	-£22,538

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,628	0.082	£3,263	-£19,930
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£282	0.058	£1,436	-£4,883
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£28	0.037	£764	-£760
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£234	0.021	£178	£11,362
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,379	0.192	£9,210	-£28,082
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,223	0.128	£5,789	-£25,128
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,300	0.065	£2,600	-£20,016
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,536	0.054	£2,608	-£28,627
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£680	0.036	£1,399	-£18,940
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£10	0.019	£363	£530

Full Results: Discount Rate of 1.5%

Table 88: Optimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB	ICER (£/QALY)
TOTAL	**-£813**	**0.065**	**£2,110**	**-£12,528**
Single Subgroups				
IMD 1 (least deprived)	-£742	0.064	£2,018	-£11,621
IMD 2	-£700	0.064	£1,987	-£10,880
IMD 3	-£831	0.066	£2,155	-£12,549
IMD 4	-£908	0.069	£2,290	-£13,135
IMD 5 (most deprived)	-£991	0.062	£2,231	-£15,986
Age < 40	-£1,018	0.049	£2,007	-£20,595
Age 40-59	-£977	0.065	£2,287	-£14,931

Age 60-74	-£641	0.085	£2,338	-£7,558
Age >= 75	-£109	0.062	£1,357	-£1,740
BMI < 25 (White) OR BMI < 23 (BME)	-£773	0.060	£1,971	-£12,918
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£714	0.064	£1,998	-£11,132
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£863	0.068	£2,223	-£12,681
BMI >= 35 (White OR BME)	-£1,158	0.073	£2,627	-£15,773
Ethnicity White	-£775	0.065	£2,076	-£11,911
Ethnicity BME	-£1,125	0.063	£2,395	-£17,731
Sex Male	-£672	0.063	£1,936	-£10,636
Sex Female	-£984	0.067	£2,323	-£14,702
HbA1c 6-6.1	-£1,212	0.090	£3,016	-£13,438
HbA1c 6.2-6.4	-£1,746	0.112	£3,983	-£15,607
FPG 5.5-5.9	-£536	0.050	£1,530	-£10,797
FPG 6-6.4	-£886	0.072	£2,326	-£12,302
FPG 6.5-6.9	-£1,201	0.083	£2,859	-£14,490
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,471**	**0.101**	**£3,485**	**-£14,612**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,407*	*0.112*	*£3,641*	*-£12,591*
1) HbA1c 6-6.4, BMI >=35	-£1,854	0.101	£3,873	-£18,367
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,791	0.116	£4,119	-£15,390
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,210	0.088	£2,971	-£13,739
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£875	0.125	£3,369	-£7,019
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£443	0.097	£2,377	-£4,579
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,193	0.106	£4,320	-£20,617
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,602	0.089	£3,374	-£18,084

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,724	0.103	£3,777	-£16,798
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£1,229	0.091	£3,054	-£13,472
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£639**	**0.056**	**£1,756**	**-£11,444**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,190*	*0.093*	*£3,048*	*-£12,813*
1) FPG 5.5-6.9, BMI >=35	-£1,022	0.069	£2,397	-£14,870
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,265	0.081	£2,884	-£15,624
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£954	0.076	£2,465	-£12,619
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£627	0.054	£1,706	-£11,619
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£560	0.091	£2,372	-£6,174
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£496	0.082	£2,128	-£6,072
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£253	0.065	£1,547	-£3,912
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,352	0.068	£2,715	-£19,833
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£983	0.065	£2,279	-£15,178
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£568	0.042	£1,404	-£13,593
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,003	0.079	£2,584	-£12,689
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£684	0.065	£1,982	-£10,524
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£432	0.042	£1,265	-£10,352

Table 89: Conservative Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£411**	**0.040**	**£1,144**	**-£10,275**
Single Subgroups				
IMD 1 (least deprived)	-£383	0.039	£1,164	-£9,822
IMD 2	-£338	0.040	£1,140	-£8,414
IMD 3	-£428	0.040	£1,230	-£10,683
IMD 4	-£467	0.043	£1,321	-£10,934
IMD 5 (most deprived)	-£503	0.038	£1,264	-£13,224
Age < 40	-£526	0.030	£1,120	-£17,731
Age 40-59	-£510	0.040	£1,310	-£12,751
Age 60-74	-£311	0.053	£1,369	-£5,887
Age >= 75	£1	0.040	£807	£24
BMI < 25 (White) OR BMI < 23 (BME)	-£377	0.036	£1,101	-£10,419
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£341	0.040	£1,136	-£8,597
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£466	0.042	£1,297	-£11,217
BMI >= 35 (White OR BME)	-£629	0.047	£1,571	-£13,342
Ethnicity White	-£388	0.040	£1,196	-£9,594
Ethnicity BME	-£603	0.037	£1,334	-£16,517
Sex Male	-£307	0.039	£1,095	-£7,783
Sex Female	-£537	0.041	£1,351	-£13,204
HbA1c 6-6.1	-£638	0.053	£1,703	-£11,973
HbA1c 6.2-6.4	-£1,021	0.071	£2,440	-£14,398
FPG 5.5-5.9	-£242	0.030	£852	-£7,952
FPG 6-6.4	-£454	0.045	£1,348	-£10,153
FPG 6.5-6.9	-£635	0.057	£1,766	-£11,220
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£824**	**0.062**	**£2,060**	**-£13,321**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£777*	*0.075*	*£2,278*	*-£10,348*
1) HbA1c 6-6.4, BMI >=35	-£1,037	0.064	£2,311	-£16,281
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,113	0.071	£2,525	-£15,766
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£653	0.053	£1,713	-£12,314
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£477	0.081	£2,096	-£5,894
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£177	0.056	£1,304	-£3,143
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,282	0.067	£2,626	-£19,081
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£864	0.053	£1,933	-£16,154
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£987	0.066	£2,315	-£14,853
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£637	0.052	£1,671	-£12,327
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£305**	**0.035**	**£996**	**-£8,818**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£623*	*0.074*	*£2,109*	*-£8,394*
1) FPG 5.5-6.9, BMI >=35	-£546	0.044	£1,433	-£12,323
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£747	0.060	£1,938	-£12,533
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£528	0.047	£1,458	-£11,351
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£320	0.032	£964	-£9,924
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£193	0.066	£1,510	-£2,924
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£229	0.050	£1,228	-£4,592
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£74	0.042	£909	-£1,780
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£748	0.043	£1,598	-£17,587
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£482	0.040	£1,283	-£12,024

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£249	0.025	£752	-£9,905
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£362	0.048	£1,318	-£7,581
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£291	0.039	£1,075	-£7,444
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£172	0.025	£678	-£6,801

Table 90: Pessimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£46**	**0.017**	**£392**	**-£2,646**
Single Subgroups				
IMD 1 (least deprived)	-£26	0.017	£370	-£1,525
IMD 2	-£20	0.018	£377	-£1,135
IMD 3	-£31	0.018	£388	-£1,720
IMD 4	-£76	0.018	£428	-£4,290
IMD 5 (most deprived)	-£95	0.016	£411	-£6,041
Age < 40	-£97	0.013	£359	-£7,422
Age 40-59	-£84	0.017	£428	-£4,855
Age 60-74	-£5	0.022	£448	-£211
Age >= 75	£124	0.018	£245	£6,711
BMI < 25 (White) OR BMI < 23 (BME)	-£35	0.016	£346	-£2,264
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£17	0.017	£358	-£995
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£56	0.018	£411	-£3,142
BMI >= 35 (White OR BME)	-£155	0.021	£585	-£7,225
Ethnicity White	-£33	0.018	£384	-£1,865
Ethnicity BME	-£153	0.015	£457	-£10,093

Sex Male	£6	0.017	£328	£362
Sex Female	-£109	0.018	£469	-£6,045
HbA1c 6-6.1	-£131	0.022	£580	-£5,855
HbA1c 6.2-6.4	-£312	0.031	£932	-£10,071
FPG 5.5-5.9	£20	0.013	£242	£1,531
FPG 6-6.4	-£60	0.019	£443	-£3,121
FPG 6.5-6.9	-£143	0.025	£645	-£5,714
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£219**	**0.027**	**£750**	**-£8,243**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£199*	*0.035*	*£889*	*-£5,762*
1) HbA1c 6-6.4, BMI >=35	-£328	0.028	£883	-£11,838
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£341	0.031	£955	-£11,103
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£100	0.021	£514	-£4,807
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£73	0.036	£802	-£2,013
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£53	0.025	£440	£2,165
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£406	0.029	£978	-£14,188
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£247	0.024	£719	-£10,482
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£322	0.029	£893	-£11,272
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£129	0.022	£573	-£5,819
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£4**	**0.015**	**£301**	**-£245**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£173*	*0.049*	*£1,153*	*-£3,524*
1) FPG 5.5-6.9, BMI >=35	-£122	0.020	£529	-£5,987
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£178	0.025	£687	-£6,979
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£58	0.019	£445	-£2,981

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£11	0.014	£285	-£804
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£60	0.023	£410	£2,541
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£44	0.022	£405	£1,959
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£92	0.017	£245	£5,463
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£179	0.019	£549	-£9,663
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£91	0.019	£463	-£4,889
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£24	0.011	£189	£2,246
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£57	0.021	£469	-£2,790
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£11	0.015	£284	£771
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£42	0.011	£186	£3,719

Table 91: Optimistic Metformin Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£96**	**0.043**	**£960**	**-£2,226**
Single Subgroups				
IMD 1 (least deprived)	-£50	0.043	£908	-£1,171
IMD 2	-£8	0.043	£865	-£182
IMD 3	-£103	0.045	£1,000	-£2,305
IMD 4	-£169	0.045	£1,069	-£3,750
IMD 5 (most deprived)	-£229	0.041	£1,056	-£5,529
Age < 40	-£98	0.032	£747	-£3,027
Age 40-59	-£173	0.043	£1,036	-£4,010

Age 60-74	-£83	0.057	£1,214	-£1,459
Age >= 75	£122	0.044	£761	£2,757
BMI < 25 (White) OR BMI < 23 (BME)	-£69	0.041	£886	-£1,684
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£16	0.043	£875	-£369
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£147	0.044	£1,032	-£3,328
BMI >= 35 (White OR BME)	-£344	0.048	£1,303	-£7,170
Ethnicity White	-£71	0.043	£938	-£1,646
Ethnicity BME	-£302	0.042	£1,149	-£7,118
Sex Male	£43	0.041	£786	£1,048
Sex Female	-£266	0.045	£1,172	-£5,879
HbA1c 6-6.1	-£535	0.060	£1,745	-£8,843
HbA1c 6.2-6.4	-£1,081	0.078	£2,646	-£13,819
FPG 5.5-5.9	£202	0.032	£446	£6,224
FPG 6-6.4	-£173	0.047	£1,121	-£3,649
FPG 6.5-6.9	-£522	0.059	£1,699	-£8,871
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£800**	**0.069**	**£2,182**	**-£11,581**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£788*	*0.082*	*£2,424*	*-£9,628*
1) HbA1c 6-6.4, BMI >=35	-£1,023	0.068	£2,379	-£15,102
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,126	0.078	£2,679	-£14,487
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£512	0.059	£1,682	-£8,744
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£474	0.089	£2,258	-£5,309
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£1	0.066	£1,322	£13
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,356	0.074	£2,835	-£18,332
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£824	0.059	£2,010	-£13,894

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,110	0.074	£2,595	-£14,937
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£565	0.062	£1,807	-£9,108
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£91**	**0.037**	**£643**	**£2,481**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£507*	*0.072*	*£1,945*	*-£7,049*
1) FPG 5.5-6.9, BMI >=35	-£203	0.045	£1,102	-£4,512
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£633	0.056	£1,746	-£11,385
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£252	0.048	£1,212	-£5,257
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£110	0.035	£582	£3,175
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£34	0.066	£1,362	-£516
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£27	0.054	£1,117	-£499
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£182	0.044	£693	£4,165
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£583	0.047	£1,519	-£12,443
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£119	0.044	£996	-£2,704
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£282	0.027	£252	£10,562
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£466	0.055	£1,564	-£8,485
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£30	0.043	£899	-£699
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£312	0.028	£246	£11,180

Table 92: Conservative Metformin Intervention vs Control, assuming that HbA1c effect is neither stratified nor persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**£182**	**0.026**	**£342**	**£6,957**
Single Subgroups				
IMD 1 (least deprived)	£224	0.026	£296	£8,607
IMD 2	£231	0.026	£288	£8,906
IMD 3	£204	0.027	£329	£7,657
IMD 4	£129	0.028	£428	£4,630
IMD 5 (most deprived)	£83	0.025	£414	£3,358
Age < 40	£245	0.019	£140	£12,710
Age 40-59	£149	0.026	£364	£5,803
Age 60-74	£144	0.035	£553	£4,135
Age >= 75	£200	0.028	£366	£7,074
BMI < 25 (White) OR BMI < 23 (BME)	£216	0.025	£278	£8,740
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£237	0.026	£286	£9,051
BMI 30–34 (White) OR BMI 27.5-34 (BME)	£136	0.027	£396	£5,103
BMI >= 35 (White OR BME)	£4	0.030	£587	£134
Ethnicity White	£197	0.026	£330	£7,469
Ethnicity BME	£60	0.025	£438	£2,416
Sex Male	£281	0.025	£223	£11,155
Sex Female	£62	0.027	£487	£2,266
HbA1c 6-6.1	-£132	0.036	£847	-£3,681
HbA1c 6.2-6.4	-£562	0.049	£1,544	-£11,454
FPG 5.5-5.9	£398	0.019	-£13	£20,651
FPG 6-6.4	£134	0.029	£438	£4,683
FPG 6.5-6.9	-£100	0.038	£860	-£2,619
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£341**	**0.042**	**£1,185**	**-£8,071**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£398*	*0.055*	*£1,498*	*-£7,223*
1) HbA1c 6-6.4, BMI >=35	-£497	0.041	£1,326	-£11,990
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£601	0.049	£1,586	-£12,204
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£136	0.034	£818	-£3,972
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£159	0.057	£1,304	-£2,779
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£157	0.041	£654	£3,878
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£741	0.045	£1,640	-£16,498
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£263	0.035	£966	-£7,502
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£577	0.047	£1,510	-£12,378
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£132	0.036	£854	-£3,658
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£320**	**0.022**	**£120**	**£14,546**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£269*	*0.052*	*£1,315*	*-£5,148*
1) FPG 5.5-6.9, BMI >=35	£107	0.027	£440	£3,904
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£185	0.038	£938	-£4,917
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£57	0.029	£517	£1,997
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£324	0.020	£73	£16,335
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£173	0.039	£600	£4,483
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£154	0.034	£522	£4,548
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£305	0.026	£221	£11,587
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£60	0.032	£691	-£1,906
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£194	0.026	£326	£7,464

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£489	0.016	-£170	£30,639
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	£45	0.027	£502	£1,645
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£286	0.027	£254	£10,599
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£488	0.017	-£155	£29,302

Table 93: Optimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£677**	**0.063**	**£1,943**	**-£10,689**
Single Subgroups				
IMD 1 (least deprived)	-£650	0.066	£1,967	-£9,862
IMD 2	-£637	0.064	£1,927	-£9,884
IMD 3	-£674	0.064	£1,958	-£10,500
IMD 4	-£729	0.064	£2,016	-£11,323
IMD 5 (most deprived)	-£727	0.056	£1,852	-£12,919
Age < 40	-£670	0.037	£1,406	-£18,212
Age 40-59	-£837	0.060	£2,040	-£13,911
Age 60-74	-£691	0.093	£2,546	-£7,445
Age >= 75	-£155	0.082	£1,802	-£1,887
BMI < 25 (White) OR BMI < 23 (BME)	-£726	0.065	£2,034	-£11,095
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£671	0.066	£2,000	-£10,107
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£668	0.061	£1,897	-£10,886
BMI >= 35 (White OR BME)	-£596	0.051	£1,620	-£11,632
Ethnicity White	-£656	0.064	£1,939	-£10,220
Ethnicity BME	-£851	0.056	£1,976	-£15,131

Sex Male	-£577	0.063	£1,833	-£9,196
Sex Female	-£797	0.064	£2,077	-£12,466
HbA1c 6-6.1	-£987	0.084	£2,668	-£11,739
HbA1c 6.2-6.4	-£1,517	0.113	£3,787	-£13,369
FPG 5.5-5.9	-£462	0.050	£1,460	-£9,263
FPG 6-6.4	-£866	0.077	£2,411	-£11,215
FPG 6.5-6.9	-£1,303	0.101	£3,324	-£12,898
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,244**	**0.098**	**£3,210**	**-£12,653**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£914*	*0.078*	*£2,478*	*-£11,689*
1) HbA1c 6-6.4, BMI >=35	-£928	0.065	£2,228	-£14,267
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,442	0.105	£3,542	-£13,733
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£930	0.078	£2,487	-£11,955
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,064	0.157	£4,209	-£6,766
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£554	0.106	£2,680	-£5,211
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,007	0.100	£4,015	-£19,980
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,339	0.077	£2,879	-£17,397
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,688	0.121	£4,112	-£13,923
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£1,083	0.092	£2,931	-£11,724
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£583**	**0.058**	**£1,740**	**-£10,079**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£740*	*0.077*	*£2,275*	*-£9,631*
1) FPG 5.5-6.9, BMI >=35	-£562	0.051	£1,572	-£11,118
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,233	0.095	£3,135	-£12,971
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£882	0.076	£2,401	-£11,609

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£478	0.050	£1,472	-£9,636
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£866	0.144	£3,748	-£6,010
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£648	0.114	£2,931	-£5,681
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£357	0.078	£1,917	-£4,578
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,822	0.091	£3,652	-£19,916
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,047	0.064	£2,330	-£16,327
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£488	0.040	£1,285	-£12,236
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,473	0.121	£3,899	-£12,145
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£899	0.081	£2,518	-£11,100
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£470	0.049	£1,441	-£9,663

Table 94: Conservative Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£327**	**0.040**	**£1,118**	**-£8,274**
Single Subgroups				
IMD 1 (least deprived)	-£323	0.041	£1,150	-£7,804
IMD 2	-£303	0.040	£1,106	-£7,538
IMD 3	-£320	0.040	£1,120	-£8,006
IMD 4	-£362	0.040	£1,169	-£8,984
IMD 5 (most deprived)	-£343	0.035	£1,042	-£9,793
Age < 40	-£309	0.022	£752	-£13,923
Age 40-59	-£426	0.037	£1,170	-£11,438

