

**Title: Benchmarking the cost-effectiveness of interventions delaying
diabetes: a simulation study based on NAVIGATOR data**

Short title: Cost-effectiveness of delaying type 2 diabetes

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Abstract

Objective: To estimate using the United Kingdom Prospective Diabetes Study Outcomes Model Version 2 (UKPDS-OM2) the impact of delaying type 2 diabetes onset on costs and quality-adjusted life expectancy using trial participants who developed diabetes in the NAVIGATOR study.

Research design and methods: We simulated the impact of delaying diabetes onset by one to nine years, utilising data from the 3058 of 9306 NAVIGATOR trial participants who developed type 2 diabetes. Costs and utility weights associated with diabetes and diabetes-related complications were obtained for US and UK settings, with costs expressed in 2017 values. We estimated discounted lifetime costs and quality-adjusted life years (QALYs) with 95% confidence intervals.

Results: Gains in QALYs increased from 0.02 (95% CI: 0.01, 0.03; US setting) to 0.15 (95% CI: 0.11, 0.20; US setting) as the imposed time to diabetes onset was increased from one to nine years, respectively. Savings in complication costs increased from \$1,388 (95%CI: \$1,092, \$1,669) for one-year delay to \$8,437 (95% CI: \$5603, \$8630) for a delay of nine years. Interventions costing up to \$567-\$2,680 and £201-£947 per year would be cost-effective at \$100,000 per QALY and £20,000 per QALY thresholds in the US and UK, respectively, as the modelled delay in diabetes onset was increased from one to nine years.

Conclusions: Simulating a hypothetical diabetes-delaying intervention provides guidance concerning the maximum cost and minimum delay in diabetes onset needed to be cost-effective. These results can inform the ongoing debate about diabetes prevention strategies and the design of future intervention studies.

A number of trials, including the Da Qing IGT and Diabetes Study,(1) the Finnish Diabetes Prevention Study,(2) and the Diabetes Prevention Program,(3; 4) have reported that lifestyle and pharmacological interventions could significantly reduce the risk of type 2 diabetes in people with impaired glucose tolerance (IGT), as did a systematic review and meta-analysis of such trials in 2007 (5). Using the results of such studies, a number of trial-based or computer-simulation studies have estimated the cost-effectiveness of interventions intended to delay or arrest the progression of IGT to type 2 diabetes.(6-10) These have typically concluded that both lifestyle and pharmaceutical interventions are a cost-effective use of health care resources, although at least one study reached less favourable conclusions(10; 11).

Rather than evaluate a specific intervention in a specific setting, we have taken a different approach by using simulation modelling of a contemporaneous population to address the question “what is the maximum annual cost and minimum delay in diabetes onset needed for an intervention to be cost-effective in US and UK settings?”. We used data from the NAVIGATOR trial(12; 13), specifically the characteristics of the 3058 of 9306 participants who developed type 2 diabetes during the trial, to simulate the potential effect of a hypothetical intervention designed to delay diabetes onset on predicted costs and quality-adjusted life expectancy. We explore the impact of varying the incidence of type 2 diabetes in the absence of intervention, and the number of years that the hypothetical intervention would delay diabetes onset. This permitted us to evaluate the expected cost-effectiveness of such an intervention across different scenarios, and to estimate the maximum annual expenditure on an intervention whilst remaining cost-effective in US and UK settings.

Methods

Patient sample

NAVIGATOR was a double-blind, randomised controlled clinical trial in which 9,306 patients with either cardiovascular disease or cardiovascular risk factors and IGT were assigned to receive valsartan (up to 160mg daily) or placebo, and nateglinide (up to 60mg three times daily) or placebo, in a 2-by-2 factorial design. These were given in addition to participation in a structured programme of lifestyle modification. Participants were followed-up for a median of 5.0 years for the type 2 diabetes onset endpoint, and a median of 6.5 years for the mortality endpoint(12; 13).

IGT was defined as a fasting plasma glucose (FPG) level ≥ 5.3 mmol/l but < 7.0 mmol/l and a 2-hour 75g oral glucose tolerance test (OGTT) 7.8 mmol/l but < 11.1 mmol/l. New onset diabetes was defined as a FPG of ≥ 7 mmol/l or a 2-hour OGTT ≥ 11.1 mmol/l on two consecutive valid glycaemic measurements within 12 weeks. Participants returned for study visits every 6 months, with FPG level measured every 6 months for 3 years and annually thereafter, and OGTT and HbA_{1c} measurements performed annually. See trial protocol for more details on data collection(13). An independent committee, whose members were unaware of the randomised treatment assignments, adjudicated cases in which diabetes was diagnosed by other means.

Data required for the UKPDS Outcomes Model version 2 (UKPDS-OM2), *i.e.* HbA_{1c}, systolic blood pressure, smoking status, total cholesterol and HDL-cholesterol, were

available for 3058 trial participants at diagnosis of new-onset diabetes (from all arms of the trial). Where risk factor values were missing, the closest values measured at the time point nearest (before or after) to the date of diagnosis were used instead. The rationale for using the NAVIGATOR participants, rather than a hypothetical cohort, was to capture the heterogeneity of a contemporary newly-diagnosed type 2 diabetes population in the analysis and the predicted outcomes. The rate of progression to diabetes was derived from the placebo group in the NAVIGATOR trial (80.4 per 1000 patient years)(13).

Simulation model

We evaluated the impact of a hypothetical intervention aimed at delaying the onset of diabetes in individuals with cardiovascular disease or cardiovascular risk factors and IGT. This “at risk of diabetes” population was simulated progressing to diabetes or death over their lifetime and was assumed to share the same baseline characteristics as the NAVIGATOR participants at the time they were diagnosed with diabetes. The simulation assumed that the hypothetical intervention would delay diabetes onset in the “at risk of diabetes” population by one to nine years.

Costs, mortality, life expectancy and quality adjusted life years (QALYs) were estimated using UKPDS-OM2, which is a computer simulation model for forecasting the occurrence of major diabetes-related complications and death in patients with diabetes(14). Summaries of the characteristics of the NAVIGATOR trial patients

used in the simulation, and the UKPDS patients used to develop UKPDS-OM2, are shown in Table A.1 (Online Appendix).

The UKPDS-OM2 predicts an individual's absolute probability of experiencing any of eight complications (first and second myocardial infarction (MI), first and second stroke, heart failure, ischaemic heart disease, first and second amputation, blindness and foot ulcer) and death. These predictions are conditional on the patient's age, ethnicity, sex, and time-varying clinical risk factors (including duration of diabetes, systolic blood pressure [SBP], HbA_{1c}, lipid levels, smoking status, and history of previous complications). Model outputs include annual event probabilities, life expectancy, quality-adjusted life expectancy and lifetime costs.

In the UKPDS-OM2, holding all else constant, the absolute risk of a complication will generally increase with higher values of risk factors, age at diagnosis and with history of complications. Duration of diabetes can also increase the absolute risk of some complications such as ischaemic heart disease, myocardial infarction (for women), heart failure, stroke and amputation. The risk of these complications increases more rapidly in the first years from diabetes onset (see Table A.2, Online Appendix), holding everything else constant(14).

To simplify the analysis and the interpretation of results, the risk factor time paths needed to inform UKPDS-OM2 (SBP, smoking status, HbA_{1c}, LDL, HDL, white blood cell count, haemoglobin, eGFR, peripheral vascular disease, atrial fibrillation, micro/macro albuminuria, heart rate and BMI) were assumed to hold constant from baseline onwards.

Costs and health utilities in US and UK

We obtained costs and utilities associated with diabetes management and diabetes-related complications (15-21) for US and UK settings (Table A.3, Online Appendix, for more details). Diabetes-related costs comprised non-inpatient costs (e.g. physician/outpatient visits, emergency department visit, medications, etc.) and inpatient costs. Costs were expressed in 2017 values, inflated to that year if required using price inflation indices. We assumed the utilities associated with diabetes to also apply to the “at risk of diabetes” population. The management costs of IGT (excluding complications) in the US and UK were estimated by applying the ratio of IGT and diabetes costs reported in Khan et al.(0.74) and the DPP trial(0.77), respectively,(22; 23) to the costs of diabetes management(17; 21).

Progression to diabetes and simulating impact of hypothetical intervention

We simulated individuals over a maximum period of 50 years so that the youngest individuals in the sample could be simulated up to age 100 years or death. In any given year, an individual could develop diabetes, die or remain in the “at risk of diabetes” state (Figure A.1, online Appendix).

The relative effectiveness of the hypothetical intervention was modelled by applying a hazard ratio to the rate of progression to diabetes that reflected a delay in median time to diabetes by 1, 3, 5, 7 or 9 years in the absence of competing risks (see appendix for more details).

We estimated mortality, costs, life years and QALYs for “at risk of diabetes” and “diabetes” health states, in any given year, using UKPDS-OM2 software (<https://www.dtu.ox.ac.uk/outcomesmodel/>). We assumed the risk of complications in the “at risk of diabetes” state to be the same as that of a newly diagnosed diabetes population, with the same characteristics, risk factors and history of complications. Hence, in the “at risk of diabetes” state, diabetes duration was reset to zero for each year of simulation in UKPDS-OM2 from baseline until progression to “diabetes” state occurred. As mentioned above, the risk of some complications increases with diabetes duration and the benefit of the hypothetical intervention is therefore due to a maintenance of the baseline risk. In the “at risk of diabetes” state, the age and complication history was updated to incorporate all predicted complications in a given year and inform the predictions for the following year. A complication was predicted to have occurred if it happened in more than 50% of repeated simulations for a given individual. Following diabetes onset, diabetes duration began to accumulate and the remaining lifetime costs, life years and QALYs were simulated from that point onwards allowing the model to update age, event histories and diabetes duration. Lifetime costs and health outcomes were discounted at 3% (US)(24) and 3.5% (UK)(25).

Analysis

The hypothetical intervention was deemed to be cost-effective if the incremental cost-effectiveness ratio was below the threshold of \$100,000 per QALY in the US(26) or £20,000 per QALY in the UK(25). Using the base case rate of progression

(80.4 per 1000 person years), we estimated the maximum annual costs the intervention could reach while not exceeding the cost-effectiveness thresholds.

We accounted for three types of uncertainty in the analysis: Monte-Carlo simulation error, parameter uncertainty and sampling variation of mean costs and QALYs (see online appendix for details). We report discounted mean costs and QALYs estimates with 95% confidence intervals.

In sensitivity analysis, we explored the impact of varying the diabetes incidence rate per 1000 patient years between 45.5 (obtained from meta-analysis of observational IGT cohorts⁽²⁷⁾ which translates to a 4% annual probability of developing diabetes: $1 - \exp(-0.0455)$), 114.3 (obtained from placebo group in DPP trial⁽²²⁾, 11% annual probability of developing diabetes), 288 (assuming a 25% annual probability of developing diabetes: $1 - \exp(-0.288)$) and 693 (assuming a 50% annual probability of developing diabetes: $1 - \exp(-0.693)$). We also explored the impact of modelling the effectiveness of the hypothetical intervention by shifting diabetes onset for all individuals by 1, 3, 5, 7 or 9 years (i.e. 100% effectiveness in preventing diabetes onset in the first 1, 3, 5, 7 or 9 years). We also explored the impact of setting the management costs of IGT to be the same as those of diabetes (e.g. \$9,158 rather than \$6,762 in the US setting). In the US setting, we evaluated the impact of changing risk factors trajectories over time by exploring two scenarios: 1) individuals' risk factors were predicted annually from baseline onwards regardless of diabetes onset; and 2) individuals' risk factors were held constant up to diabetes onset and then predicted annually from that point onwards (see online appendix for details). Finally, we estimated the maximum annual cost of the intervention in the US setting

varying the rate of progression to diabetes and adopting cost-effectiveness thresholds of \$50,000 and \$200,000 per QALY(26).