Age 60-74	-£343	0.058	£1,509	-£5,877
Age >= 75	-£31	0.054	£1,111	-£582
BMI < 25 (White) OR BMI < 23 (BME)	-£357	0.040	£1,164	-£8,842
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£321	0.042	£1,154	-£7,717
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£322	0.038	£1,084	-£8,459
BMI >= 35 (White OR BME)	-£287	0.033	£950	-£8,670
Ethnicity White	-£316	0.040	£1,120	-£7,845
Ethnicity BME	-£424	0.034	£1,102	-£12,492
Sex Male	-£260	0.039	£1,047	-£6,620
Sex Female	-£408	0.040	£1,204	-£10,253
HbA1c 6-6.1	-£488	0.050	£1,491	-£9,735
HbA1c 6.2-6.4	-£886	0.073	£2,347	-£12,119
FPG 5.5-5.9	-£194	0.031	£821	-£6,204
FPG 6-6.4	-£456	0.048	£1,421	-£9,465
FPG 6.5-6.9	-£697	0.065	£2,001	-£10,701
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£681**	**0.061**	**£1,905**	**-£11,113**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£482*	*0.054*	*£1,562*	*-£8,931*
1) HbA1c 6-6.4, BMI >=35	-£476	0.042	£1,312	-£11,392
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£844	0.066	£2,168	-£12,750
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£454	0.046	£1,383	-£9,763
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£600	0.103	£2,658	-£5,834
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£247	0.065	£1,546	-£3,801
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,189	0.063	£2,454	-£18,782
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£684	0.046	£1,606	-£14,830

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£995	0.078	£2,561	-£12,710
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£551	0.054	£1,633	-£10,197
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£271**	**0.036**	**£997**	**-£7,480**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£366*	*0.058*	*£1,523*	*-£6,329*
1) FPG 5.5-6.9, BMI >=35	-£267	0.033	£923	-£8,155
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£630	0.061	£1,853	-£10,304
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£457	0.047	£1,390	-£9,804
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£206	0.031	£824	-£6,669
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£468	0.093	£2,322	-£5,043
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£344	0.073	£1,796	-£4,742
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£134	0.051	£1,152	-£2,642
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£974	0.057	£2,120	-£16,991
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£565	0.039	£1,350	-£14,395
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£201	0.024	£687	-£8,270
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£796	0.082	£2,429	-£9,748
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£464	0.050	£1,471	-£9,207
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£202	0.030	£804	-£6,704

Table 95: Pessimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£14**	**0.017**	**£349**	**-£844**
Single Subgroups				
IMD 1 (least deprived)	-£6	0.017	£354	-£358
IMD 2	-£5	0.017	£343	-£292
IMD 3	-£20	0.018	£374	-£1,132
IMD 4	-£29	0.017	£374	-£1,697
IMD 5 (most deprived)	-£21	0.015	£311	-£1,428
Age < 40	-£1	0.010	£193	-£100
Age 40-59	-£57	0.016	£371	-£3,634
Age 60-74	-£21	0.024	£502	-£872
Age >= 75	£101	0.024	£379	£4,210
BMI < 25 (White) OR BMI < 23 (BME)	-£17	0.016	£346	-£1,039
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£9	0.018	£359	-£518
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£12	0.016	£337	-£759
BMI >= 35 (White OR BME)	-£29	0.016	£350	-£1,818
Ethnicity White	-£8	0.017	£350	-£488
Ethnicity BME	-£63	0.014	£346	-£4,454
Sex Male	£24	0.016	£304	£1,436
Sex Female	-£60	0.017	£404	-£3,475
HbA1c 6-6.1	-£70	0.020	£473	-£3,471
HbA1c 6.2-6.4	-£268	0.032	£909	-£8,339
FPG 5.5-5.9	£42	0.013	£226	£3,107
FPG 6-6.4	-£74	0.020	£483	-£3,596
FPG 6.5-6.9	-£196	0.027	£733	-£7,284
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£166**	**0.026**	**£684**	**-£6,388**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£63*	*0.025*	*£555*	*-£2,551*
1) HbA1c 6-6.4, BMI >=35	-£110	0.019	£490	-£5,761
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£243	0.028	£811	-£8,569
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£55	0.019	£440	-£2,860
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£146	0.045	£1,047	-£3,234
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£31	0.027	£507	£1,154
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£419	0.028	£985	-£14,825
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£142	0.018	£506	-£7,791
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£299	0.034	£984	-£8,714
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£84	0.021	£494	-£4,087
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£7**	**0.015**	**£301**	**£467**
FPG 6.5-6.9, BMI >=35, Age >= 60	*£10*	*0.031*	*£615*	*£310*
1) FPG 5.5-6.9, BMI >=35	-£23	0.016	£343	-£1,421
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£169	0.024	£651	-£7,014
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£60	0.020	£465	-£2,980
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£33	0.013	£227	£2,554
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£70	0.036	£796	-£1,922
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£12	0.030	£618	-£407
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£69	0.021	£354	£3,279
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£340	0.024	£812	-£14,445
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£123	0.017	£455	-£7,435

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£46	0.010	£163	£4,423
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£294	0.030	£888	-£9,893
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£87	0.020	£493	-£4,305
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£47	0.012	£202	£3,793

Table 96: Optimistic Metformin Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£79**	**0.035**	**£775**	**-£2,275**
Single Subgroups				
IMD 1 (least deprived)	-£14	0.034	£689	-£407
IMD 2	£12	0.031	£606	£401
IMD 3	-£76	0.035	£780	-£2,148
IMD 4	-£170	0.038	£935	-£4,433
IMD 5 (most deprived)	-£231	0.039	£1,006	-£5,956
Age < 40	-£194	0.037	£934	-£5,233
Age 40-59	-£229	0.045	£1,139	-£5,034
Age 60-74	£122	0.032	£516	£3,825
Age >= 75	£280	0.001	-£265	£374,855
BMI < 25 (White) OR BMI < 23 (BME)	£414	0.010	-£205	£39,652
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£20	0.030	£582	£651
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£369	0.049	£1,349	-£7,517
BMI >= 35 (White OR BME)	-£1,021	0.081	£2,637	-£12,636
Ethnicity White	-£51	0.034	£725	-£1,515
Ethnicity BME	-£310	0.044	£1,183	-£7,110

Sex Male	-£35	0.038	£797	-£915
Sex Female	-£133	0.031	£747	-£4,317
HbA1c 6-6.1	-£281	0.037	£1,023	-£7,560
HbA1c 6.2-6.4	-£1,234	0.069	£2,604	-£18,007
FPG 5.5-5.9	£134	0.029	£456	£4,529
FPG 6-6.4	-£730	0.066	£2,041	-£11,139
FPG 6.5-6.9	-£1,834	0.114	£4,106	-£16,145
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£742**	**0.052**	**£1,788**	**-£14,178**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,056*	*0.086*	*£2,784*	*-£12,228*
1) HbA1c 6-6.4, BMI >=35	-£2,167	0.119	£4,541	-£18,262
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,819	0.094	£3,707	-£19,275
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£581	0.055	£1,673	-£10,655
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£64	0.029	£650	-£2,178
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£255	0.019	£120	£13,585
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,793	0.083	£3,460	-£21,530
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£567	0.045	£1,472	-£12,534
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£168	0.018	£525	-£9,380
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	£228	0.012	£19	£18,439
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£131**	**0.041**	**£942**	**-£3,223**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,309*	*0.134*	*£3,995*	*-£9,749*
1) FPG 5.5-6.9, BMI >=35	-£1,148	0.089	£2,935	-£12,845
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,063	0.130	£4,666	-£15,846
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,065	0.082	£2,702	-£13,016

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£117	0.041	£929	-£2,883
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£179	0.045	£1,073	-£3,996
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£95	0.031	£525	£3,065
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£327	0.017	£8	£19,527
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,299	0.119	£4,671	-£19,393
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£860	0.070	£2,252	-£12,357
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£152	0.031	£463	£4,934
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£423	0.043	£1,278	-£9,885
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£109	0.023	£343	£4,826
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£557	0.010	-£360	£56,642

Table 97: Conservative Metformin Intervention vs Control, assuming that HbA1c effect is stratified but not persistent: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**£179**	**0.021**	**£248**	**£8,387**
Single Subgroups				
IMD 1 (least deprived)	£222	0.020	£185	£10,898
IMD 2	£239	0.019	£138	£12,668
IMD 3	£184	0.022	£255	£8,389
IMD 4	£120	0.024	£357	£5,022
IMD 5 (most deprived)	£77	0.024	£400	£3,228
Age < 40	£163	0.023	£297	£7,093
Age 40-59	£102	0.028	£451	£3,689

Age 60-74	£259	0.020	£132	£13,262
Age >= 75	£295	0.000	-£288	£787,487
BMI < 25 (White) OR BMI < 23 (BME)	£500	0.006	-£378	£82,084
BMI 25-29 (White) OR BMI 23-27.4 (BME)	£248	0.018	£117	£13,601
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£10	0.030	£611	-£349
BMI >= 35 (White OR BME)	-£451	0.051	£1,475	-£8,802
Ethnicity White	£196	0.021	£217	£9,489
Ethnicity BME	£33	0.027	£500	£1,243
Sex Male	£223	0.023	£244	£9,549
Sex Female	£125	0.019	£251	£6,647
HbA1c 6-6.1	-£7	0.022	£446	-£301
HbA1c 6.2-6.4	-£693	0.044	£1,578	-£15,648
FPG 5.5-5.9	£360	0.018	-£6	£20,357
FPG 6-6.4	-£255	0.041	£1,073	-£6,231
FPG 6.5-6.9	-£1,015	0.072	£2,448	-£14,178
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£339**	**0.033**	**£994**	**-£10,336**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£550*	*0.056*	*£1,660*	*-£9,896*
1) HbA1c 6-6.4, BMI >=35	-£1,297	0.076	£2,821	-£17,032
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,068	0.062	£2,301	-£17,317
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£203	0.032	£849	-£6,288
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£76	0.018	£292	£4,113
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£321	0.011	-£96	£28,590
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,043	0.053	£2,101	-£19,698
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£170	0.027	£714	-£6,265

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	£0	0.011	£220	£40
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	£326	0.007	-£192	£48,683
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**£173**	**0.025**	**£323**	**£6,970**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£769*	*0.091*	*£2,587*	*-£8,456*
1) FPG 5.5-6.9, BMI >=35	-£509	0.057	£1,642	-£8,993
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,137	0.081	£2,755	-£14,051
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£496	0.052	£1,530	-£9,587
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	£194	0.024	£287	£8,065
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£109	0.024	£376	£4,486
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£233	0.020	£160	£11,867
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£390	0.010	-£189	£38,873
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,299	0.074	£2,772	-£17,650
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£302	0.042	£1,140	-£7,196
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	£420	0.018	-£55	£23,004
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£124	0.024	£601	-£5,219
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	£329	0.014	-£50	£23,586
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	£639	0.006	-£524	£111,364

Table 98: Optimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£4,434**	**0.181**	**£8,048**	**-£24,531**
Single Subgroups				
IMD 1 (least deprived)	-£3,949	0.185	£7,640	-£21,396
IMD 2	-£3,950	0.178	£7,515	-£22,164
IMD 3	-£4,326	0.182	£7,961	-£23,803
IMD 4	-£4,771	0.186	£8,493	-£25,641
IMD 5 (most deprived)	-£5,622	0.174	£9,092	-£32,399
Age < 40	-£8,206	0.191	£12,025	-£42,967
Age 40-59	-£4,396	0.197	£8,334	-£22,325
Age 60-74	-£1,738	0.183	£5,406	-£9,473
Age >= 75	-£238	0.097	£2,172	-£2,464
BMI < 25 (White) OR BMI < 23 (BME)	-£5,066	0.177	£8,597	-£28,692
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£4,012	0.182	£7,651	-£22,057
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£4,188	0.181	£7,805	-£23,153
BMI >= 35 (White OR BME)	-£4,923	0.187	£8,658	-£26,360
Ethnicity White	-£4,179	0.179	£7,756	-£23,363
Ethnicity BME	-£6,535	0.196	£10,457	-£33,332
Sex Male	-£4,157	0.184	£7,840	-£22,575
Sex Female	-£4,769	0.177	£8,299	-£27,015
HbA1c 6-6.1	-£5,484	0.220	£9,881	-£24,943
HbA1c 6.2-6.4	-£5,825	0.182	£9,459	-£32,061
FPG 5.5-5.9	-£3,885	0.169	£7,269	-£22,952
FPG 6-6.4	-£4,520	0.193	£8,375	-£23,452
FPG 6.5-6.9	-£4,853	0.193	£8,721	-£25,090
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£5,650**	**0.201**	**£9,678**	**-£28,058**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£2,639*	*0.162*	*£5,875*	*-£16,310*
1) HbA1c 6-6.4, BMI >=35	-£5,889	0.190	£9,687	-£31,009
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£5,463	0.181	£9,080	-£30,213
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,994	0.215	£9,290	-£23,251
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,865	0.185	£5,572	-£10,060
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,367	0.212	£5,615	-£6,438
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£8,301	0.189	£12,077	-£43,978
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£7,802	0.240	£12,596	-£32,547
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£6,707	0.176	£10,218	-£38,202
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£6,294	0.220	£10,702	-£28,561
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£4,064**	**0.175**	**£7,572**	**-£23,172**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£2,159*	*0.135*	*£4,855*	*-£16,020*
1) FPG 5.5-6.9, BMI >=35	-£4,697	0.188	£8,449	-£25,037
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,483	0.197	£8,421	-£22,771
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,370	0.190	£8,177	-£22,960
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,743	0.170	£7,141	-£22,039
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,316	0.165	£4,614	-£7,979
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,200	0.161	£4,416	-£7,462
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£847	0.139	£3,633	-£6,079
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£6,873	0.203	£10,929	-£33,898
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,887	0.218	£10,241	-£27,044

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,807	0.184	£8,487	-£26,119
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£5,429	0.187	£9,177	-£28,967
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£5,070	0.180	£8,671	-£28,156
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£4,311	0.164	£7,600	-£26,218

Table 99: Conservative Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£3,166**	**0.129**	**£5,745**	**-£24,554**
Single Subgroups				
IMD 1 (least deprived)	-£2,813	0.132	£5,447	-£21,356
IMD 2	-£2,801	0.128	£5,368	-£21,822
IMD 3	-£3,158	0.129	£5,741	-£24,443
IMD 4	-£3,427	0.132	£6,073	-£25,905
IMD 5 (most deprived)	-£3,996	0.122	£6,445	-£32,627
Age < 40	-£5,895	0.136	£8,613	-£43,371
Age 40-59	-£3,168	0.140	£5,975	-£22,576
Age 60-74	-£1,175	0.131	£3,805	-£8,938
Age >= 75	-£109	0.069	£1,492	-£1,579
BMI < 25 (White) OR BMI < 23 (BME)	-£3,608	0.126	£6,119	-£28,735
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£2,867	0.128	£5,435	-£22,331
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£3,008	0.130	£5,608	-£23,135
BMI >= 35 (White OR BME)	-£3,501	0.137	£6,243	-£25,536
Ethnicity White	-£2,977	0.128	£5,528	-£23,337
Ethnicity BME	-£4,726	0.140	£7,533	-£33,670

Sex Male	-£2,961	0.132	£5,609	-£22,375
Sex Female	-£3,414	0.125	£5,910	-£27,358
HbA1c 6-6.1	-£3,938	0.157	£7,086	-£25,016
HbA1c 6.2-6.4	-£4,165	0.127	£6,707	-£32,766
FPG 5.5-5.9	-£2,774	0.121	£5,186	-£22,996
FPG 6-6.4	-£3,221	0.137	£5,970	-£23,433
FPG 6.5-6.9	-£3,471	0.144	£6,356	-£24,068
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£4,048**	**0.143**	**£6,903**	**-£28,358**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,777*	*0.118*	*£4,131*	*-£15,098*
1) HbA1c 6-6.4, BMI >=35	-£4,171	0.138	£6,927	-£30,275
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,919	0.125	£6,422	-£31,312
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,554	0.155	£6,651	-£22,949
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,272	0.131	£3,887	-£9,725
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£942	0.151	£3,952	-£6,257
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£6,004	0.130	£8,609	-£46,109
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,683	0.172	£9,119	-£33,076
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£4,787	0.124	£7,261	-£38,694
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£4,513	0.156	£7,636	-£28,906
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£2,900**	**0.125**	**£5,405**	**-£23,164**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,434*	*0.117*	*£3,767*	*-£12,290*
1) FPG 5.5-6.9, BMI >=35	-£3,341	0.138	£6,107	-£24,148
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,324	0.156	£6,450	-£21,268
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,105	0.136	£5,825	-£22,828

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,712	0.122	£5,147	-£22,274
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£777	0.115	£3,071	-£6,770
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£832	0.114	£3,109	-£7,303
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£566	0.100	£2,565	-£5,666
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,069	0.140	£7,875	-£36,139
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,234	0.156	£7,357	-£27,120
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,444	0.128	£5,995	-£27,004
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£3,711	0.143	£6,573	-£25,941
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£3,629	0.125	£6,134	-£28,966
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£3,048	0.118	£5,400	-£25,913

Table 100: Pessimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£1,443**	**0.062**	**£2,677**	**-£23,378**
Single Subgroups				
IMD 1 (least deprived)	-£1,260	0.062	£2,501	-£20,304
IMD 2	-£1,258	0.062	£2,501	-£20,241
IMD 3	-£1,390	0.063	£2,654	-£21,996
IMD 4	-£1,599	0.064	£2,875	-£25,053
IMD 5 (most deprived)	-£1,871	0.057	£3,017	-£32,673
Age < 40	-£2,749	0.064	£4,026	-£43,034
Age 40-59	-£1,464	0.068	£2,821	-£21,583

Age 60-74	-£472	0.063	£1,723	-£7,546
Age >= 75	£56	0.035	£635	£1,630
BMI < 25 (White) OR BMI < 23 (BME)	-£1,661	0.060	£2,868	-£27,522
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£1,292	0.061	£2,517	-£21,090
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£1,352	0.063	£2,606	-£21,573
BMI >= 35 (White OR BME)	-£1,644	0.065	£2,940	-£25,365
Ethnicity White	-£1,346	0.061	£2,570	-£21,985
Ethnicity BME	-£2,240	0.066	£3,556	-£34,064
Sex Male	-£1,326	0.063	£2,592	-£20,948
Sex Female	-£1,585	0.060	£2,780	-£26,514
HbA1c 6-6.1	-£1,826	0.075	£3,327	-£24,342
HbA1c 6.2-6.4	-£1,911	0.060	£3,115	-£31,733
FPG 5.5-5.9	-£1,252	0.057	£2,400	-£21,802
FPG 6-6.4	-£1,481	0.066	£2,802	-£22,431
FPG 6.5-6.9	-£1,526	0.068	£2,885	-£22,457
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,868**	**0.068**	**£3,225**	**-£27,534**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£801*	*0.058*	*£1,965*	*-£13,753*
1) HbA1c 6-6.4, BMI >=35	-£1,954	0.063	£3,216	-£30,971
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,829	0.060	£3,029	-£30,460
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,653	0.074	£3,142	-£22,204
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£502	0.063	£1,769	-£7,918
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£362	0.073	£1,816	-£4,985
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,760	0.061	£3,980	-£45,249
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,693	0.081	£4,321	-£33,076

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,194	0.058	£3,357	-£37,768
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£2,096	0.075	£3,605	-£27,779
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£1,314**	**0.060**	**£2,508**	**-£22,007**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£570*	*0.065*	*£1,861*	*-£8,828*
1) FPG 5.5-6.9, BMI >=35	-£1,566	0.066	£2,876	-£23,901
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,370	0.078	£2,930	-£17,561
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,403	0.065	£2,709	-£21,486
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,204	0.057	£2,354	-£20,942
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£309	0.052	£1,346	-£5,950
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£280	0.055	£1,384	-£5,066
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£151	0.048	£1,113	-£3,153
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,229	0.057	£3,378	-£38,817
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,976	0.074	£3,450	-£26,819
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,576	0.061	£2,801	-£25,713
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,651	0.065	£2,945	-£25,502
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,707	0.062	£2,945	-£27,583
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,401	0.056	£2,517	-£25,089