Results

In the base-case analysis, we evaluated the lifetime costs and quality-adjusted life years of intervening with a hypothetical intervention until patients developed diabetes, compared with doing nothing (no delay). **Figure 1** shows the cumulative incidence during the first 25 (out of 50) years of simulation by type of intervention. In the absence of hypothetical intervention, about 50% of individuals would develop diabetes by year 10 and 66% by year 25. In contrast, for individuals treated with a hypothetical intervention delaying onset by 1, 3, 5, 7 or 9 years, the corresponding proportions would be respectively 46%, 40%, 35%, 32% and 29% by year 10, and 62%, 57%, 52%, 47% and 44% by year 25.

Table 1 shows the simulated cumulative incidence of diabetes, discounted quality-adjusted life expectancy and costs (excluding intervention) for a rate of progression of 80.4 per 1000 patient years. The hypothetical intervention resulted in gains in QALYs and savings in costs of complications in both the US and UK setting. In the US setting, the gains in QALYs (discounted at 3%) increased from 0.02 (95% CI: 0.01 to 0.03) to 0.15 (95% CI: 0.10 to 0.21) as the delay in progression to diabetes increased from 1 to 9 years, respectively. In terms of costs (excluding intervention), the longer the delay in progression to diabetes the greater the incremental savings relative to no delay (e.g. -\$1,388 for one-year delay and -\$8,437 for a delay of 9 years). In the UK setting, the longer the delay in progression to diabetes the greater

the savings in diabetes costs (e.g. -£205 for a delay of one year and -£1,257 for a delay of 9 years). The savings were considerably lower in the UK setting due to lower management costs of the disease compared with the US setting.

The maximum annual cost, which the intervention could reach while remaining below the cost-effectiveness thresholds (\$100,000/QALY for US and £20,000/QALY for UK), varied conditional on the effectiveness of the hypothetical intervention and country. The maximum annual costs varied between \$567 (1-year delay, 95%CI: \$462-\$672) and \$2,680 (9-year delay, 95%CI: \$2,150-\$3,210) in the US setting and £201 (1-year delay, 95%CI: £151-£250) and £947 (9-year delay, 95%CI: £699-£1,195) in the UK setting. Hence, combining QALYs and costs, the intervention could support higher annual costs the longer it could delay diabetes onset, as the additional costs were offset by the potential gains in QALYs.

Appendix Figure A.2 reports the impact of parameter uncertainty on incremental costs (excluding intervention costs) and QALYs associated with a delay on diabetes onset compared with no delay in diabetes onset. In both US and UK settings, the interventions were significantly more effective compared with no delay. In the US setting compared to the UK, the interventions led to significantly higher cost savings compared with no delay.

Sensitivity analysis

Using standard cost-effectiveness thresholds of \$100,000 per QALY in the US and £20,000 per QALY in the UK, **Table 2** reports the maximum annual cost of the hypothetical intervention as the rate of progression to diabetes is varied. The higher the rate of progression, the higher the maximum that can be spent on the

hypothetical interventions in both US and UK settings while remaining cost-effective. For example, if 25% of individuals were predicted to develop diabetes in year 1 (288 per 1000 person years), the intervention could cost up to \$2,857 and £1,041 and remain cost-effective if it delayed onset by a single year in the US and UK, respectively. In contrast, if progression to diabetes was lower than the base case (45.5 per 1000 person years), the intervention could cost a maximum of \$225 (US) and £79 (UK) if it delayed diabetes onset by a single year.

We also modelled the effectiveness of the hypothetical intervention by shifting diabetes onset for all individuals by 1, 3, 5, 7 or 9 years (see Figure A.3, Online appendix). Table A.4 in Online appendix reports the incremental costs and QALYs across these scenarios. The resulting incremental QALYs were higher for the interventions compared with the base case in both US and UK settings. Cost-savings increased in the US and UK settings after assuming that all individuals postponed their diabetes onset by a given year (100% effectiveness) relative to the base case (e.g. -\$1,828 compared with -\$1,388 for the one-year delay scenario). Hence, the maximum annual costs now varied between \$864 (1-year delay, 95%CI: \$764-\$964) and \$3,795 (9-year delay, 95%CI: \$3,176-\$4,413) in the US setting and £478 (1-year delay, 95% CI: £384-£573) and £1,533 (9-year delay, 95%CI: £1,143-£1,922) in the UK setting (Tables A.4 and A.5 in Online Appendix).

We modelled the management costs of IGT to be the same as for diabetes. Table A.6 in the Online appendix reports the incremental QALYs and costs running this scenario in the US and UK settings. In both settings we estimated lower cost-savings for any given delay scenario compared to the base case. For example, in the US

setting, we observed estimated savings of -\$436 compared to -\$1,388 for a delay of one year and -\$2,672 compared to -\$8,437 for a delay of 9 years. In the US and UK settings, the intervention could support lower annual costs relative to the base case for each effectiveness and rate of progression scenario examined (Tables A.6 and A.7 in the Online Appendix). Using the base case rate of progression (80.4 per 1000 person years), the maximum annual costs now varied between \$427 (1-year delay, 95%CI: \$350-\$503) and \$2,013 (9-year delay, 95%CI: \$1,632-\$2,393) in the US setting. In the UK setting, the maximum annual costs now varied between £182 (1-year delay, 95%CI: £151-£214) and £858 (9-year delay, 95%CI: £698-£1,017).