Table 101: Optimistic Metformin Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£2,841**	**0.127**	**£5,383**	**-£22,349**
Single Subgroups				
IMD 1 (least deprived)	-£2,463	0.130	£5,054	-£19,014
IMD 2	-£2,465	0.126	£4,986	-£19,559
IMD 3	-£2,778	0.129	£5,367	-£21,454
IMD 4	-£3,124	0.129	£5,709	-£24,172
IMD 5 (most deprived)	-£3,729	0.122	£6,165	-£30,622
Age < 40	-£5,529	0.135	£8,225	-£41,026
Age 40-59	-£2,785	0.138	£5,545	-£20,184
Age 60-74	-£898	0.128	£3,453	-£7,029
Age >= 75	£14	0.071	£1,404	£197
BMI < 25 (White) OR BMI < 23 (BME)	-£3,322	0.126	£5,840	-£26,394
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£2,522	0.128	£5,073	-£19,772
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£2,665	0.126	£5,194	-£21,076
BMI >= 35 (White OR BME)	-£3,179	0.130	£5,785	-£24,402
Ethnicity White	-£2,649	0.126	£5,163	-£21,074
Ethnicity BME	-£4,421	0.139	£7,194	-£31,877
Sex Male	-£2,592	0.130	£5,186	-£19,985
Sex Female	-£3,142	0.124	£5,620	-£25,354
HbA1c 6-6.1	-£3,804	0.154	£6,891	-£24,644
HbA1c 6.2-6.4	-£4,167	0.126	£6,689	-£33,045
FPG 5.5-5.9	-£2,330	0.120	£4,721	-£19,492
FPG 6-6.4	-£2,926	0.135	£5,620	-£21,713
FPG 6.5-6.9	-£3,258	0.136	£5,970	-£24,020
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£3,980**	**0.141**	**£6,794**	**-£28,295**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,708*	*0.117*	*£4,054*	*-£14,562*
1) HbA1c 6-6.4, BMI >=35	-£4,048	0.131	£6,673	-£30,848
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,925	0.122	£6,372	-£32,078
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,388	0.150	£6,391	-£22,565
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,198	0.131	£3,819	-£9,146
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£709	0.150	£3,710	-£4,727
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£6,001	0.130	£8,596	-£46,257
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,608	0.169	£8,989	-£33,173
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£4,869	0.124	£7,356	-£39,145
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£4,445	0.155	£7,553	-£28,605
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£2,499**	**0.124**	**£4,969**	**-£20,236**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,216*	*0.103*	*£3,280*	*-£11,776*
1) FPG 5.5-6.9, BMI >=35	-£2,984	0.132	£5,617	-£22,661
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,059	0.141	£5,887	-£21,632
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,840	0.132	£5,485	-£21,478
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,249	0.120	£4,647	-£18,767
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£604	0.114	£2,880	-£5,310
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£537	0.112	£2,786	-£4,780
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£261	0.099	£2,231	-£2,644
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,753	0.126	£7,280	-£37,610
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,883	0.153	£6,934	-£25,452

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,918	0.129	£5,491	-£22,682
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£3,625	0.148	£6,585	-£24,496
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£3,343	0.126	£5,869	-£26,457
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,623	0.118	£4,982	-£22,227

Table 102: Conservative Metformin Intervention vs Control, assuming that HbA1c effect is persistent but not stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£1,882**	**0.090**	**£3,677**	**-£20,962**
Single Subgroups				
IMD 1 (least deprived)	-£1,618	0.091	£3,440	-£17,751
IMD 2	-£1,598	0.089	£3,375	-£17,986
IMD 3	-£1,819	0.091	£3,642	-£19,961
IMD 4	-£2,125	0.093	£3,980	-£22,925
IMD 5 (most deprived)	-£2,503	0.085	£4,211	-£29,313
Age < 40	-£3,744	0.095	£5,639	-£39,518
Age 40-59	-£1,868	0.097	£3,810	-£19,246
Age 60-74	-£504	0.091	£2,327	-£5,524
Age >= 75	£109	0.050	£895	£2,178
BMI < 25 (White) OR BMI < 23 (BME)	-£2,190	0.089	£3,969	-£24,620
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£1,662	0.089	£3,448	-£18,609
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£1,776	0.090	£3,582	-£19,659
BMI >= 35 (White OR BME)	-£2,141	0.092	£3,990	-£23,168
Ethnicity White	-£1,742	0.089	£3,517	-£19,634
Ethnicity BME	-£3,030	0.098	£4,995	-£30,826

Sex Male	-£1,696	0.091	£3,519	-£18,598
Sex Female	-£2,107	0.088	£3,868	-£23,935
HbA1c 6-6.1	-£2,626	0.109	£4,812	-£24,023
HbA1c 6.2-6.4	-£2,890	0.087	£4,627	-£33,291
FPG 5.5-5.9	-£1,493	0.084	£3,169	-£17,823
FPG 6-6.4	-£1,944	0.095	£3,840	-£20,510
FPG 6.5-6.9	-£2,262	0.100	£4,267	-£22,566
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£2,755**	**0.098**	**£4,723**	**-£27,991**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,160*	*0.084*	*£2,833*	*-£13,871*
1) HbA1c 6-6.4, BMI >=35	-£2,826	0.091	£4,649	-£31,009
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,732	0.085	£4,437	-£32,051
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,378	0.108	£4,546	-£21,931
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£757	0.090	£2,566	-£8,367
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£406	0.107	£2,546	-£3,795
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,214	0.088	£5,974	-£47,871
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,939	0.117	£6,281	-£33,639
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£3,357	0.086	£5,077	-£39,050
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£3,028	0.110	£5,226	-£27,559
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£1,624**	**0.087**	**£3,360**	**-£18,704**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£892*	*0.081*	*£2,515*	*-£10,994*
1) FPG 5.5-6.9, BMI >=35	-£1,985	0.093	£3,845	-£21,350
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,204	0.103	£4,261	-£21,442
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,929	0.094	£3,806	-£20,557

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,436	0.085	£3,137	-£16,891
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£333	0.083	£1,985	-£4,038
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£267	0.079	£1,856	-£3,358
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£47	0.068	£1,413	-£686
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,392	0.092	£5,229	-£36,949
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,603	0.107	£4,737	-£24,383
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,916	0.090	£3,711	-£21,343
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,262	0.113	£4,521	-£20,032
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,161	0.089	£3,933	-£24,376
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,681	0.082	£3,328	-£20,399

Table 103: Optimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£3,490**	**0.167**	**£6,835**	**-£20,865**
Single Subgroups				
IMD 1 (least deprived)	-£3,289	0.180	£6,895	-£18,241
IMD 2	-£3,209	0.172	£6,640	-£18,705
IMD 3	-£3,444	0.171	£6,862	-£20,148
IMD 4	-£3,693	0.165	£6,989	-£22,413
IMD 5 (most deprived)	-£4,053	0.143	£6,907	-£28,405
Age < 40	-£5,584	0.131	£8,209	-£42,558
Age 40-59	-£3,849	0.182	£7,487	-£21,161

Age 60-74	-£1,814	0.209	£5,989	-£8,693
Age >= 75	-£297	0.130	£2,889	-£2,293
BMI < 25 (White) OR BMI < 23 (BME)	-£4,428	0.185	£8,134	-£23,889
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£3,458	0.182	£7,091	-£19,030
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£3,081	0.152	£6,112	-£20,324
BMI >= 35 (White OR BME)	-£2,181	0.105	£4,272	-£20,851
Ethnicity White	-£3,305	0.168	£6,656	-£19,729
Ethnicity BME	-£5,018	0.165	£8,316	-£30,431
Sex Male	-£3,359	0.172	£6,797	-£19,542
Sex Female	-£3,648	0.162	£6,880	-£22,572
HbA1c 6-6.1	-£4,197	0.200	£8,200	-£20,965
HbA1c 6.2-6.4	-£4,835	0.182	£8,476	-£26,557
FPG 5.5-5.9	-£3,065	0.156	£6,180	-£19,686
FPG 6-6.4	-£4,072	0.200	£8,081	-£20,318
FPG 6.5-6.9	-£4,941	0.232	£9,579	-£21,310
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£4,506**	**0.191**	**£8,334**	**-£23,546**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,565*	*0.110*	*£3,757*	*-£14,285*
1) HbA1c 6-6.4, BMI >=35	-£2,625	0.106	£4,749	-£24,707
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,253	0.162	£7,489	-£26,288
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,617	0.178	£7,179	-£20,314
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£2,225	0.245	£7,122	-£9,090
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,540	0.246	£6,468	-£6,251
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£7,201	0.173	£10,657	-£41,668
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£6,211	0.205	£10,313	-£30,282

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£6,139	0.203	£10,197	-£30,259
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£5,220	0.223	£9,676	-£23,434
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£3,360**	**0.168**	**£6,729**	**-£19,941**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,491*	*0.119*	*£3,873*	*-£12,518*
1) FPG 5.5-6.9, BMI >=35	-£2,165	0.108	£4,321	-£20,077
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,538	0.222	£8,975	-£20,459
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,718	0.182	£7,356	-£20,433
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,699	0.140	£5,508	-£19,221
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£2,029	0.286	£7,757	-£7,083
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,602	0.236	£6,326	-£6,781
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,039	0.175	£4,537	-£5,939
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£7,546	0.253	£12,601	-£29,855
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,781	0.219	£10,154	-£26,436
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,945	0.164	£7,219	-£24,100
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£6,903	0.291	£12,719	-£23,734
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£5,379	0.231	£10,008	-£23,234
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£3,909	0.174	£7,385	-£22,491

Table 104: Conservative Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£2,446**	**0.119**	**£4,826**	**-£20,562**
Single Subgroups				
IMD 1 (least deprived)	-£2,305	0.129	£4,878	-£17,915
IMD 2	-£2,235	0.122	£4,683	-£18,250
IMD 3	-£2,418	0.121	£4,828	-£20,067
IMD 4	-£2,612	0.117	£4,956	-£22,287
IMD 5 (most deprived)	-£2,840	0.101	£4,860	-£28,126
Age < 40	-£3,927	0.093	£5,781	-£42,370
Age 40-59	-£2,731	0.129	£5,306	-£21,218
Age 60-74	-£1,230	0.150	£4,228	-£8,205
Age >= 75	-£149	0.093	£2,011	-£1,606
BMI < 25 (White) OR BMI < 23 (BME)	-£3,119	0.132	£5,764	-£23,589
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£2,431	0.129	£5,010	-£18,851
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£2,145	0.108	£4,302	-£19,902
BMI >= 35 (White OR BME)	-£1,492	0.074	£2,979	-£20,079
Ethnicity White	-£2,310	0.119	£4,696	-£19,357
Ethnicity BME	-£3,574	0.116	£5,895	-£30,813
Sex Male	-£2,353	0.123	£4,805	-£19,194
Sex Female	-£2,559	0.115	£4,850	-£22,338
HbA1c 6-6.1	-£2,934	0.143	£5,796	-£20,501
HbA1c 6.2-6.4	-£3,435	0.128	£5,994	-£26,842
FPG 5.5-5.9	-£2,141	0.111	£4,358	-£19,313
FPG 6-6.4	-£2,881	0.143	£5,737	-£20,172
FPG 6.5-6.9	-£3,524	0.167	£6,864	-£21,107
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£3,176**	**0.136**	**£5,891**	**-£23,397**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,052*	*0.080*	*£2,647*	*-£13,191*
1) HbA1c 6-6.4, BMI >=35	-£1,802	0.076	£3,316	-£23,803
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,007	0.113	£5,271	-£26,561
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,493	0.126	£5,018	-£19,743
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,530	0.173	£4,983	-£8,859
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,061	0.177	£4,595	-£6,006
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,194	0.120	£7,591	-£43,331
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,382	0.146	£7,303	-£29,996
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£4,363	0.144	£7,237	-£30,363
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£3,674	0.160	£6,879	-£22,927
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£2,357**	**0.120**	**£4,758**	**-£19,636**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£1,044*	*0.095*	*£2,953*	*-£10,932*
1) FPG 5.5-6.9, BMI >=35	-£1,484	0.077	£3,015	-£19,397
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,256	0.160	£6,453	-£20,364
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£2,608	0.129	£5,197	-£20,148
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,869	0.100	£3,868	-£18,704
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,386	0.201	£5,411	-£6,886
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£1,119	0.170	£4,513	-£6,593
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£679	0.127	£3,210	-£5,366
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,506	0.182	£9,146	-£30,256
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,111	0.155	£7,216	-£26,481

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,785	0.115	£5,091	-£24,158
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£4,897	0.215	£9,189	-£22,819
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£3,862	0.164	£7,151	-£23,481
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,749	0.124	£5,233	-£22,128

Table 105: Pessimistic Intensive Lifestyle Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£1,064**	**0.056**	**£2,182**	**-£19,045**
Single Subgroups				
IMD 1 (least deprived)	-£1,012	0.060	£2,218	-£16,780
IMD 2	-£959	0.058	£2,120	-£16,527
IMD 3	-£1,042	0.057	£2,188	-£18,173
IMD 4	-£1,142	0.055	£2,239	-£20,825
IMD 5 (most deprived)	-£1,245	0.046	£2,174	-£26,828
Age < 40	-£1,741	0.043	£2,594	-£40,837
Age 40-59	-£1,215	0.060	£2,423	-£20,132
Age 60-74	-£495	0.070	£1,903	-£7,033
Age >= 75	£23	0.046	£903	£500
BMI < 25 (White) OR BMI < 23 (BME)	-£1,382	0.063	£2,634	-£22,079
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£1,061	0.060	£2,263	-£17,651
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£917	0.050	£1,927	-£18,164
BMI >= 35 (White OR BME)	-£611	0.036	£1,329	-£17,033
Ethnicity White	-£1,000	0.056	£2,124	-£17,785
Ethnicity BME	-£1,598	0.053	£2,659	-£30,112

Sex Male	-£1,010	0.057	£2,154	-£17,656
Sex Female	-£1,130	0.054	£2,215	-£20,821
HbA1c 6-6.1	-£1,310	0.067	£2,660	-£19,427
HbA1c 6.2-6.4	-£1,534	0.060	£2,726	-£25,745
FPG 5.5-5.9	-£922	0.052	£1,962	-£17,720
FPG 6-6.4	-£1,286	0.067	£2,618	-£19,314
FPG 6.5-6.9	-£1,563	0.075	£3,054	-£20,960
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£1,419**	**0.064**	**£2,692**	**-£22,300**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£374*	*0.038*	*£1,125*	*-£9,981*
1) HbA1c 6-6.4, BMI >=35	-£756	0.036	£1,467	-£21,275
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,344	0.052	£2,381	-£25,929
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,113	0.059	£2,300	-£18,760
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£637	0.081	£2,249	-£7,904
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£408	0.086	£2,124	-£4,750
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,398	0.055	£3,500	-£43,533
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,016	0.066	£3,338	-£30,480
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,945	0.068	£3,308	-£28,522
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£1,656	0.077	£3,188	-£21,615
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£1,027**	**0.056**	**£2,148**	**-£18,303**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£304*	*0.048*	*£1,259*	*-£6,378*
1) FPG 5.5-6.9, BMI >=35	-£608	0.037	£1,351	-£16,368
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,397	0.068	£2,761	-£20,472
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£1,146	0.060	£2,353	-£18,976

4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£790	0.046	£1,714	-£17,117
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£598	0.097	£2,538	-£6,164
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£435	0.080	£2,028	-£5,457
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£221	0.061	£1,433	-£3,653
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,468	0.075	£3,973	-£32,789
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,893	0.071	£3,309	-£26,755
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£1,228	0.054	£2,302	-£22,885
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£2,324	0.095	£4,219	-£24,525
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,759	0.078	£3,324	-£22,484
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£1,212	0.058	£2,376	-£20,809

Table 106: Optimistic Metformin Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£3,391**	**0.145**	**£6,295**	**-£23,356**
Single Subgroups				
IMD 1 (least deprived)	-£2,917	0.141	£5,743	-£20,641
IMD 2	-£2,842	0.132	£5,490	-£21,469
IMD 3	-£3,249	0.148	£6,201	-£22,014
IMD 4	-£3,856	0.153	£6,907	-£25,272
IMD 5 (most deprived)	-£4,567	0.163	£7,830	-£27,991
Age < 40	-£7,234	0.216	£11,562	-£33,424
Age 40-59	-£3,324	0.178	£6,879	-£18,705

Age 60-74	-£380	0.074	£1,856	-£5,154
Age >= 75	£273	0.002	-£237	£151,191
BMI < 25 (White) OR BMI < 23 (BME)	-£808	0.042	£1,658	-£19,008
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£2,861	0.124	£5,340	-£23,089
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£4,812	0.203	£8,865	-£23,742
BMI >= 35 (White OR BME)	-£8,583	0.350	£15,589	-£24,499
Ethnicity White	-£3,166	0.141	£5,991	-£22,415
Ethnicity BME	-£5,252	0.178	£8,811	-£29,515
Sex Male	-£3,446	0.164	£6,724	-£21,027
Sex Female	-£3,324	0.122	£5,773	-£27,151
HbA1c 6-6.1	-£3,139	0.120	£5,545	-£26,091
HbA1c 6.2-6.4	-£4,923	0.139	£7,698	-£35,468
FPG 5.5-5.9	-£3,135	0.140	£5,929	-£22,449
FPG 6-6.4	-£6,506	0.265	£11,802	-£24,566
FPG 6.5-6.9	-£10,079	0.401	£18,092	-£25,155
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£4,002**	**0.129**	**£6,587**	**-£30,966**
HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£2,545*	*0.152*	*£5,593*	*-£16,705*
1) HbA1c 6-6.4, BMI >=35	-£9,782	0.323	£16,238	-£30,309
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£6,677	0.189	£10,451	-£35,387
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,625	0.182	£8,257	-£25,464
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£372	0.042	£1,222	-£8,763
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£9	0.045	£883	£195
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£7,308	0.167	£10,643	-£43,830
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,703	0.149	£7,675	-£31,644

8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,450	0.032	£2,088	-£45,405
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£597	0.030	£1,193	-£20,048
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£4,142**	**0.177**	**£7,685**	**-£23,386**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£3,817*	*0.288*	*£9,579*	*-£13,246*
1) FPG 5.5-6.9, BMI >=35	-£9,803	0.405	£17,906	-£24,198
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£11,417	0.463	£20,671	-£24,673
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£7,932	0.326	£14,460	-£24,301
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,390	0.191	£8,217	-£22,936
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£729	0.093	£2,595	-£7,817
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£340	0.072	£1,782	-£4,713
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£107	0.040	£701	£2,646
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£13,027	0.446	£21,949	-£29,203
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£8,199	0.300	£14,209	-£27,284
10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£4,015	0.161	£7,227	-£25,000
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£4,278	0.128	£6,847	-£33,298
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£2,468	0.087	£4,208	-£28,376
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£788	0.047	£1,732	-£16,677

Table 107: Conservative Metformin Intervention vs Control, assuming that HbA1c effect is persistent and stratified: Full cost-effectiveness results for each subgroup. Discount Rate = 1.5%.

Subgroup	Incremental Costs (£)	Incremental QALYs	NMB (£)	ICER (£/QALY)
TOTAL	**-£2,427**	**0.103**	**£4,490**	**-£23,524**
Single Subgroups				
IMD 1 (least deprived)	-£2,075	0.100	£4,072	-£20,776
IMD 2	-£2,005	0.094	£3,883	-£21,352
IMD 3	-£2,315	0.105	£4,419	-£21,998
IMD 4	-£2,772	0.109	£4,961	-£25,327
IMD 5 (most deprived)	-£3,327	0.115	£5,636	-£28,822
Age < 40	-£5,363	0.154	£8,452	-£34,716
Age 40-59	-£2,342	0.126	£4,867	-£18,551
Age 60-74	-£138	0.052	£1,171	-£2,667
Age >= 75	£289	0.001	-£267	£256,749
BMI < 25 (White) OR BMI < 23 (BME)	-£415	0.030	£1,011	-£13,929
BMI 25-29 (White) OR BMI 23-27.4 (BME)	-£1,992	0.087	£3,730	-£22,933
BMI 30–34 (White) OR BMI 27.5-34 (BME)	-£3,501	0.143	£6,365	-£24,458
BMI >= 35 (White OR BME)	-£6,609	0.256	£11,722	-£25,852
Ethnicity White	-£2,257	0.100	£4,267	-£22,458
Ethnicity BME	-£3,831	0.125	£6,336	-£30,595
Sex Male	-£2,459	0.116	£4,788	-£21,111
Sex Female	-£2,387	0.087	£4,126	-£27,456
HbA1c 6-6.1	-£2,253	0.085	£3,953	-£26,516
HbA1c 6.2-6.4	-£3,605	0.095	£5,503	-£37,998
FPG 5.5-5.9	-£2,187	0.099	£4,171	-£22,059
FPG 6-6.4	-£4,861	0.189	£8,640	-£25,718
FPG 6.5-6.9	-£7,809	0.286	£13,522	-£27,341
Subgroup Combinations: HbA1c Defined				
HbA1c 6-6.4 Total	**-£2,908**	**0.090**	**£4,703**	**-£32,397**

HbA1c 6.2-6.4, BMI >=35, Age >= 60	*-£1,742*	*0.104*	*£3,820*	*-£16,770*
1) HbA1c 6-6.4, BMI >=35	-£7,465	0.230	£12,072	-£32,405
2) HbA1c 6.2-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£4,904	0.128	£7,462	-£38,341
3) HbA1c 6-6.1, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,370	0.127	£5,916	-£26,478
4) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£179	0.030	£777	-£5,971
5) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£129	0.031	£494	£4,146
6) HbA1c 6.2-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£5,326	0.111	£7,547	-£47,944
7) HbA1c 6-6.1, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£3,406	0.104	£5,484	-£32,781
8) HbA1c 6.2-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£958	0.021	£1,369	-£46,591
9) HbA1c 6-6.1, BMI <25 (White) OR BMI < 23 (BME)	-£301	0.021	£723	-£14,245
Subgroup Combinations: FPG Defined				
FPG 5.5-6.9 Total	**-£2,990**	**0.126**	**£5,511**	**-£23,730**
FPG 6.5-6.9, BMI >=35, Age >= 60	*-£2,795*	*0.206*	*£6,924*	*-£13,537*
1) FPG 5.5-6.9, BMI >=35	-£7,578	0.296	£13,501	-£25,590
2) FPG 6.5-6.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£8,613	0.322	£15,050	-£26,763
3) FPG 6-6.4, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£5,899	0.231	£10,511	-£25,582
4) FPG 5.5-5.9, BMI 30-34 (White) OR BMI 27.5-34 (BME)	-£3,160	0.135	£5,869	-£23,338
5) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£374	0.066	£1,686	-£5,701
6) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	-£105	0.052	£1,136	-£2,038
7) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age >= 60	£218	0.028	£339	£7,834
8) FPG 6.5-6.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£9,863	0.301	£15,888	-£32,741
9) FPG 6-6.4, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£6,072	0.208	£10,235	-£29,175

10) FPG 5.5-5.9, BMI 25-29 (White) OR BMI 23-27.4 (BME), Age < 60	-£2,809	0.114	£5,090	-£24,634
11) FPG 6.5-6.9, BMI <25 (White) OR BMI < 23 (BME)	-£3,122	0.094	£4,994	-£33,353
12) FPG 6-6.4, BMI <25 (White) OR BMI < 23 (BME)	-£1,636	0.061	£2,864	-£26,663
13) FPG 5.5-5.9, BMI <25 (White) OR BMI < 23 (BME)	-£361	0.033	£1,028	-£10,813

Appendix 4: Total Results Cost-Effectiveness Planes

Cost-effectiveness Planes: Discount Rate of 3.5%

Figure 118: Assuming HbA1c effect is neither stratified nor persistent: Cost-effectiveness estimates from 1000 PSA runs plotted on the cost-effectiveness plane. The dotted line represents the willingness to pay threshold at £20,000 per QALY. Discount rate of 3.5%.

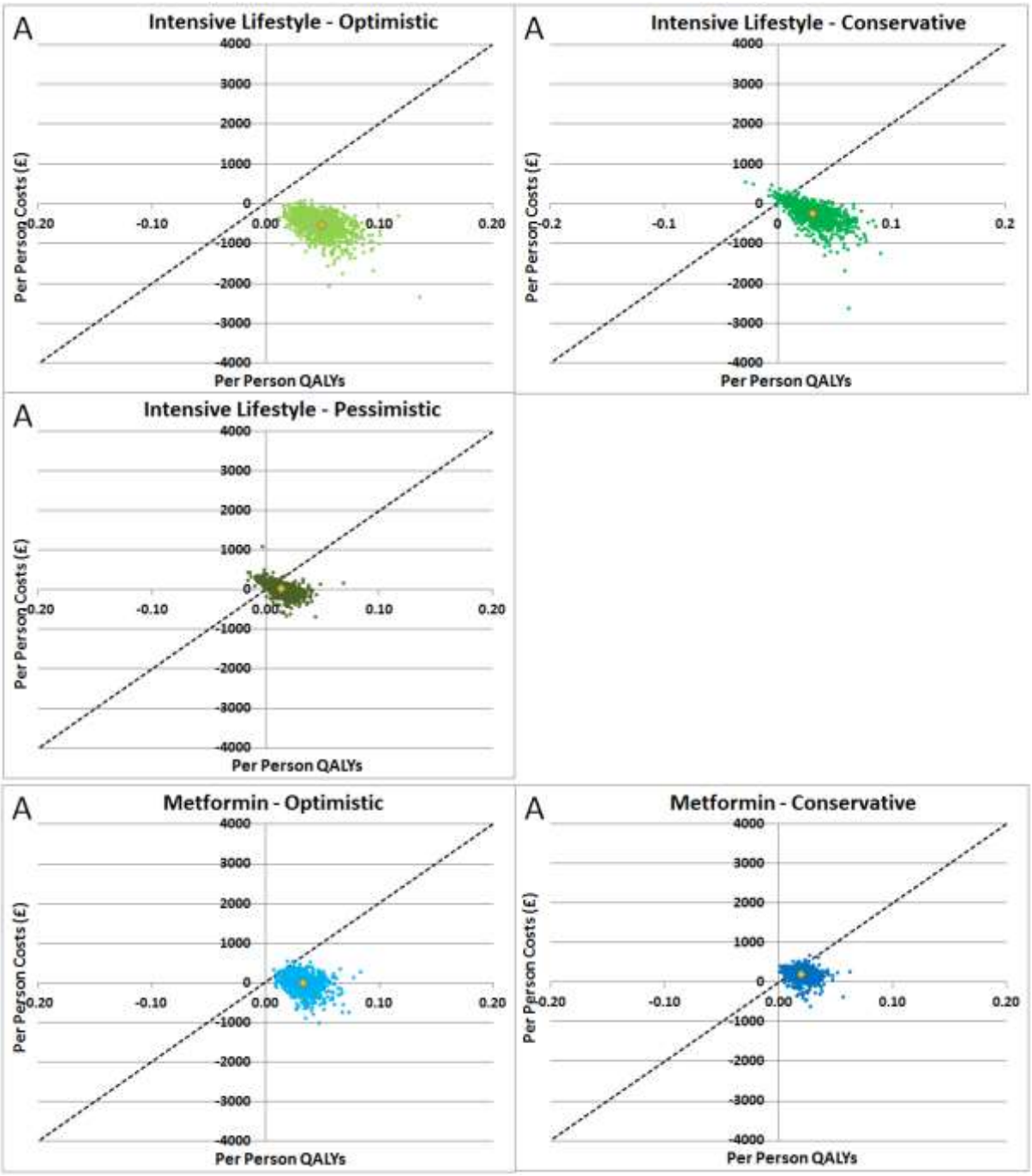


Figure 119: Assuming HbA1c effect is stratified but not persistent: Cost-effectiveness estimates from 1000 PSA runs plotted on the cost-effectiveness plane. The dotted line represents the willingness to pay threshold at £20,000 per QALY. Discount rate of 3.5%.

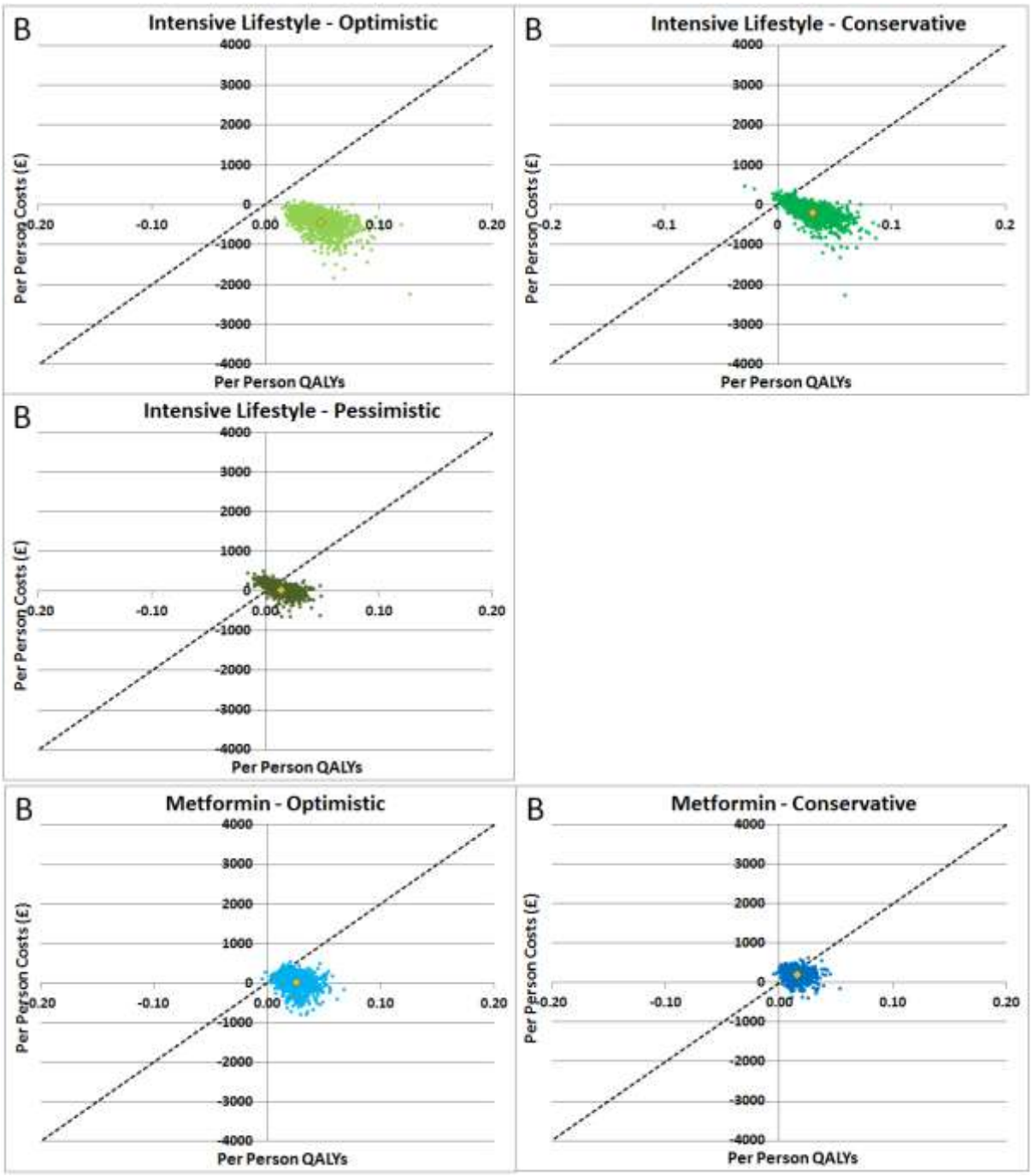


Figure 120: Assuming HbA1c effect is persistent but not stratified: Cost-effectiveness estimates from 1000 PSA runs plotted on the cost-effectiveness plane. The dotted line represents the willingness to pay threshold at £20,000 per QALY. Discount rate of 3.5%.

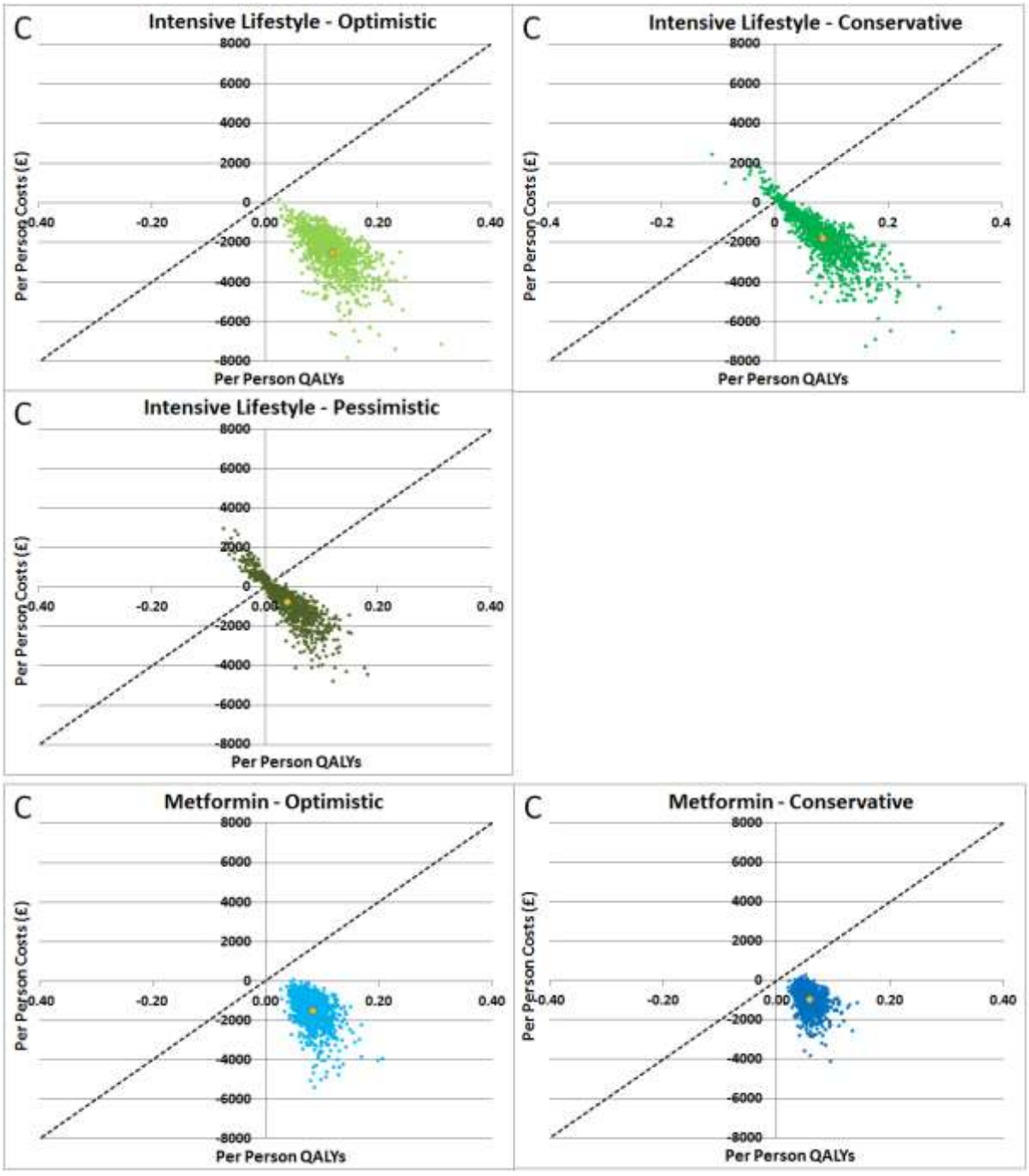
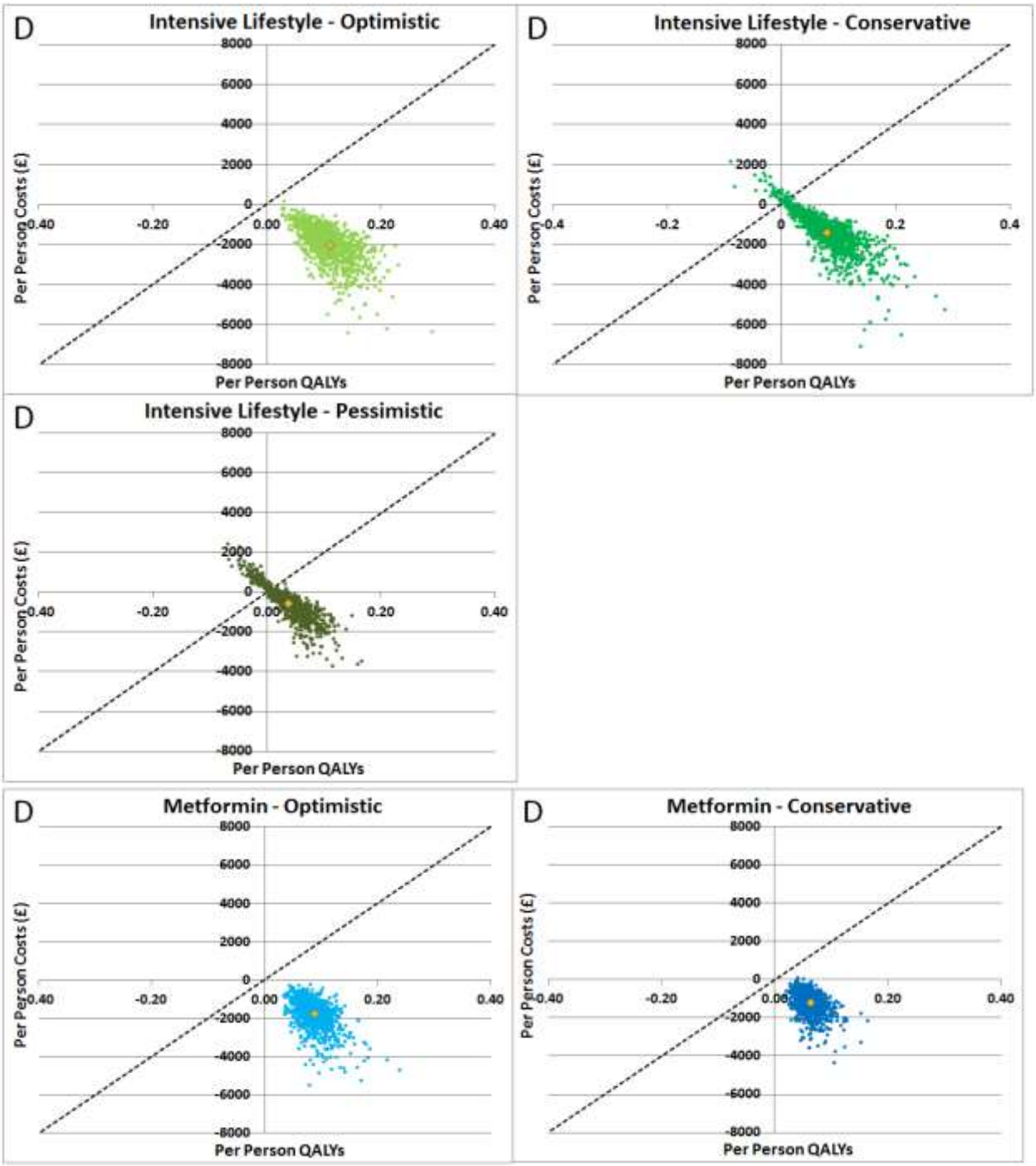


Figure 121: Assuming HbA1c effect is both persistent and stratified: Cost-effectiveness estimates from 1000 PSA runs plotted on the cost-effectiveness plane. The dotted line represents the willingness to pay threshold at £20,000 per QALY. Discount rate of 3.5%.