We modelled risk factors to change over time for the US setting (Table A.8 and Figure A.4 in the Online Appendix). We found the results to be similar to the base-case assumption of holding risk factors constant. Using the base case rate of progression (80.4 per 1000 person years), the maximum annual costs varied between \$599-\$619 (1-year delay, scenario 1 and 2) and \$2,516-\$2,582 (9-year delay, scenario 1 and 2).

Finally, using a cost-effectiveness threshold of \$200,000 per QALY and the base case rate of progression (80.4 per 1000 person years), the maximum intervention costs varied between \$930 (1-year delay, 95%CI: \$703-\$1,156) and \$4,383 (9-year delay, 95%CI: \$3,239-\$5,527) in the US setting. In contrast, using a threshold of \$50,000 per QALY and the same rate of progression, the maximum annual costs varied between \$386 (1-year delay, 95%CI: \$342-\$430) and \$1,828 (9-year delay, 95%CI: \$1,605-\$2,051) (Table A.9 in the Online Appendix).

Discussion

As the prevalence of type 2 diabetes worldwide continues to increase, there has been considerable interest in finding ways of delaying its onset in those at increased risk. Previous studies of the cost-effectiveness of interventions intended to delay the progression of IGT to diabetes have used a range of data sources and methods, but have typically been trial-based analyses or computer-simulation studies.(7-11; 22) These studies have been based directly or indirectly either on the STOP-NIDDM trial(7; 8) or the Diabetes Prevention Program (DPP), and have reported the within-trial or lifetime cost-effectiveness of the trial results,(22) simulated the application of a DPP-type intervention in different country settings,(9) or evaluated the trial results using different assumptions.(11)

Here, we have taken a different approach, which poses the question of how effective an intervention would have to be, and at what cost, to be considered cost-effective in two different jurisdictions. We used patient-level characteristics at the time of diabetes diagnosis during the NAVIGATOR trial, a more recent study than DPP, which recruited patients at 806 centres in 40 countries between January 2002 and January 2004, with median follow-up of 5.0 years for the incidence of diabetes.(12) The characteristics of NAVIGATOR patients used in this study are therefore likely to be more representative of contemporary demographic and biometric variables, risk factor values, history of cardiovascular disease, and use of concomitant medications in such individuals across a wide international spectrum. We illustrated our approach using sets of resource use, unit costs, utility weights and other variables for the US

and for the UK, but the same analytic framework could readily be extended to any country setting.

Our analytical framework could aid the translation of early research into clinical practice in jurisdictions where cost-effectiveness evidence is needed. Similarly, it can inform the design of novel care pathways in diabetes by ascertaining which of several options have the greatest potential in terms of cost-effectiveness.

Furthermore, our findings provide guidance on the maximum costs and the required effectiveness to facilitate the adoption of novel interventions and biomarkers in the US and UK settings. For example, this will be of use to researchers deciding on which novel agent or biomarker to invest time and resources translating from lab bench to bedside as well as to funding bodies supporting translational research in diabetes. By facilitating decisions at an early stage of development, it may avoid waste of resources by industry, researchers, healthcare providers and funding bodies.

Our simulation study highlights the potential cost-effectiveness of preventative interventions that can effectively delay the progression to diabetes across a range of cost scenarios. Interventions costing a maximum of between \$567 and \$2,680 per year in the US and £201 and £947 per year in the UK are cost-effective at \$100,000 per QALY and £20,000 per QALY if diabetes onset is delayed by one to nine years, respectively. These costs are conditional on the rate of progression to diabetes in the absence of the intervention and on the difference in management costs between individuals at high risk of diabetes (IGT) and those with diabetes, particularly in the US setting. Higher rates of diabetes progression translated into a higher annual

ceiling costs for preventative interventions in both UK and US settings. However, the US can accommodate higher ceiling costs because the costs of diabetes and its complications are considerably higher than in the UK.

A number of previous studies have reported quite substantial delays in onset of diabetes; for example, the DPP group reported on the basis of their simulation studies of DPP-type interventions that, compared with a placebo group, a lifestyle intervention would delay the onset of diabetes by 11 years and metformin would delay onset by 3 years,(22) while the STOP-NIDDM group reported a mean delay in progression to diabetes as a result of acarbose therapy of 3.3 years.(8) The 1-9 year range examined in our study therefore seems reasonable.

Similarly, the DPP group reported that the incremental costs compared with placebo were approximately \$400 to \$1200 annually for a lifestyle intervention and \$500 to \$1200 for a metformin intervention,(22) while the STOP-NIDDM group reported an additional cost of approximately SEK2000 per patient over 40 months in the acarbose group compared with placebo, or around \$70 per patient per year.(8) The range of potential therapy costs estimated in our simulation therefore covers the spectrum of previously reported values.

Our study is not without limitations. We used the UKPDS-OM2 to model disease progression in “at risk of diabetes” and type 2 diabetes patients. Therefore, we assumed the risk of complications in individuals at risk of diabetes to be the same as that of newly diagnosed diabetes patients (with the same characteristics, risk factor values and history of events). This was due to: 1) the lack of robust models to

simulate populations at risk of diabetes; and 2) to avoid introducing bias in risk of complications that reflected differences in data sources (informing models) rather than true differences in disease progression(10). Our analysis also held risk factors constant from baseline onwards, due to lack of longitudinal data and to simplify comparisons. This conservative assumption did not capture the potential benefits of the intervention on glucose levels, weight, lipids or blood pressure levels of individuals at risk of diabetes. Capturing these effects would likely have increased the value of the hypothetical interventions. However, a supplementary analysis showed that these changes were small compared to the expected cost-effectiveness of delaying diabetes onset in isolation. In addition, simulation models such as the UKPDS-OM2 may not capture the harmful effect of diabetes on conditions considered not to be diabetes-related and the resulting benefits and cost-savings accruing from its delay. For treatments that have beneficial effects in addition to delaying diabetes our estimates provide a conservative benchmark to determine the maximum cost and minimum delay in diabetes onset needed to be cost-effective. Full cost-effectiveness analyses of such interventions would need to account for both diabetes prevention as well as improvements in other risk factors and knock-on effects on other conditions not related to diabetes.

In this study, we report the likely cost-effectiveness of a hypothetical intervention to delay progression to type 2 diabetes, using a range of plausible intervention costs and varying the rate of progression. By simulating these scenarios over a lifetime and capturing the potential cost savings and health gains as well as the intervention costs, a clear picture emerges of the costs and effect sizes an intervention would have to attain to have an acceptable cost-effectiveness profile. We hope that these

results will inform the ongoing debate about diabetes prevention strategies and inform the modelling strategies used to estimate their value for money.

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Duality of interest

J.L., R.P., O.R.A., Y.L., and A.M.G. report no conflict of interest.

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Author contributions

J.L. performed the statistical analysis, interpreted the findings and wrote the initial draft of the manuscript. J.L., S.D.R., O.R.A. and A.M.G. designed the methodological framework to estimate the maximum cost of the interventions. S.D.R., A.M.G. and R.R.H. designed the study.

S.D.R. provided US cost weights, interpreted the findings, and reviewed and edited the manuscript.

R.P. programmed the UKPDS-OM2 to perform the analysis, and reviewed and edited the manuscript.

O.R.A. provided the UK cost weights, interpreted the findings and reviewed and edited the manuscript.

Y.L. programmed the statistical analysis to identify the individuals with type 2 diabetes in NAVIGATOR and their risk factor levels at diagnosis, generated the dataset used for analysis in this manuscript, and reviewed the manuscript.

R.M.C. was clinical investigator in the NAVIGATOR trial. K.A.S., R.R.H. and R.M.C. interpreted the findings, reviewed and edited the manuscript.

J.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability

All requests and enquiries concerning access to the cost-effectiveness data should be directed to the study's corresponding author (J.L.).

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Tables

Table 1. Outcomes of US and UK population at risk of diabetes conditional on effectiveness of hypothetical intervention (mean and 95%CI)

Outcomes (over 50 years)	No delay	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
Cumulative incidence of diabetes, %	67.0	63.8	58.2	53.4	49.3	45.7
Hazard ratio vs no delay	-	0.92	0.79	0.69	0.61	0.55
US setting*						
Life years	11.90 (11.67-12.13)	11.92 (11.70-12.14)	11.97 (11.77-12.17)	12.00 (11.82-12.18)	12.03 (11.86-12.20)	12.05 (11.89-12.21)
Quality adjusted life expectancy (QALYs)	9.51 (9.33-9.69)	9.53 (9.36-9.71)	9.57 (9.42-9.73)	9.60 (9.46-9.75)	9.63 (9.50-9.77)	9.65 (9.53-9.78)
Costs (excluding intervention)	\$161,457 (156721-166781)	\$160,069 (155468-165305)	\$157,737 (153347-162816)	\$155,856 (151640-160803)	\$154,311 (150239-158942)	\$153,020 (149068-157321)
Δ Life years vs no delay	-	0.03 (0.01 to 0.04)	0.07 (0.04 to 0.10)	0.10 (0.06 to 0.15)	0.13 (0.07 to 0.19)	0.15 (0.08 to 0.22)
Δ QALY vs no delay	-	0.02 (0.01 to 0.03)	0.07 (0.04 to 0.09)	0.10 (0.07 to 0.14)	0.13 (0.08 to 0.18)	0.15 (0.10 to 0.21)
Δ Costs vs no delay (excluding intervention)	-	-\$1,388 (-1669 to -1092)	-\$3,721 (-4483 to -2923)	-\$5,601 (-6757 to -4395)	-\$7,146 (-8630 to -5603)	-\$8,437 (-10197 to -6611)
Max annual cost of intervention to be cost-effective at \$100,000/QALY	-	\$567 (462-672)	\$1,389 (1126-1652)	\$1,954 (1578-2331)	\$2,367 (1904-2829)	\$2,680 (2150-3210)
UK setting†						
Life years	11.43 (11.21-11.63)	11.45 (11.25-11.64)	11.49 (11.30-11.67)	11.52 (11.35-11.68)	11.54 (11.38-11.69)	11.56 (11.41-11.70)
Quality adjusted life expectancy (QALYs)	9.13 (8.97-9.29)	9.15 (9.00-9.31)	9.19 (9.05-9.33)	9.22 (9.09-9.35)	9.24 (9.12-9.37)	9.26 (9.15-9.38)
Costs (excluding intervention)	£38,321 (37181-39450)	£38,116 (37021-39200)	£37,769 (36756-38780)	£37,489 (36545-38436)	£37,257 (36371-38149)	£37,063 (36226-37944)
Δ Life years vs no delay	-	0.02 (0.01 to 0.03)	0.06 (0.04 to 0.09)	0.09 (0.05 to 0.13)	0.11 (0.07 to 0.17)	0.13 (0.08 to 0.20)
Δ QALY vs no delay	-	0.02 (0.01 to 0.03)	0.06 (0.04 to 0.08)	0.09 (0.06 to 0.12)	0.11 (0.08 to 0.16)	0.13 (0.09 to 0.18)
Δ Costs vs no delay (excluding intervention)	-	-£205 (-269 to -145)	-£552 (-727 to -389)	-£832 (-1098 to -585)	-£1,064 (-1404 to -745)	-£1,257 (-1660 to -878)
Max annual cost of intervention to be cost-effective at £20,000/QALY	-	£201 (151-250)	£491 (367-616)	£691 (513-868)	£836 (619-1054)	£947 (699-1195)