Cost-effectiveness Planes: Discount Rate of 1.5%

Figure 122: Assuming HbA1c effect is neither stratified nor persistent: Cost-effectiveness estimates from 1000 PSA runs plotted on the cost-

effectiveness plane. The dotted line represents the willingness to pay threshold at £20,000 per QALY. Discount rate of 1.5%.

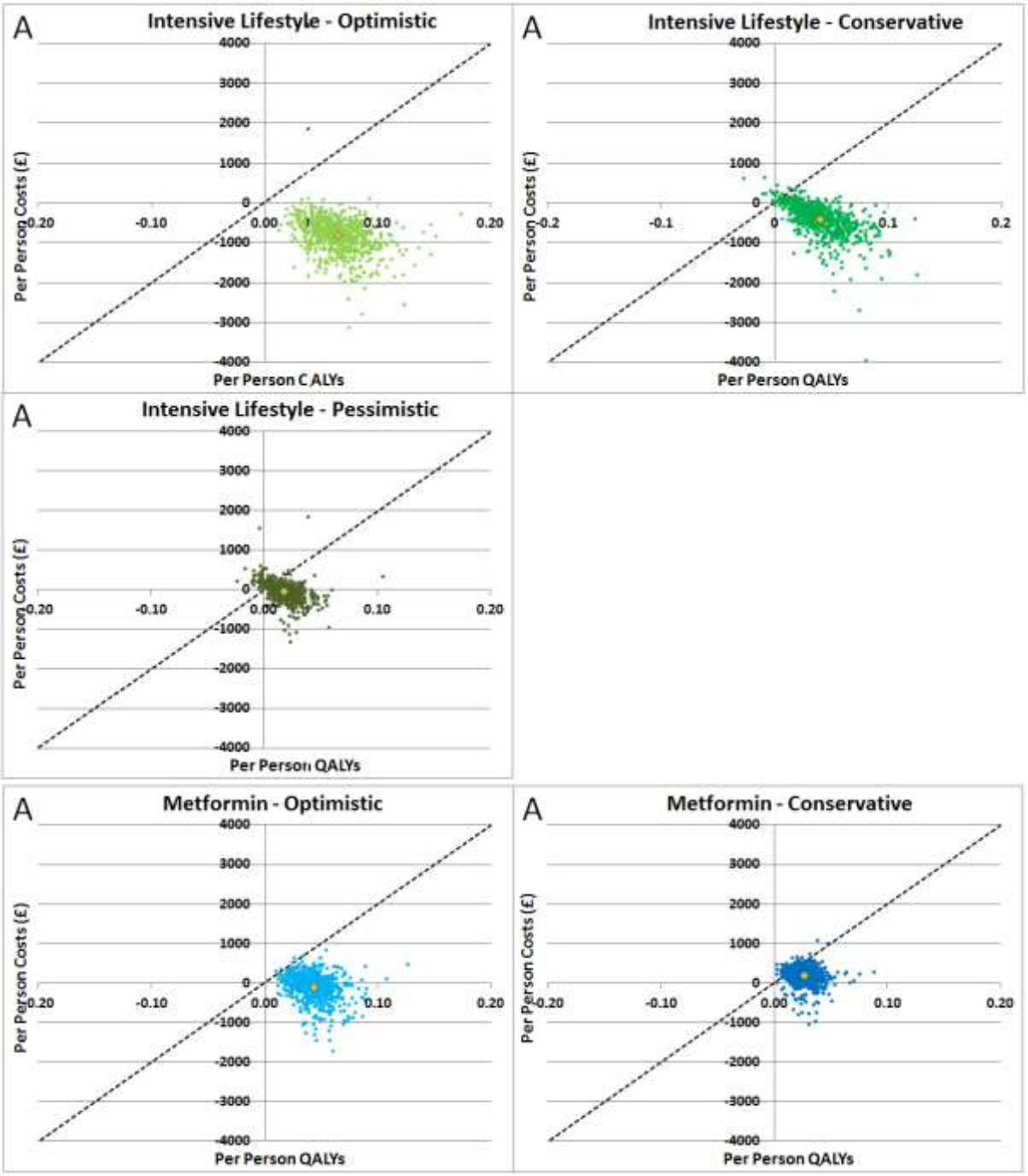


Figure 123: Assuming HbA1c effect is stratified but not persistent: Cost-effectiveness estimates from 1000 PSA runs plotted on the cost-effectiveness plane. The dotted line represents the willingness to pay threshold at £20,000 per QALY. Discount rate of 1.5%.

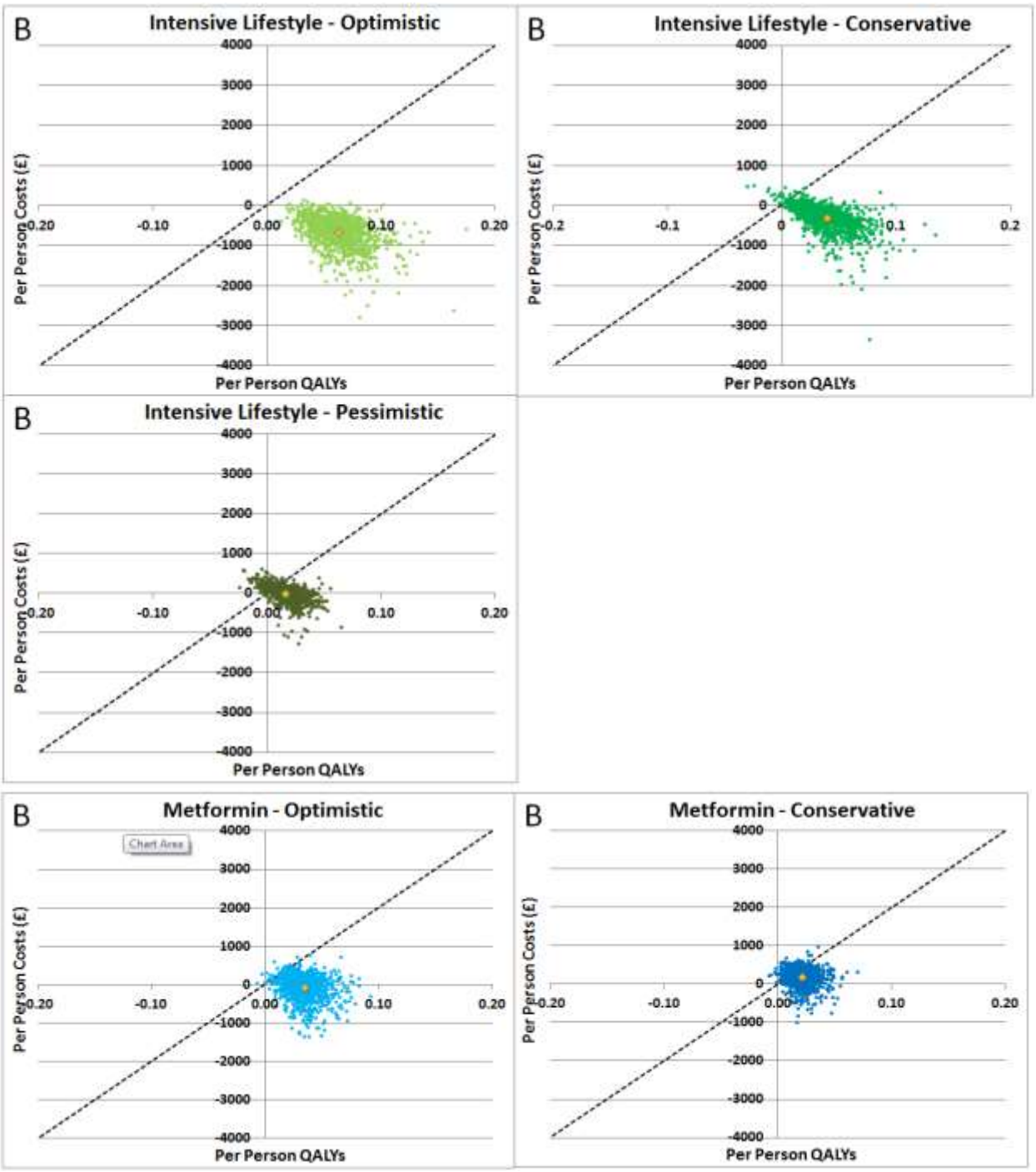


Figure 124: Assuming HbA1c effect is persistent but not stratified: Cost-effectiveness estimates from 1000 PSA runs plotted on the cost-effectiveness plane. The dotted line represents the willingness to pay threshold at £20,000 per QALY. Discount rate of 1.5%.

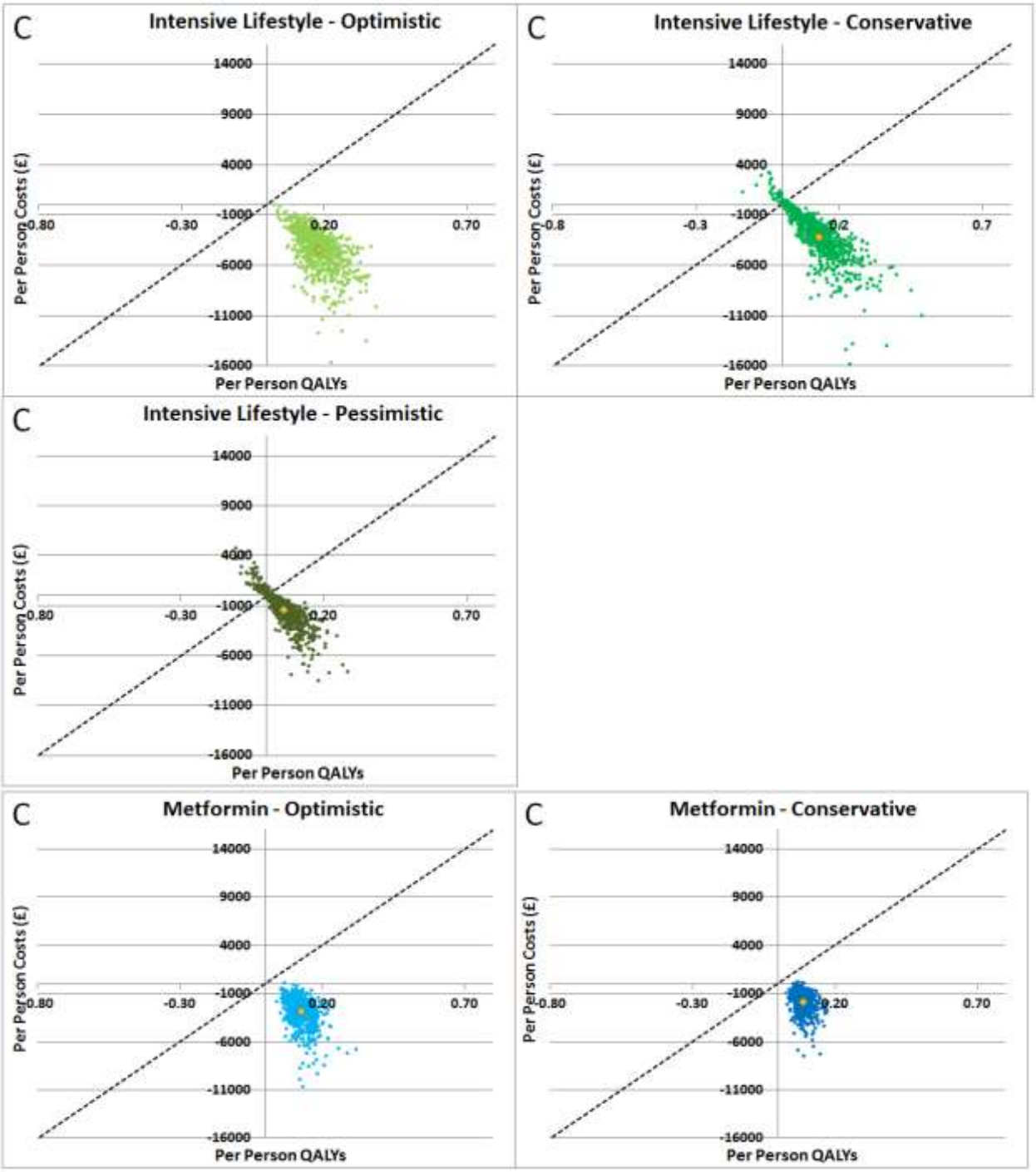
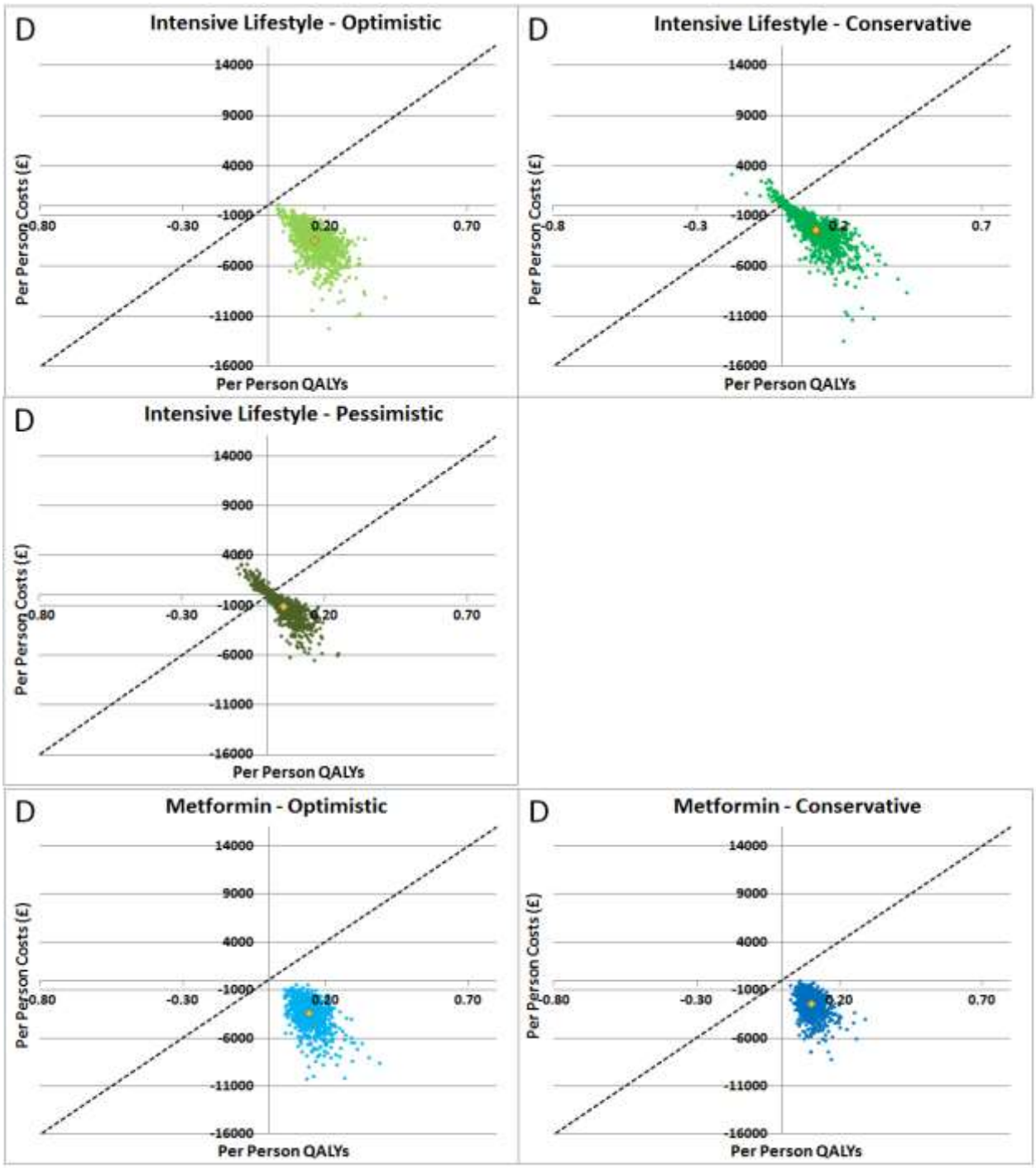


Figure 125: Assuming HbA1c effect is both persistent and stratified: Cost-effectiveness estimates from 1000 PSA runs plotted on the cost-effectiveness plane. The dotted line represents the willingness to pay threshold at £20,000 per QALY. Discount rate of 1.5%.



Appendix 5: Full Budget Impact Tables

Table 108: Cumulative budget impact table for conservative intensive lifestyle intervention assuming stratification but no persistence of HbA1c effect

compared to control. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+.

		Year 1	Year 2	Year 3	Year 4	Year 5
TOTAL	**TOTAL COST**	**£20,806,455**	**£19,185,066**	**£17,164,143**	**£14,824,180**	**£12,367,845**
	NHS Costs	-£1,493,545	-£3,114,934	-£5,135,857	-£7,475,820	-£9,932,155
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
IMD Q1	**TOTAL COST**	**£20,920,444**	**£19,378,938**	**£17,413,125**	**£15,169,913**	**£12,765,663**
	NHS Costs	-£1,379,556	-£2,921,062	-£4,886,875	-£7,130,087	-£9,534,337
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
IMD Q2	**TOTAL COST**	**£20,709,755**	**£19,049,010**	**£17,017,422**	**£14,690,752**	**£12,225,577**
	NHS Costs	-£1,590,245	-£3,250,990	-£5,282,578	-£7,609,248	-£10,074,423
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
IMD Q3	**TOTAL COST**	**£20,835,928**	**£19,171,089**	**£17,160,141**	**£14,799,687**	**£12,350,114**
	NHS Costs	-£1,464,072	-£3,128,911	-£5,139,859	-£7,500,313	-£9,949,886
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
IMD Q4	**TOTAL COST**	**£20,834,455**	**£19,169,163**	**£17,107,201**	**£14,679,915**	**£12,095,559**
	NHS Costs	-£1,465,545	-£3,130,837	-£5,192,799	-£7,620,085	-£10,204,441
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
IMD Q5	**TOTAL COST**	**£20,773,335**	**£19,191,020**	**£17,153,742**	**£14,770,737**	**£12,396,811**
	NHS Costs	-£1,526,665	-£3,108,980	-£5,146,258	-£7,529,263	-£9,903,189

	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
Age	**TOTAL COST**	**£21,650,621**	**£20,835,293**	**£19,776,634**	**£18,532,727**	**£17,216,389**
< 40	NHS Costs	-£649,379	-£1,464,707	-£2,523,366	-£3,767,273	-£5,083,611
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
Age	**TOTAL COST**	**£21,145,504**	**£19,743,624**	**£17,941,955**	**£15,752,858**	**£13,391,366**
40-59	NHS Costs	-£1,154,496	-£2,556,376	-£4,358,045	-£6,547,142	-£8,908,634
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
Age	**TOTAL COST**	**£20,188,299**	**£17,961,076**	**£15,108,073**	**£11,727,022**	**£8,089,970**
60-74	NHS Costs	-£2,111,701	-£4,338,924	-£7,191,927	-£10,572,978	-£14,210,030
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
Age	**TOTAL COST**	**£18,778,856**	**£15,586,328**	**£12,051,421**	**£8,495,492**	**£5,174,941**
75+	NHS Costs	-£3,521,144	-£6,713,672	-£10,248,579	-£13,804,508	-£17,125,059
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
BMI	**TOTAL COST**	**£21,168,815**	**£19,830,466**	**£18,109,035**	**£16,111,639**	**£14,023,984**
< 25	NHS Costs	-£1,131,185	-£2,469,534	-£4,190,965	-£6,188,361	-£8,276,016
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
BMI	**TOTAL COST**	**£20,934,925**	**£19,345,212**	**£17,382,689**	**£15,081,938**	**£12,665,190**
25-29	NHS Costs	-£1,365,075	-£2,954,788	-£4,917,311	-£7,218,062	-£9,634,810
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
BMI	**TOTAL COST**	**£20,572,956**	**£18,805,943**	**£16,601,389**	**£14,054,415**	**£11,355,305**

30-34	NHS Costs	-£1,727,044	-£3,494,057	-£5,698,611	-£8,245,585	-£10,944,695
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
BMI	**TOTAL COST**	**£19,955,964**	**£17,839,932**	**£15,267,991**	**£12,390,419**	**£9,406,589**
35+	NHS Costs	-£2,344,036	-£4,460,068	-£7,032,009	-£9,909,581	-£12,893,411
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
	TOTAL COST	**£20,745,951**	**£19,088,305**	**£17,022,337**	**£14,649,002**	**£12,162,222**
Eth White	NHS Costs	-£1,554,049	-£3,211,695	-£5,277,663	-£7,650,998	-£10,137,778
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
Eth	**TOTAL COST**	**£21,307,138**	**£19,985,775**	**£18,337,609**	**£16,273,805**	**£14,069,403**
BME	NHS Costs	-£992,862	-£2,314,225	-£3,962,391	-£6,026,195	-£8,230,597
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
Sex	**TOTAL COST**	**£20,937,705**	**£19,526,658**	**£17,784,060**	**£15,799,219**	**£13,696,586**
Male	NHS Costs	-£1,362,295	-£2,773,342	-£4,515,940	-£6,500,781	-£8,603,414
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
	TOTAL COST	**£20,646,695**	**£18,769,272**	**£16,409,566**	**£13,637,342**	**£10,750,473**
Sex Female	NHS Costs	-£1,653,305	-£3,530,728	-£5,890,434	-£8,662,658	-£11,549,527
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
HbA1c	**TOTAL COST**	**£20,809,934**	**£19,246,179**	**£17,197,792**	**£14,714,351**	**£11,866,123**
6-6.1	NHS Costs	-£1,490,066	-£3,053,821	-£5,102,208	-£7,585,649	-£10,433,877
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000

	TOTAL COST	**£19,971,970**	**£16,699,110**	**£12,517,847**	**£7,533,228**	**£2,488,964**
HbA1c 6.2-6.4	NHS Costs	-£2,328,030	-£5,600,890	-£9,782,153	-£14,766,772	-£19,811,036
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
FPG	**TOTAL COST**	**£20,988,151**	**£19,661,653**	**£18,058,454**	**£16,240,051**	**£14,338,683**
5.5-5.9	NHS Costs	-£1,311,849	-£2,638,347	-£4,241,546	-£6,059,949	-£7,961,317
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
FPG	**TOTAL COST**	**£20,538,873**	**£18,583,493**	**£16,109,438**	**£13,207,986**	**£10,258,108**
6-6.4	NHS Costs	-£1,761,127	-£3,716,507	-£6,190,562	-£9,092,014	-£12,041,892
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
FPG	**TOTAL COST**	**£20,040,106**	**£17,298,886**	**£13,922,903**	**£9,895,327**	**£5,665,271**
6.5-6.9	NHS Costs	-£2,259,894	-£5,001,114	-£8,377,097	-£12,404,673	-£16,634,729
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
HbA1c	**TOTAL COST**	**£20,404,620**	**£18,014,189**	**£14,934,153**	**£11,240,919**	**£7,330,492**
6-6.4	NHS Costs	-£1,895,380	-£4,285,811	-£7,365,847	-£11,059,081	-£14,969,508
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
HbA2_ Bmi4_	**TOTAL COST**	**£18,683,610**	**£14,937,025**	**£9,934,862**	**£4,256,211**	**-£1,863,050**
AgeHI	NHS Costs	-£3,616,390	-£7,362,975	-£12,365,138	-£18,043,789	-£24,163,050
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
1) HbA_	**TOTAL COST**	**£19,564,542**	**£16,874,704**	**£13,473,506**	**£9,581,039**	**£5,432,184**
Bmi4	NHS Costs	-£2,735,458	-£5,425,296	-£8,826,494	-£12,718,961	-£16,867,816

	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
2) HbA2_ Bmi3	**TOTAL COST**	**£19,755,526**	**£16,338,071**	**£11,995,922**	**£6,811,833**	**£1,535,085**
	NHS Costs	-£2,544,474	-£5,961,929	-£10,304,078	-£15,488,167	-£20,764,915
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
3) HbA1_ Bmi3	**TOTAL COST**	**£20,739,117**	**£19,106,310**	**£16,899,728**	**£14,231,262**	**£11,150,660**
	NHS Costs	-£1,560,883	-£3,193,690	-£5,400,272	-£8,068,738	-£11,149,340
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
4) HbA2_ Bmi2_ AgeHI	**TOTAL COST**	**£19,066,506**	**£14,770,688**	**£9,563,395**	**£3,445,110**	**-£2,765,391**
	NHS Costs	-£3,233,494	-£7,529,312	-£12,736,605	-£18,854,890	-£25,065,391
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
5) HbA1_ Bmi2_ AgeHI	**TOTAL COST**	**£20,143,239**	**£18,064,907**	**£15,396,011**	**£12,324,845**	**£9,036,536**
	NHS Costs	-£2,156,761	-£4,235,093	-£6,903,989	-£9,975,155	-£13,263,464
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
6) HbA2_ Bmi2_ AgeLO	**TOTAL COST**	**£20,927,523**	**£18,311,430**	**£14,815,297**	**£10,455,071**	**£6,014,392**
	NHS Costs	-£1,372,477	-£3,988,570	-£7,484,703	-£11,844,929	-£16,285,608
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
7) HbA1_ Bmi2_ AgeLO	**TOTAL COST**	**£21,533,060**	**£20,390,993**	**£18,840,720**	**£16,762,864**	**£14,248,592**
	NHS Costs	-£766,940	-£1,909,007	-£3,459,280	-£5,537,136	-£8,051,408

	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
8) HbA2_ Bmi1	**TOTAL COST**	**£20,209,564**	**£17,182,894**	**£13,281,281**	**£8,651,468**	**£4,107,746**
	NHS Costs	-£2,090,436	-£5,117,106	-£9,018,719	-£13,648,532	-£18,192,254
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
9) HbA1_ Bmi1	**TOTAL COST**	**£21,131,083**	**£19,816,651**	**£18,069,589**	**£15,931,227**	**£13,408,499**
	NHS Costs	-£1,168,917	-£2,483,349	-£4,230,411	-£6,368,773	-£8,891,501
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
FPG 5.5-6.9	**TOTAL COST**	**£20,852,859**	**£19,333,971**	**£17,470,759**	**£15,328,835**	**£13,107,734**
	NHS Costs	-£1,447,141	-£2,966,029	-£4,829,241	-£6,971,165	-£9,192,266
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
FPG3_ Bmi4_ AgeHI	**TOTAL COST**	**£18,252,127**	**£14,486,192**	**£10,451,850**	**£5,742,285**	**£324,450**
	NHS Costs	-£4,047,873	-£7,813,808	-£11,848,150	-£16,557,715	-£21,975,550
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
1) FPG_ Bmi4	**TOTAL COST**	**£20,051,736**	**£18,027,614**	**£15,527,474**	**£12,743,153**	**£9,901,631**
	NHS Costs	-£2,248,264	-£4,272,386	-£6,772,526	-£9,556,847	-£12,398,369
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
2) FPG3_ Bmi3	**TOTAL COST**	**£20,084,690**	**£17,315,487**	**£13,855,256**	**£9,707,881**	**£5,174,735**
	NHS Costs	-£2,215,310	-£4,984,513	-£8,444,744	-£12,592,119	-£17,125,265
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
3) FPG2_	**TOTAL COST**	**£20,322,406**	**£18,228,055**	**£15,562,615**	**£12,504,269**	**£9,347,725**

Bmi3	NHS Costs	-£1,977,594	-£4,071,945	-£6,737,385	-£9,795,731	-£12,952,275
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
4) FPG1_	**TOTAL COST**	**£20,740,763**	**£19,271,898**	**£17,507,292**	**£15,471,954**	**£13,329,794**
Bmi3	NHS Costs	-£1,559,237	-£3,028,102	-£4,792,708	-£6,828,046	-£8,970,206
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
5) FPG3_	**TOTAL COST**	**£19,176,982**	**£15,619,896**	**£11,046,645**	**£6,065,233**	**£1,115,487**
Bmi2_	NHS Costs	-£3,123,018	-£6,680,104	-£11,253,355	-£16,234,767	-£21,184,513
AgeHI	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
6) FPG2_ Bmi2_	**TOTAL COST**	**£19,685,888**	**£16,770,537**	**£13,426,759**	**£9,411,092**	**£5,343,789**
AgeHI	NHS Costs	-£2,614,112	-£5,529,463	-£8,873,241	-£12,888,908	-£16,956,211
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
7) FPG1_ Bmi2_	**TOTAL COST**	**£20,134,037**	**£17,966,778**	**£15,413,193**	**£12,595,263**	**£9,776,969**
AgeHI	NHS Costs	-£2,165,963	-£4,333,222	-£6,886,807	-£9,704,737	-£12,523,031
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
8) FPG3_ Bmi2_	**TOTAL COST**	**£20,747,299**	**£18,726,466**	**£16,275,441**	**£13,293,796**	**£9,703,081**
AgeLO	NHS Costs	-£1,552,701	-£3,573,534	-£6,024,559	-£9,006,204	-£12,596,919
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
9) FPG2_ Bmi2_	**TOTAL COST**	**£21,341,826**	**£20,023,726**	**£18,335,033**	**£16,211,014**	**£14,010,625**
AgeLO	NHS Costs	-£958,174	-£2,276,274	-£3,964,967	-£6,088,986	-£8,289,375

	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
10) FPG1_ Bmi2_ AgeLO	**TOTAL COST**	**£21,567,617**	**£20,698,470**	**£19,612,383**	**£18,346,761**	**£16,972,617**
	NHS Costs	-£732,383	-£1,601,530	-£2,687,617	-£3,953,239	-£5,327,383
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
11) FPG3_ Bmi1	**TOTAL COST**	**£20,224,634**	**£17,808,598**	**£14,247,608**	**£9,783,626**	**£5,974,317**
	NHS Costs	-£2,075,366	-£4,491,402	-£8,052,392	-£12,516,374	-£16,325,683
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
12) FPG2_ Bmi1	**TOTAL COST**	**£20,973,333**	**£19,360,478**	**£17,171,963**	**£14,629,491**	**£12,163,124**
	NHS Costs	-£1,326,667	-£2,939,522	-£5,128,037	-£7,670,509	-£10,136,876
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000
13) FPG1_ Bmi1	**TOTAL COST**	**£21,347,940**	**£20,286,567**	**£19,012,763**	**£17,565,215**	**£16,021,598**
	NHS Costs	-£952,060	-£2,013,433	-£3,287,237	-£4,734,785	-£6,278,402
	Intervention Costs	£22,300,000	£22,300,000	£22,300,000	£22,300,000	£22,300,000

Table 109: Cumulative budget impact table for conservative metformin intervention assuming stratification but not persistence of HbA1c effect compared to control. Key to combinatorial subgroups is as follows: HBA1 = HbA1c 6-6.1%; HBA2 = HbA1c 6.2-6.4%; FPG1 = FPG 5.5-5.9; FPG2 = FPG 6-6.4; FPG3 = FPG 6.5-6.9; BMI1 = BMI < 25 (white) or BMI < 23 (BME); BMI2 = BMI 25-29.9 (white) or BMI 23-27.49 (BME); BMI3 = BMI 30-34.9 (white) or BMI 27.5-34.9 (BME); BMI4 = BMI 35+; AgeLO = Age < 60; AgeHI = Age 60+. Discount rate of 3.5%.

		Year 1	Year 2	Year 3	Year 4	Year 5
TOTAL	**TOTAL COST**	**£12,600,613**	**£16,656,383**	**£19,717,201**	**£21,821,798**	**£23,621,085**
	NHS Costs	-£581,626	-£1,457,131	-£2,590,939	-£3,967,569	-£5,437,911
	Intervention Costs	£13,182,239	£18,113,514	£22,308,140	£25,789,368	£29,058,996

IMD Q1	**TOTAL COST**	**£12,677,981**	**£16,841,954**	**£20,010,077**	**£22,267,123**	**£24,244,757**
	NHS Costs	-£506,033	-£1,288,948	-£2,342,363	-£3,604,038	-£4,947,491
	Intervention Costs	£13,184,014	£18,130,902	£22,352,440	£25,871,160	£29,192,248
IMD Q2	**TOTAL COST**	**£12,570,112**	**£16,650,798**	**£19,783,738**	**£22,003,989**	**£23,917,743**
	NHS Costs	-£588,823	-£1,421,285	-£2,461,908	-£3,702,379	-£5,040,037
	Intervention Costs	£13,158,935	£18,072,083	£22,245,646	£25,706,368	£28,957,780
IMD Q3	**TOTAL COST**	**£12,605,706**	**£16,668,038**	**£19,775,152**	**£21,880,390**	**£23,750,608**
	NHS Costs	-£569,375	-£1,438,184	-£2,529,302	-£3,917,510	-£5,337,309
	Intervention Costs	£13,175,081	£18,106,222	£22,304,454	£25,797,900	£29,087,917
IMD Q4	**TOTAL COST**	**£12,591,679**	**£16,565,569**	**£19,538,482**	**£21,512,990**	**£23,183,086**
	NHS Costs	-£605,263	-£1,568,196	-£2,792,716	-£4,295,535	-£5,881,179
	Intervention Costs	£13,196,942	£18,133,765	£22,331,198	£25,808,524	£29,064,265
IMD Q5	**TOTAL COST**	**£12,557,112**	**£16,510,372**	**£19,367,653**	**£21,208,491**	**£22,664,277**
	NHS Costs	-£652,117	-£1,635,007	-£2,967,825	-£4,590,296	-£6,369,152
	Intervention Costs	£13,209,229	£18,145,379	£22,335,478	£25,798,787	£29,033,429
Age	**TOTAL COST**	**£12,931,932**	**£17,249,478**	**£20,595,880**	**£23,021,752**	**£25,185,274**
< 40	NHS Costs	-£394,571	-£1,161,181	-£2,220,130	-£3,524,592	-£4,937,232
	Intervention Costs	£13,326,503	£18,410,659	£22,816,010	£26,546,344	£30,122,506
Age	**TOTAL COST**	**£12,608,202**	**£16,573,318**	**£19,522,774**	**£21,432,050**	**£23,031,176**
40-59	NHS Costs	-£685,304	-£1,761,701	-£3,154,958	-£4,893,901	-£6,758,979

	Intervention Costs	£13,293,506	£18,335,019	£22,677,732	£26,325,950	£29,790,155
Age	**TOTAL COST**	**£12,362,178**	**£16,285,271**	**£19,215,152**	**£21,213,851**	**£22,870,685**
60-74	NHS Costs	-£785,443	-£1,738,818	-£2,915,481	-£4,282,534	-£5,742,342
	Intervention Costs	£13,147,621	£18,024,089	£22,130,633	£25,496,384	£28,613,027
Age	**TOTAL COST**	**£12,196,724**	**£16,126,723**	**£19,061,576**	**£21,162,461**	**£22,935,897**
75+	NHS Costs	-£321,965	-£682,022	-£1,096,200	-£1,526,167	-£1,910,215
	Intervention Costs	£12,518,689	£16,808,744	£20,157,776	£22,688,628	£24,846,112
BMI	**TOTAL COST**	**£12,978,818**	**£17,601,494**	**£21,403,103**	**£24,427,845**	**£27,216,919**
< 25	NHS Costs	-£202,899	-£467,320	-£790,335	-£1,158,406	-£1,533,595
	Intervention Costs	£13,181,717	£18,068,814	£22,193,437	£25,586,251	£28,750,514
BMI	**TOTAL COST**	**£12,713,433**	**£16,922,435**	**£20,218,358**	**£22,634,911**	**£24,822,109**
25-29	NHS Costs	-£467,646	-£1,191,470	-£2,090,906	-£3,154,503	-£4,235,531
	Intervention Costs	£13,181,079	£18,113,906	£22,309,264	£25,789,414	£29,057,640
BMI	**TOTAL COST**	**£12,415,145**	**£16,164,729**	**£18,813,475**	**£20,389,157**	**£21,607,639**
30-34	NHS Costs	-£759,670	-£1,958,099	-£3,534,390	-£5,480,252	-£7,579,635
	Intervention Costs	£13,174,815	£18,122,827	£22,347,865	£25,869,409	£29,187,274
BMI	**TOTAL COST**	**£11,667,681**	**£14,440,834**	**£15,725,493**	**£15,588,037**	**£14,812,476**
35+	NHS Costs	-£1,535,477	-£3,760,003	-£6,773,265	-£10,525,631	-£14,730,132
	Intervention Costs	£13,203,158	£18,200,837	£22,498,758	£26,113,668	£29,542,609
Eth White	**TOTAL COST**	**£12,581,926**	**£16,633,841**	**£19,695,662**	**£21,804,739**	**£23,614,403**