*discounted at 3% and using cost-effectiveness threshold of \$100,000 per QALY; † discounted at 3.5% and using cost-effectiveness threshold of £20,000 per QALY; Δ incremental

Table 2: Maximum annual cost of intervention in the US and UK for intervention to be cost-effective relative to no delay by varying the rate of progression to diabetes

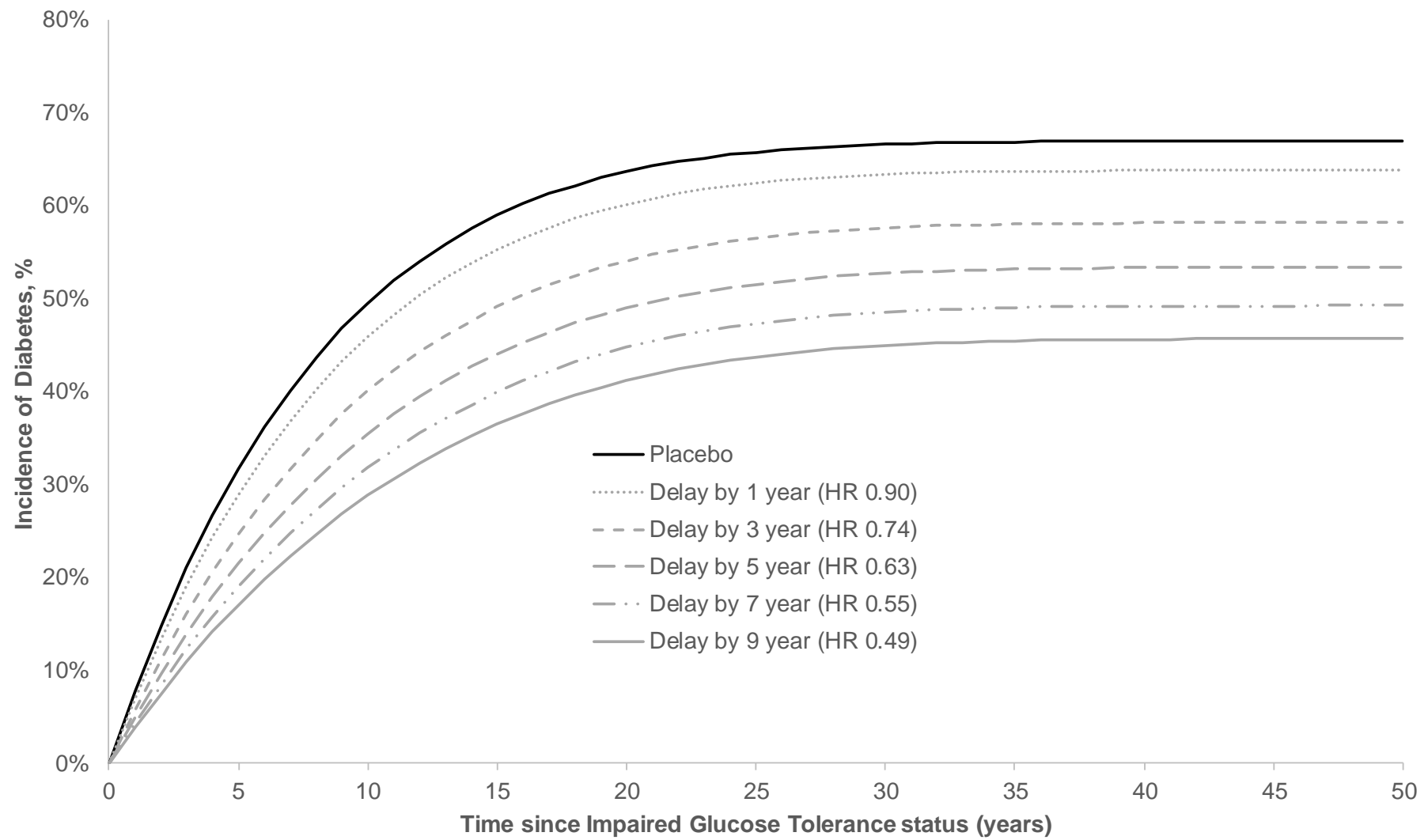
Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
US setting*					
45.5	\$225	\$596	\$891	\$1,129	\$1,327
80.4 (base case)	\$567	\$1,389	\$1,954	\$2,367	\$2,680
114.3	\$947	\$2,170	\$2,921	\$3,428	\$3,792
288	\$2,857	\$5,144	\$6,110	\$6,636	\$6,964
693	\$6,144	\$8,238	\$8,818	\$9,085	\$9,235
UK setting†					
45.5	£79	£209	£313	£397	£466
80.4 (base case)	£201	£491	£691	£836	£947
114.3	£337	£771	£1,038	£1,218	£1,347
288	£1,041	£1,865	£2,209	£2,396	£2,512
693	£2,318	£3,058	£3,251	£3,338	£3,385

*discounted at 3% and using cost-effectiveness threshold of \$100,000 per QALY; † discounted at 3.5% and using cost-effectiveness threshold of £20,000 per QALY