	NHS Costs	-£588,118	-£1,456,392	-£2,573,726	-£3,927,627	-£5,365,459
	Intervention Costs	£13,170,044	£18,090,233	£22,269,387	£25,732,366	£28,979,862
Eth	**TOTAL COST**	**£12,755,249**	**£16,842,913**	**£19,895,438**	**£21,962,970**	**£23,676,374**
BME	NHS Costs	-£527,902	-£1,463,249	-£2,733,385	-£4,298,100	-£6,037,455
	Intervention Costs	£13,283,151	£18,306,162	£22,628,823	£26,261,070	£29,713,829
Sex	**TOTAL COST**	**£12,646,029**	**£16,776,533**	**£19,939,147**	**£22,176,436**	**£24,134,880**
Male	NHS Costs	-£538,358	-£1,358,019	-£2,416,516	-£3,692,653	-£5,042,871
	Intervention Costs	£13,184,387	£18,134,552	£22,355,663	£25,869,090	£29,177,751
	TOTAL COST	**£12,545,332**	**£16,510,132**	**£19,447,042**	**£21,390,127**	**£22,995,683**
Sex Female	NHS Costs	-£634,293	-£1,577,773	-£2,803,250	-£4,302,202	-£5,918,761
	Intervention Costs	£13,179,625	£18,087,906	£22,250,293	£25,692,330	£28,914,443
HbA1c	**TOTAL COST**	**£12,633,957**	**£16,921,694**	**£20,260,598**	**£22,578,957**	**£24,436,675**
6-6.1	NHS Costs	-£525,258	-£1,222,255	-£2,151,273	-£3,386,925	-£4,851,716
	Intervention Costs	£13,159,215	£18,143,949	£22,411,871	£25,965,883	£29,288,391
	TOTAL COST	**£12,118,169**	**£14,573,167**	**£15,317,063**	**£14,548,910**	**£13,211,118**
HbA1c 6.2-6.4	NHS Costs	-£1,002,428	-£3,054,370	-£5,819,061	-£9,172,297	-£12,583,763
	Intervention Costs	£13,120,597	£17,627,538	£21,136,124	£23,721,207	£25,794,881
FPG	**TOTAL COST**	**£12,686,070**	**£16,964,960**	**£20,356,407**	**£22,897,872**	**£25,201,537**
5.5-5.9	NHS Costs	-£512,966	-£1,236,805	-£2,158,508	-£3,258,036	-£4,445,250
	Intervention Costs	£13,199,036	£18,201,764	£22,514,915	£26,155,908	£29,646,787

FPG	**TOTAL COST**	**£12,294,586**	**£15,713,327**	**£17,873,994**	**£18,797,651**	**£19,325,898**
6-6.4	NHS Costs	-£874,591	-£2,379,439	-£4,409,451	-£6,969,253	-£9,708,421
	Intervention Costs	£13,169,177	£18,092,765	£22,283,444	£25,766,904	£29,034,320
FPG	**TOTAL COST**	**£11,808,447**	**£13,937,257**	**£14,420,471**	**£13,317,493**	**£11,532,257**
6.5-6.9	NHS Costs	-£1,342,119	-£4,078,026	-£7,689,738	-£12,153,039	-£17,022,549
	Intervention Costs	£13,150,566	£18,015,282	£22,110,209	£25,470,532	£28,554,807
HbA1c	**TOTAL COST**	**£12,384,476**	**£15,785,738**	**£17,869,463**	**£18,694,910**	**£19,006,994**
6-6.4	NHS Costs	-£756,060	-£2,108,429	-£3,925,343	-£6,185,248	-£8,591,624
	Intervention Costs	£13,140,536	£17,894,167	£21,794,806	£24,880,158	£27,598,618
HbA2_ Bmi4_	**TOTAL COST**	**£10,919,039**	**£12,315,029**	**£11,491,422**	**£9,087,644**	**£5,548,072**
AgeHI	NHS Costs	-£2,055,519	-£5,144,209	-£9,486,799	-£14,533,477	-£20,237,391
	Intervention Costs	£12,974,558	£17,459,239	£20,978,222	£23,621,121	£25,785,463
1) HbA_	**TOTAL COST**	**£11,186,987**	**£12,702,775**	**£12,032,685**	**£9,330,337**	**£5,502,519**
Bmi4	NHS Costs	-£1,979,731	-£5,338,461	-£10,101,320	-£16,138,921	-£22,983,206
	Intervention Costs	£13,166,718	£18,041,236	£22,134,005	£25,469,258	£28,485,725
2) HbA2_	**TOTAL COST**	**£11,780,152**	**£13,503,549**	**£13,263,257**	**£11,272,206**	**£8,742,452**
Bmi3	NHS Costs	-£1,321,684	-£4,165,637	-£8,016,368	-£12,717,550	-£17,457,048
	Intervention Costs	£13,101,836	£17,669,186	£21,279,625	£23,989,756	£26,199,500
3) HbA1_	**TOTAL COST**	**£12,464,712**	**£16,494,904**	**£19,489,783**	**£21,313,044**	**£22,548,123**
Bmi3	NHS Costs	-£688,739	-£1,655,835	-£2,957,239	-£4,736,463	-£6,901,727

	Intervention Costs	£13,153,451	£18,150,738	£22,447,022	£26,049,507	£29,449,850
4) HbA2_ Bmi2_ AgeHI	**TOTAL COST**	**£12,359,689**	**£15,759,695**	**£17,855,193**	**£18,783,059**	**£19,366,881**
	NHS Costs	-£545,341	-£1,435,925	-£2,580,285	-£3,965,186	-£5,199,512
	Intervention Costs	£12,905,030	£17,195,620	£20,435,478	£22,748,245	£24,566,393
5) HbA1_ Bmi2_ AgeHI	**TOTAL COST**	**£12,465,314**	**£16,819,863**	**£20,317,389**	**£22,983,295**	**£25,351,795**
	NHS Costs	-£507,275	-£981,319	-£1,544,798	-£2,200,037	-£2,886,835
	Intervention Costs	£12,972,589	£17,801,183	£21,862,187	£25,183,332	£28,238,630
6) HbA2_ Bmi2_ AgeLO	**TOTAL COST**	**£12,294,763**	**£14,600,293**	**£15,248,864**	**£14,410,856**	**£13,170,174**
	NHS Costs	-£1,008,768	-£3,392,932	-£6,461,663	-£10,071,933	-£13,537,825
	Intervention Costs	£13,303,531	£17,993,225	£21,710,526	£24,482,789	£26,707,999
7) HbA1_ Bmi2_ AgeLO	**TOTAL COST**	**£12,922,026**	**£17,325,285**	**£20,826,715**	**£23,279,447**	**£25,293,847**
	NHS Costs	-£382,597	-£1,085,395	-£2,012,118	-£3,293,461	-£4,806,415
	Intervention Costs	£13,304,623	£18,410,681	£22,838,833	£26,572,909	£30,100,262
8) HbA2_ Bmi1	**TOTAL COST**	**£12,803,625**	**£16,610,249**	**£19,178,997**	**£20,649,641**	**£21,598,853**
	NHS Costs	-£312,085	-£855,105	-£1,558,946	-£2,395,023	-£3,219,374
	Intervention Costs	£13,115,710	£17,465,354	£20,737,943	£23,044,664	£24,818,227
9) HbA1_ Bmi1	**TOTAL COST**	**£12,962,322**	**£17,700,313**	**£21,636,645**	**£24,788,680**	**£27,637,724**
	NHS Costs	-£188,117	-£404,312	-£679,772	-£996,199	-£1,343,157

	Intervention Costs	£13,150,439	£18,104,625	£22,316,417	£25,784,879	£28,980,881
FPG 5.5-6.9	**TOTAL COST**	**£12,566,411**	**£16,574,767**	**£19,584,893**	**£21,631,260**	**£23,388,518**
	NHS Costs	-£624,133	-£1,595,670	-£2,863,196	-£4,412,163	-£6,080,725
	Intervention Costs	£13,190,544	£18,170,437	£22,448,089	£26,043,423	£29,469,243
FPG3_ Bmi4_ AgeHI	**TOTAL COST**	**£10,653,979**	**£11,476,384**	**£9,867,537**	**£6,790,074**	**£2,227,412**
	NHS Costs	-£2,333,252	-£6,221,121	-£11,699,222	-£17,884,203	-£25,197,391
	Intervention Costs	£12,987,231	£17,697,505	£21,566,759	£24,674,277	£27,424,803
1) FPG_ Bmi4	**TOTAL COST**	**£11,620,007**	**£14,291,441**	**£15,433,074**	**£15,095,455**	**£14,098,230**
	NHS Costs	-£1,586,745	-£3,948,813	-£7,167,496	-£11,206,433	-£15,751,314
	Intervention Costs	£13,206,752	£18,240,254	£22,600,569	£26,301,888	£29,849,543
2) FPG3_ Bmi3	**TOTAL COST**	**£11,696,866**	**£13,547,841**	**£13,546,599**	**£11,849,911**	**£9,488,093**
	NHS Costs	-£1,426,621	-£4,450,755	-£8,583,144	-£13,690,917	-£19,201,945
	Intervention Costs	£13,123,487	£17,998,597	£22,129,743	£25,540,829	£28,690,038
3) FPG2_ Bmi3	**TOTAL COST**	**£12,124,671**	**£15,228,236**	**£16,962,348**	**£17,199,656**	**£17,047,370**
	NHS Costs	-£1,033,601	-£2,869,999	-£5,354,810	-£8,638,732	-£12,101,595
	Intervention Costs	£13,158,272	£18,098,236	£22,317,158	£25,838,388	£29,148,965
4) FPG1_ Bmi3	**TOTAL COST**	**£12,536,155**	**£16,584,870**	**£19,634,851**	**£21,779,902**	**£23,609,243**
	NHS Costs	-£656,894	-£1,616,104	-£2,888,327	-£4,395,747	-£6,066,396
	Intervention Costs	£13,193,049	£18,200,974	£22,523,178	£26,175,649	£29,675,639
5) FPG3_	**TOTAL COST**	**£12,201,037**	**£15,642,943**	**£17,801,535**	**£19,101,921**	**£20,188,516**

Bmi2_	NHS Costs	-£747,966	-£1,854,004	-£3,334,579	-£4,850,119	-£6,219,970
AgeHI	Intervention Costs	£12,949,003	£17,496,947	£21,136,114	£23,952,040	£26,408,486
6) FPG2_ Bmi2_	**TOTAL COST**	**£12,363,582**	**£16,226,117**	**£19,072,852**	**£20,849,648**	**£22,348,195**
AgeHI	NHS Costs	-£582,175	-£1,370,532	-£2,332,456	-£3,585,240	-£4,811,672
	Intervention Costs	£12,945,757	£17,596,650	£21,405,308	£24,434,888	£27,159,867
7) FPG1_ Bmi2_	**TOTAL COST**	**£12,491,303**	**£16,749,814**	**£20,138,368**	**£22,727,900**	**£25,096,609**
AgeHI	NHS Costs	-£464,460	-£964,752	-£1,550,471	-£2,200,522	-£2,829,250
	Intervention Costs	£12,955,763	£17,714,566	£21,688,839	£24,928,422	£27,925,859
8) FPG3_ Bmi2_	**TOTAL COST**	**£11,798,477**	**£14,029,527**	**£15,038,153**	**£14,509,909**	**£13,461,152**
AgeLO	NHS Costs	-£1,518,951	-£4,348,746	-£7,693,504	-£11,867,321	-£16,291,816
	Intervention Costs	£13,317,428	£18,378,273	£22,731,657	£26,377,230	£29,752,967
9) FPG2_ Bmi2_	**TOTAL COST**	**£12,611,800**	**£16,300,190**	**£18,839,067**	**£20,303,548**	**£21,467,123**
AgeLO	NHS Costs	-£694,375	-£2,085,892	-£3,948,509	-£6,206,665	-£8,589,223
	Intervention Costs	£13,306,175	£18,386,082	£22,787,577	£26,510,213	£30,056,346
10) FPG1_	**TOTAL COST**	**£12,916,481**	**£17,362,931**	**£21,011,122**	**£23,862,722**	**£26,564,448**
Bmi2_	NHS Costs	-£391,627	-£1,062,117	-£1,884,934	-£2,859,183	-£3,875,394
AgeLO	Intervention Costs	£13,308,108	£18,425,048	£22,896,056	£26,721,905	£30,439,842
11) FPG3_	**TOTAL COST**	**£12,648,316**	**£16,295,092**	**£18,826,048**	**£20,306,058**	**£21,584,594**
Bmi1	NHS Costs	-£480,899	-£1,550,643	-£2,876,329	-£4,456,423	-£5,924,825

	Intervention Costs	£13,129,215	£17,845,735	£21,702,377	£24,762,481	£27,509,419
12) FPG2_ Bmi1	**TOTAL COST**	**£12,834,511**	**£17,177,826**	**£20,577,914**	**£23,197,902**	**£25,553,833**
	NHS Costs	-£331,115	-£836,076	-£1,512,923	-£2,238,910	-£2,996,036
	Intervention Costs	£13,165,626	£18,013,902	£22,090,837	£25,436,812	£28,549,869
13) FPG1_ Bmi1	**TOTAL COST**	**£13,015,971**	**£17,746,558**	**£21,742,406**	**£25,014,311**	**£28,115,478**
	NHS Costs	-£188,343	-£440,324	-£726,753	-£1,058,994	-£1,411,146
	Intervention Costs	£13,204,314	£18,186,882	£22,469,158	£26,073,305	£29,526,624

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Appendix J: Excluded studies

J.1 Clinical studies

J.1.1 Review question 1

Study id	Title	Date	Reason for exclusion
Ackermann (2008)	Translating the Diabetes Prevention Program into the community. The DEPLOY Pilot Study.	2008	Incorrect population: HbA1c at baseline <6.0% and baseline FPG not reported. Inclusion based on casual capillary blood glucose.
Ackermann (2015)	A randomized comparative effectiveness trial of a primary care-community linkage for preventing type 2 diabetes	2015	Abstract only - no full text article available
Admiraal (2013)	Intensive lifestyle intervention in general practice to prevent type 2 diabetes among 18 to 60-year-old South Asians: 1-year effects on the weight status and metabolic profile of participants in a randomized controlled trial	2013	Incorrect study population: Baseline FPG<5.5mmol/L and baseline HBA1c <42mmol/L
Alibasic (2013)	Prevention of diabetes in family medicine	2013	Incorrect study type: no random allocation to groups.
Allende-Vigo (2015)	Diabetes mellitus prevention	2015	Incorrect study type: non-systematic review
Aroda (2015)	The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: The diabetes prevention program outcomes study 10-year follow-up	2015	Secondary publication of the US diabetes prevention program. Does not report additional outcomes of interest. Reports subgroup data for women with gestational diabetes at 10 years post randomisation, but data cannot be used as all groups received lifestyle intervention during follow up study.
Bhopal (2014)	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	2014	Incorrect intervention Did not meet at least 9/12 NICEcriteria for lifestyle interventions (5 criteria met)
Biddle (2015)	A randomised controlled trial to reduce sedentary time in young adults at risk of type 2 diabetes mellitus: Project STAND (Sedentary Time and Diabetes)	2015	Incorrect study population: baseline FPG <5.5 mmol/L and HBA1c <42 mmol/L
Bo (2007)	Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial.	2007	Incorrect intervention: Does not meet >=9 NICE criteria for lifestyle interventions.

Study id	Title	Date	Reason for exclusion
Braun (2013)	Metformin modifies the exercise training effects on risk factors for cardiovascular disease in impaired glucose tolerant adults	2013	Incorrect study design: Not a randomised controlled trial (paper does not report random allocation).
Brazeau (2014)	Group-based activities with on-site childcare and online support improve glucose tolerance in women within 5 years of gestational diabetes pregnancy	2014	Incorrect study design: not an RCT (all participants received the lifestyle intervention)
Chae (2012)	Supervised exercise program, BMI, and risk of type 2 diabetes in subjects with normal or impaired fasting glucose.	2012	Incorrect study type: Not a randomised controlled trial
Chasan-Taber (2015)	Lifestyle interventions to reduce risk of diabetes among women with prior gestational diabetes mellitus	2015	Systematic review: used for cross checking
Conroy (2012)	Defining and predicting adherence to an online lifestyle program: 12-month results from the phit study	2012	Incorrect publication type: conference abstract
Dawes (2015)	Preventing diabetes in primary care: a feasibility cluster randomized trial	2015	Follow-up less than 12 months.
Diabetes (2012)	The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS	2012	Secondary publication from US diabetes prevention program trials. Does not report outcomes of interest.
Duijzer (2015)	Type 2 diabetes prevention from evidence to practice: The SLIMMER lifestyle intervention	2015	Abstract only - no full text version available.
Dunbar (2015)	Challenges of diabetes prevention in the real world: Results and lessons from the melbourne diabetes prevention study	2015	Incorrect population and intervention: mean baseline FPG<5.5 mmol/L for both control and intervention group; intervention does not meet 9/12 criteria specified in PH38.
Ferrara (2016)	The Comparative Effectiveness of Diabetes Prevention Strategies to Reduce Postpartum Weight Retention in Women with Gestational Diabetes Mellitus: The Gestational Diabetes' Effects on Moms (GEM) Cluster Randomized Controlled Trial	2016	Incorrect intervention: telephone/mail delivered
Fianu (2016)	Long-term effectiveness of a lifestyle intervention for the primary prevention of type 2 diabetes in a low socio-economic community - an intervention follow-up study on reunion island	2016	Incorrect study population and intervention: all included participants had baseline HBA1c<6.0%; intervention does not meet 9/12 criteria specified in PH38.
Fischer (2015)	Text messaging versus usual care for weight loss in patients with pre-diabetes	2015	Abstract only: no full text version available

Study id	Title	Date	Reason for exclusion
Florez (2012)	Impact of lifestyle intervention and metformin on health-related quality of life: the diabetes prevention program randomized trial	2012	Secondary publication of the US DPP: does not report additional relevant outcome data.
Goldberg (2009)	Effect of progression from impaired glucose tolerance to diabetes on cardiovascular risk factors and its amelioration by lifestyle and metformin intervention	2009	Secondary publication of US diabetes prevention programme: does not report outcomes or subgroup analyses of interest.
Goldberg (2012)	Targeting the consequences of the metabolic syndrome in the Diabetes Prevention Program	2012	Secondary publication of the US diabetes prevention program. Does not report additional relevant outcomes.
Hellgren (2014)	Feasibility of a randomized controlled intervention with physical activity in participants with impaired glucose tolerance recruited by FINDRISC: A pilot study	2014	Intervention did not meet at least 9/12 NICE criteria for lifestyle interventions (1 criterion met)
Hellgren (2016)	A lifestyle intervention in primary care prevents deterioration of insulin resistance in patients with impaired glucose tolerance: A randomised controlled trial	2016	Baseline fasting plasma glucose not reported. Baseline HbA1c < 6%
Hesselink (2015)	Effects of a lifestyle program in subjects with Impaired Fasting Glucose, a pragmatic cluster-randomized controlled trial	2015	Incorrect intervention: does not meet at least 9 NICE criteria for lifestyle interventions.
Jarrett (1979)	Worsening to diabetes in men with impaired glucose tolerance ("borderline diabetes").	1979	Incorrect intervention: lifestyle intervention does not meet at least 9 NICE criteria for lifestyle interventions.
Kosaka (2005)	Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males.	2005	Incorrect intervention: Lifestyle intervention did not meet at least 9 NICE criteria for lifestyle interventions.
Lakerveld (2013)	The effects of a lifestyle intervention on leisure-time sedentary behaviors in adults at risk: the Hoorn Prevention Study, a randomized controlled trial	2013	Baseline fasting blood glucose and HBa1c not reported.
Li (1999)	Effect of metformin on patients with impaired glucose tolerance.	1999	Incorrect population: Mean fasting plasma glucose 6.9mmol/l and HbA1c > 6.4% at baseline
Li (2008)	The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study.	2008	Incorrect intervention: intensive lifestyle intervention does not meet 9 or more NICE criteria for lifestyle interventions.
Liao (2002)	Improvement of BMI, body composition, and body fat distribution with lifestyle modification in Japanese	2002	Incorrect intervention: Lifestyle intervention did not meet at least 9 NICE criteria for lifestyle interventions.