Figure legends

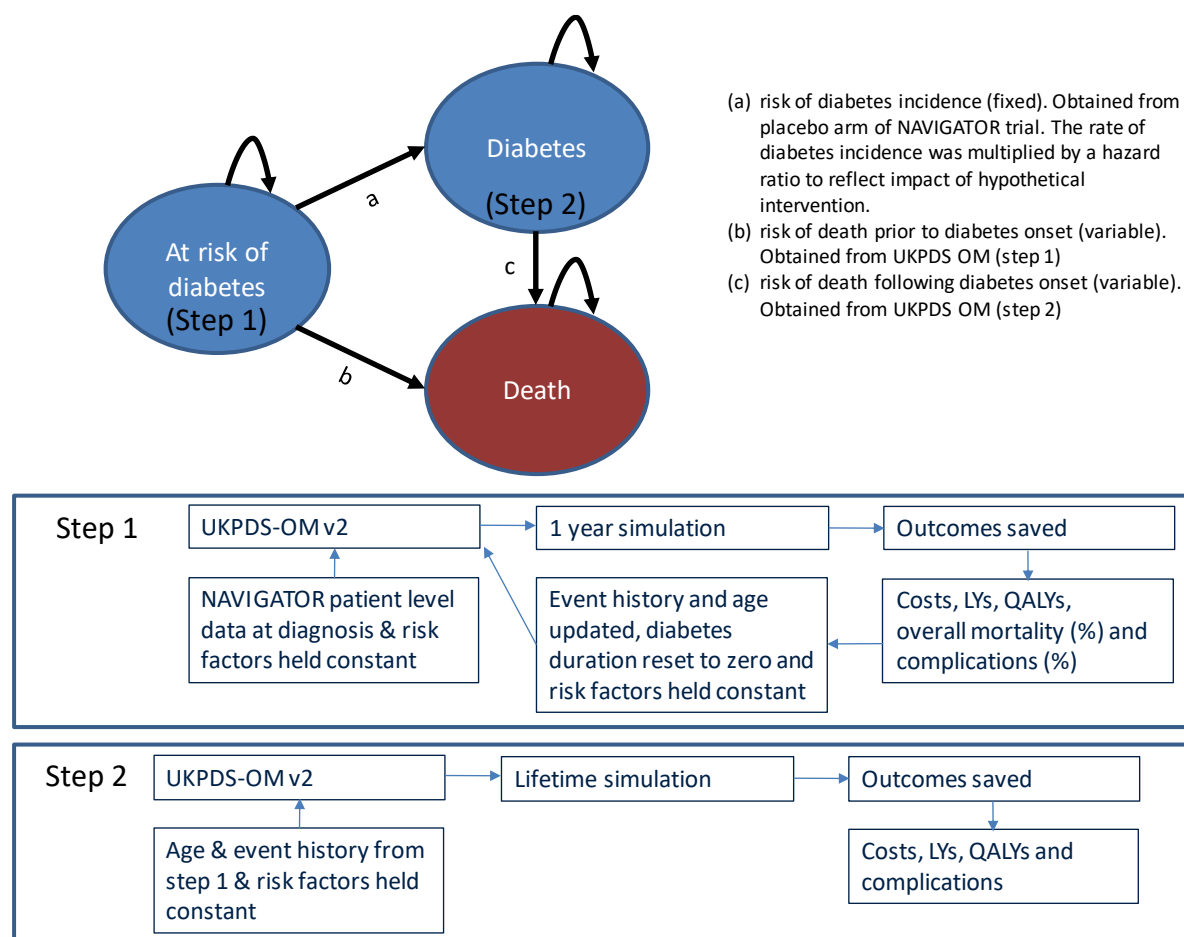
Figure 1. Simulating impact of delaying onset of diabetes in at risk population*

*Simulated cumulative incidence of diabetes among individuals with IGT using the observed rate from NAVIGATOR (placebo arm, 80.4 per 1000 person years) allowing for death as a competing risk. The relative effectiveness of each hypothetical intervention was modelled as a hazard ratio derived from postponing the median time to diabetes by 1, 3, 5, 7 and 9 years (in the absence of death as a competing risk).



Online appendix

Figure A.1. Modelling framework to estimate



Step 1 was used to estimate outcomes (costs, life years and QALYs) and mortality prior to diabetes onset for each year and each individual in the ‘at risk of diabetes’ health state. Individual-level mortality rate estimated in Step 1 was used to determine the transition to ‘death’ state from ‘at risk of diabetes’ state. Step 2 was used following progression to diabetes health state to produce costs, life years and QALYs from diabetes onset to end of simulation.

Relative effectiveness of hypothetical intervention

We estimated the median time to diabetes using the formula: $\ln(2)/\text{rate}$. For example, the median time in the placebo arm of the NAVIGATOR trial was 8.6 years (80.4 per 1000 person years). We then added 1, 3, 5, 7 and 9 years to the median time and converted it back to a rate. Hence, the new rate of diabetes incidence if the intervention delayed onset by one year was 72.0 per 1000 person years (median time to diabetes 9.6 years).

The hazard ratio was estimated by dividing the new rate of diabetes incidence following intervention by the rate in the placebo arm. Using the example above, for an intervention delaying the onset of diabetes by 1 year the hazard ratio was estimated to be 0.90 (72.0/80.4). Hence, the hazard ratios for interventions delaying the onset of diabetes by 3, 5, 7 and 9 years were 0.74 (59.6/80.4), 0.63 (50.9/80.4), 0.55 (44.4/80.4) and 0.49 (39.3/80.4), respectively.

The estimated hazard ratios were then applied to the rate of diabetes incidence to simulate the impact of the hypothetical interventions. It is worth noting that the hazard ratios were estimated in a scenario that excluded death as a competing risk. Therefore, once death was allowed as a competing risk in the modelling framework the delay in the median time to diabetes onset was larger than 1, 3, 5, 7 and 9 years respectively.

Propagating uncertainty

We reduced Monte-Carlo simulation error for predicted outcomes when using UKPDS-OM2 by averaging 5,000 simulations per patient. We propagated parameter

uncertainty through the model into the different outcomes by performing 300 random draws of the sets of fully correlated coefficients from all risk event equations.