Study id	Title	Date	Reason for exclusion
	Americans with impaired glucose tolerance.		
Lindahl (2009)	A randomized lifestyle intervention with 5-year follow-up in subjects with impaired glucose tolerance: pronounced short-term impact but long-term adherence problems.	2009	Incorrect intervention: intensive lifestyle intervention does not meet 9 or more NICE criteria for lifestyle interventions.
Lu (2011)	Outcome of intensive integrated intervention in participants with impaired glucose regulation in China.	2011	Incorrect intervention: intervention was a combination of a lifestyle programme and metformin or acarbose.
Malin (2012)	Independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes	2012	Only reports outcomes after 12 weeks.
Marrero (2014)	Impact of diagnosis of diabetes on health-related quality of life among high risk individuals: the Diabetes Prevention Program outcomes study	2014	Secondary publication of US diabetes prevention programme - does not report additional relevant outcomes (quality of life reported separately for those with and without diabetes)
Marrero (2016)	Comparison of Commercial and Self-Initiated Weight Loss Programs in People With Prediabetes: A Randomized Control Trial	2016	Incorrect comparator - study compares 2 lifestyle interventions. Control group received a counselling session and materials for a self-initiated weight loss and activity programme (Your Game Plan to Prevent Type 2 Diabetes)
Molitch (2003)	The diabetes prevention program and its global implications	2003	Secondary publication for diabetes prevention programme (Knowler 2002). Does not report additional relevant outcome data.
Nanditha (2016)	Impact of lifestyle intervention in primary prevention of Type 2 diabetes did not differ by baseline age and BMI among Asian-Indian people with impaired glucose tolerance	2016	Incorrect study type: pooled analysis of previous studies, not systematic review
O'Brien (2015)	The feasibility, acceptability, and preliminary effectiveness of a Promotora-Led Diabetes Prevention Program (PL-DPP) in Latinas: a pilot study	2015	Mean Baseline fasting blood glucose < 5.5mmol/l and baseline HBA1c < 6%
O'Dea (2015)	Can the Onset of Type 2 Diabetes Be Delayed by a Group-Based Lifestyle Intervention in Women with Prediabetes following Gestational Diabetes Mellitus (GDM)? Findings from a Randomized Control Mixed Methods Trial	2015	Incorrect study population: Both treatment groups had a mean FPG<5.5mmol/l

Study id	Title	Date	Reason for exclusion
O'Reilly (2016)	Mothers after Gestational Diabetes in Australia (MAGDA): A Randomised Controlled Trial of a Postnatal Diabetes Prevention Program	2016	Both HbA1c and fasting blood glucose below threshold.
Pan (1997)	Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study.	1997	Incorrect intervention: intensive lifestyle intervention does not meet 9 or more NICE criteria for lifestyle interventions.
Peacock (2015)	A randomised controlled trial to delay or prevent type 2 diabetes after gestational diabetes: Walking for exercise and nutrition to prevent diabetes for you	2015	Study had only a 3-month follow-up.
Penn (2009)	Prevention of type 2 diabetes in adults with impaired glucose tolerance: the European Diabetes Prevention RCT in Newcastle upon Tyne, UK.	2009	Incorrect intervention: intensive lifestyle intervention does not meet 9 or more NICE criteria for lifestyle interventions.
Perez-Ferre (2015)	Diabetes mellitus and abnormal glucose tolerance development after gestational diabetes: A three-year, prospective, randomized, clinical-based, Mediterranean lifestyle interventional study with parallel groups	2015	Intervention did not meet at least 9/12 NICE criteria for lifestyle interventions (2 criteria met)
Preiss (2014)	Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial	2014	Incorrect population: mean fasting plasma glucose falls below included range (<5.5mmol/l).
Ram (2014)	Improvement in diet habits, independent of physical activity helps to reduce incident diabetes among prediabetic Asian Indian men	2014	Incorrect population: Baseline fasting plasma glucose and HbA1c not reported so unable to assess whether meet population criteria.
Ramachandran (2006)	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).	2006	Incorrect intervention: intensive lifestyle intervention does not meet 9 or more NICE criteria for lifestyle interventions (included in metformin review)
Ratner (2006)	An update on the Diabetes Prevention Program	2006	Secondary publication from US diabetes prevention programme: does not report additional outcomes of interest.
Saito (2011)	Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial.	2011	Incorrect intervention: lifestyle intervention did not meet at least 9 NICE criteria for lifestyle interventions. Control group also received individual goals and 4 visits with healthcare professionals.

Study id	Title	Date	Reason for exclusion
Sakane (2011)	Prevention of type 2 diabetes in a primary healthcare setting: three-year results of lifestyle intervention in Japanese subjects with impaired glucose tolerance.	2011	Incorrect intervention: intensive lifestyle intervention does not meet 9 or more NICE criteria for lifestyle interventions.
Sakane (2014)	Effect of baseline HbA1c level on the development of diabetes by lifestyle intervention in primary healthcare settings: insights from subanalysis of the Japan Diabetes Prevention Program	2014	Intervention does not meet at least 9/12 NICE criteria for lifestyle interventions.
Sakane (2015)	Effects of telephone-delivered lifestyle support on the development of diabetes in participants at high risk of type 2 diabetes: J-DOIT1, a pragmatic cluster randomised trial	2015	Incorrect intervention: telephone delivered change programme.
Sattin (2014)	Effects on weight of a cluster-randomized, controlled trial of a faith-based adaption of the diabetes prevention program within African-American churches	2014	Conference abstract: no full text article available.
Sattin (2016)	Community Trial of a Faith-Based Lifestyle Intervention to Prevent Diabetes Among African-Americans	2016	Fasting plasma glucose < 5.5mmol/l at baseline and HBa1c < 6% at baseline.
Schmiedel (2015)	Effects of the lifestyle intervention program GLICEMIA in people at risk for type 2 diabetes: A cluster-randomized controlled trial	2015	Baseline fasting plasma glucose and HBa1c not reported.
Schuster (2004)	Impact of metformin on glucose metabolism in nondiabetic, obese African Americans: a placebo-controlled, 24-month randomized study	2004	Incorrect population: Population does not meet baseline plasma glucose criteria in review protocol - baseline glucose measurements not reported and population described as normal glucose tolerant.
Shek (2014)	Lifestyle modifications in the development of diabetes mellitus and metabolic syndrome in Chinese women who had gestational diabetes mellitus: a randomized interventional trial	2014	Did not meet at least 9/12 NICE criteria for lifestyle interventions (3 criteria met)
Sussman (2015)	Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program	2015	Secondary publication from US diabetes prevention programme: does not report additional outcomes of interest.
Tokunaga-Nakawatase (2014)	Computer-supported indirect-form lifestyle-modification support program using Lifestyle Intervention Support Software for Diabetes Prevention (LISS-DP) for people with a family history of type 2 diabetes in a medical	2014	Incorrect population: Baseline FPG<5.5 mmol/l and HbA1c<6%

Study id	Title	Date	Reason for exclusion
	checkup setting: a randomized controlled trial		
Tuomilehto (2001)	Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.	2001	Incorrect intervention: Lifestyle intervention does not meet at least 9 NICE criteria for lifestyle interventions.
Umpierrez (2014)	Primary prevention of type 2 diabetes by lifestyle intervention in primary care setting	2014	Incorrect study type: narrative review
Vincent (2014)	The effects of a community-based, culturally tailored diabetes prevention intervention for high-risk adults of Mexican descent	2014	Baseline fasting plasma glucose and HbA1c not reported.
Wein (1999)	A trial of simple versus intensified dietary modification for prevention of progression to diabetes mellitus in women with impaired glucose tolerance.	1999	Incorrect intervention: Does not meet at least 9 NICE criteria for lifestyle interventions.
Wennehorst (2016)	A Comprehensive Lifestyle Intervention to Prevent Type 2 Diabetes and Cardiovascular Diseases: the German CHIP Trial	2016	HbA1c and fasting blood levels below range. Outcomes for subset of participants with impaired blood glucose not provided.
Worsley (2015)	Metformin for overweight women at midlife: a double-blind, randomized, controlled trial	2015	Incorrect population: baseline plasma glucose <5.5mmol/l
Xu (2013)	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	2013	Intervention does not meet at least 9 of NICE criteria for lifestyle interventions (3 criteria met)
Zhang (2015)	More effective glycaemic control by metformin in African Americans than in Whites in the prediabetic population	2015	Secondary publication of the US diabetes prevention program. Does not report additional relevant outcomes (outcomes reported for metformin group only).
Zhang (2015)	More effective glycaemic control by metformin in African Americans than in Whites in the prediabetic population	2015	Secondary publication from the US diabetes prevention program. Does not report additional relevant outcomes (outcomes reported for metformin group only).

J.1.2 Review question 2

Short Title	Title	Year	Reason for exclusion
Aroda (2015)	The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up	2015	Incorrect population - concerns 10-year follow-up of women with history of gestational diabetes who had all previously been enrolled in the DPP trial and were subsequently offered the DPP

Short Title	Title	Year	Reason for exclusion
			lifestyle intervention as part of the the DPPOS study.
Bernstein (2014)	Management of prediabetes through lifestyle modification in overweight and obese African-American women: the Fitness, Relaxation, and Eating to Stay Healthy (FRESH) randomized controlled trial	2014	Intervention does not meet 9 of NICE criteria for lifestyle interventions.
Bo (2007)	Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial	2007	Incorrect intervention - does not meet 9 of the 12 NICE criteria for lifestyle interventions.
Diabetes (2009)	10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study	2009	Incorrect population - concerns 10-year follow-up of participants who had all previously been enrolled in the DPP trial and were subsequently offered the DPP lifestyle intervention as part of the DPPOS study.
Duan (2014)	A compliance evaluation model of lifestyle intervention in prediabetes	2014	Incorrect publication type - conference abstract
Herman (2013)	Effectiveness and cost-effectiveness of diabetes prevention among adherent participants	2013	Incorrect population - participants had previously been enrolled in the DPP trial and were subsequently offered the DPP lifestyle intervention as part of the the DPPOS study.
Janus (2012)	Scaling-up from an implementation trial to state-wide coverage: results from the preliminary Melbourne Diabetes Prevention Study	2012	Incorrect patient population - baseline FPG and HbA1c outside ranges specified in review protocol
Kujala (2011)	Increase in physical activity and cardiometabolic risk profile change during lifestyle intervention in primary healthcare: 1-year follow-up study among individuals at high risk for type 2 diabetes	2011	Secondary publication for Finnish Diabetes Prevention Study. Does not report uptake / adherence data as specified in review protocol.
Kulzer (2009)	Prevention of diabetes self-management program (PREDIAS): effects on weight, metabolic risk factors, and behavioral outcomes.	2009	Does not report uptake, adherence or number of dropouts for intervention group
Lau (2011)	The effects of adding group-based lifestyle counselling to individual counselling on	2011	Incorrect intervention: did not meet 9/12 NICE

Short Title	Title	Year	Reason for exclusion
	changes in plasma glucose levels in a randomized controlled trial: the Inter99 study		criteria for lifestyle interventions.
Limaye (2016)	Efficacy of a virtual assistance-based lifestyle intervention in reducing risk factors for Type 2 diabetes in young employees in the information technology industry in India: LIMIT, a randomized controlled trial	2016	Incorrect population: baseline FPG outside range specified in review protocol. HbA1c not reported.
Lindström (2006)	Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study	2006	Secondary publication for Finnish Diabetes Prevention Study (7-year follow-up). No intervention uptake/adherence information reported.
Linmans (2011)	Effect of lifestyle intervention for people with diabetes or prediabetes in real-world primary care: propensity score analysis	2011	Incorrect population - includes patients with T2DM; Incorrect intervention: does not meet 9 NICE criteria for lifestyle interventions.
Ma (2013)	Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial.	2013	Does not report uptake, adherence or number of dropouts for intervention group
Pedley (2015)	Healthy living partnerships to prevent diabetes (help PD): A randomized controlled trialto prevent diabetes through diet and exercise: 2 year effects on the metabolic syndrome	2015	Incorrect publication type - conference abstract
Penn (2013)	Importance of Weight Loss Maintenance and Risk Prediction in the Prevention of Type 2 Diabetes: Analysis of European Diabetes Prevention Study RCT	2013	Analysis of combined data from 3 Europpean studies (SLIM, Finnish Diabetes Prevention Study and EDIPS-Newcastle). Does not report intervention uptake / adherence data.
Ram (2014)	Improvement in diet habits, independent of physical activity helps to reduce incident diabetes among prediabetic Asian Indian men	2014	Incorrect population: Baseline fasting plasma glucose and HbA1c not reported so unable to assess whether meet population criteria.
Ramachandran (2013)	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	2013	Duplicate study

Short Title	Title	Year	Reason for exclusion
Rautio (2012)	Participation, socioeconomic status and group or individual counselling intervention in individuals at high risk for type 2 diabetes: one-year follow-up study of the FIN-D2D-project Prevention of metabolic syndrome and components in subjects with impaired fasting glucose by telephone-delivered lifestyle intervention using self-help devices	2012	Incorrect intervention: did not meet 9/12 NICE criteria for lifestyle interventions.
Sakane (2016)	Prevention of metabolic syndrome and components in subjects with impaired fasting glucose by telephone-delivered lifestyle intervention using self-help devices	2016	Incorrect intervention (telephone delivered)
Teuschl (2012)	Factors associated with participation in a diabetes prevention program in Austria: A prospective cohort study	2012	Observational study - all participants were offered lifestyle intervention; participation not reported separately for patients with elevated FPG. Intervention does not meet 9 NICE criteria for lifestyle interventions.
Venditti (2008)	First versus repeat treatment with a lifestyle intervention program: attendance and weight loss outcomes	2008	Incorrect population - participants had all previously been enrolled in the DPP trial and were subsequently offered the DPP lifestyle intervention as part of the DPPOS study.
Vermunt (2012)	Implementation of a lifestyle intervention for type 2 diabetes prevention in Dutch primary care: opportunities for intervention delivery	2012	Incorrect outcome - reports proportion of all participants attending each scheduled visit; does not report other outcomes of relevance for inclusion in evidence review
Yank (2013)	Baseline reach and adoption characteristics in a randomized controlled trial of two weight loss interventions translated into primary care: a structured report of real-world applicability	2013	Secondary publication of Ma 2013 - no intervention uptake / adherence data reported in format required.

J.2 Economic studies

Short Title	Title	Reason for exclusion
Alouki et al, 2016	Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies	Review exclude
Aral et al, 2015	Multi-level preventive care for Type 2 diabetes	Does not include metformin
Bennet et al, 2014	Ethnicity is an independent risk indicator when estimating diabetes risk with FINDRISC scores: a cross sectional study comparing immigrants from the Middle East and native Swedes.	Not an economic analysis
Bertram 2010	Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care	Does not use QALYs as measure of health benefit
Caro et al 2004	Economic evaluation of therapeutic interventions to prevent Type 2 diabetes in Canada	Does not use QALYs as measure of health benefit
Chen et al 2016	Clinical and Economic Impact of a Digital, Remotely-Delivered Intensive Behavioral Counseling Program on Medicare Beneficiaries at Risk for Diabetes and Cardiovascular Disease	Does not use QALYs as measure of health benefit
Dall et al 2015	Value of Lifestyle Intervention to Prevent Diabetes and Sequelae	Does not include metformin
Herman et al 2003	Costs Associated With the Primary Prevention of Type 2 Diabetes Mellitus in the Diabetes Prevention Program	Costing study
Herman et al 2015	The cost-effectiveness of diabetes prevention: results from the Diabetes Prevention Program and the Diabetes Prevention Program Outcomes Study	Review article of previous economic analyses
Icks et al 2007	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	Does not use QALYs as measure of health benefit
Li et al 2010	Cost-Effectiveness of Interventions to Prevent and Control Diabetes Mellitus: A Systematic Review	Review article
Li et al 2015	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	Review article
Liu et al 2013	An economic evaluation for prevention of diabetes mellitus in a developing country: a modelling study	Does not include metformin
Palmer et al 2004	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	Does not use QALYs as measure of health benefit

Short Title	Title	Reason for exclusion
Passey et al 2012	The impact of diabetes prevention on labour force participation and income of older Australians: an economic study	Does not use QALYs as measure of health benefit
Ramachandran et al 2007	Cost-Effectiveness of the Interventions in the Primary Prevention of Diabetes Among Asian Indians	Does not use QALYs as measure of health benefit
Sagarra et al 2014	Lifestyle interventions for diabetes mellitus type 2 prevention	Does not include metformin
Smith et al 2016	Cost effectiveness of an internet-delivered lifestyle intervention in Primary care patients with high cardio vascular risk	Does not include metformin
Sultana et al 2015	Cost effectiveness of exercise intervention and lifestyle counselling in prevention and control of diabetes mellitus – a review	Review article
Tucker et al 2010	The cost effectiveness of interventions in diabetes: a review of published economic evaluations in the UK setting, with an eye on the future	Evaluation of interventions for diabetes
van Wier et al 2013	Economic evaluation of a lifestyle intervention in primary care to prevent type 2 diabetes mellitus and cardiovascular diseases: a randomized controlled trial	Does not include metformin
Vijgen et al 2006	Cost Effectiveness of Preventive Interventions in Type 2 Diabetes Mellitus	Review article
Wong et al 2016	Cost-Effectiveness of a Short Message Service Intervention to Prevent Type 2 Diabetes from Impaired Glucose Tolerance	Does not include metformin
Wylie-Rosett et al 2006	Wylie-Rosett, Judith, William H. Herman, and Ronald B. Goldberg. "Lifestyle intervention to prevent diabetes: intensive and cost effective." Current opinion in lipidology 17.1 (2006): 37-44. APA	Review article