Risk factor trajectories

In the base case, we held risk factors constant from baseline. In sensitivity analysis, we explored the impact of these assumptions by changing the trajectories of HbA1c, BMI, LDL, HDL and systolic blood pressure (SBP) over time based on their values at start of simulation. To achieve this, we used unpublished risk factor equations based on UKPDS longitudinal data. These assume the risk factors to be independent of each other and make future predictions of their values based on age, log of year, sex, risk factor value at baseline, previous year value of risk factor and ethnicity, where applicable. The equations are currently being submitted to a peer-reviewed journal.

Benchmarking the cost-effectiveness of interventions delaying diabetes

Table A.1: NAVIGATOR and UKPDS-OM2 population characteristics

Characteristics	NAVIGATOR	UKPDS-OM2
Patients	3058	5102
Median follow up post diagnosis of diabetes (years)	6.5	17.6
Age at diagnosis (years)	66 (6.9)	52 (9)
% men	52	59
% white	83	82
% Asian Indian	N/A	10
% Afro-Caribbean/Black	2	8
% Oriental	7	N/A
% Other	8	0
HbA1c (%)	6.1 (0.6)	6.5 (1.4)
SBP (mmHG)	136 (16)	135 (21)
Total cholesterol (mmol/l)	5.2 (1.1)	N/A
LDL (mmol/l)	4.0 (1.1)	3.5 (1.0)
HDL (mmol/l)	1.3 (0.3)	1.1 (0.3)
Smokers (%)*	11.2	31
BMI (kg/m ²)	31.5 (5.7)	27.7 (5.3)
Previous history (%)		
Atrial fibrillation	4	1
PVD	1	8
MI	15	0
IHD	29	0
Stroke	3	0
Amputation	0	0
Renal failure	1	0
Heart failure	1	0

N/A: not available

HbA1c First year of baseline n=4675; SBP First year of baseline n=4916; LDL First year of baseline n=4541; HDL first year of baseline n=4579; Smokers n=5,062.

Benchmarking the cost-effectiveness of interventions delaying diabetes

Table A.2: Relative risk for different types of macro and micro-vascular events from a change in duration of diabetes relative to a recently diagnosed patient, holding everything else constant*

Duration of diabetes (year)	Ischaemic heart disease	Myocardial infarction (Men)	Myocardial infarction (Women)	Heart failure	Stroke	Amputation	Blindness in one eye	Renal failure	Ulcer
1	1.42	1.00	1.59	1.86	1.76	3.19	1.00	1.00	1.00
2	1.64	1.00	1.94	2.42	2.24	5.50	1.00	1.00	1.00
3	1.80	1.00	2.20	2.88	2.62	7.87	1.00	1.00	1.00
4	1.93	1.00	2.42	3.28	2.95	10.29	1.00	1.00	1.00
5	2.04	1.00	2.61	3.64	3.24	12.75	1.00	1.00	1.00
6	2.13	1.00	2.78	3.96	3.50	15.23	1.00	1.00	1.00
7	2.22	1.00	2.93	4.27	3.74	17.75	1.00	1.00	1.00
8	2.30	1.00	3.07	4.55	3.97	20.28	1.00	1.00	1.00
9	2.37	1.00	3.20	4.82	4.18	22.84	1.00	1.00	1.00

* estimated using the UKPDS-OM2 equations based on the UKPDS data(14). We predicted the absolute risk of each event at years 1,...,9 and divided it by the predicted risk of a newly diagnosed patient.

Benchmarking the cost-effectiveness of interventions delaying diabetes

Table A.3: Quality of life mean estimates and costs† used in the simulation exercise. US costs expressed in \$2017 prices and UK costs expressed in £2017 prices

	US		UK	
Category	Mean estimate	Source	Mean estimate	Source
Quality of life decrement				
Initial utility	0.807	Alva 2014(16)	0.807	Alva 2014(16)
IHD	0.000	Alva 2014(16)	0.000	Alva 2014(16)
MI	-0.065	Alva 2014(16)	-0.065	Alva 2014(16)
Heart failure	-0.101	Alva 2014(16)	-0.101	Alva 2014(16)
Stroke	-0.165	Alva 2014(16)	-0.165	Alva 2014(16)
Amputation	-0.172	Alva 2014(16)	-0.172	Alva 2014(16)
Blindness	0.000	Alva 2014(16)	0.000	Alva 2014(16)
Renal failure	-0.330	Lung 2011 (18)	-0.330	Lung 2011 (18)
Ulcer	-0.210	Lung 2011 (18)	-0.210	Lung 2011 (18)
Costs				
IGT management costs‡	\$6,762	Khan 2017 and ADA 2018	£636-£2,149*	DPP(22) and Alva 2015(17)
Diabetes management costs‡	\$9,158	ADA 2018 (21)	£827-£2,792*	Alva 2015(17)
In the year of non-fatal event§				
IHD	\$24,617	Ward 2014 (15)	£10,276-£18,785*	Alva 2015(17)
MI	\$64,912	Ward 2014 (15)	£7,265-£13,102*	Alva 2015(17)
Heart failure	\$27,322	Ward 2014 (15)	£3,807-£6,332*	Alva 2015(17)
Stroke	\$48,437	Ward 2014 (15)	£7,092-£11,931*	Alva 2015(17)
Amputation	\$10,397	Ward 2014 (15)	£12,310-£18,918*	Alva 2015(17)
Blindness	\$3,291	Ward 2014 (15)	£2,858-£5,661*	Alva 2015(17)
Renal failure	\$82,472	Ward 2014 (15)	£20,578	NHS Blood and Transplant 2009 (20)
Ulcer	\$2,469	Ward 2014 (15)	£7,076	Kerr 2014 (19)
In the year of fatal event				
IHD	\$24,617	Ward 2014 (15)	£4,453-£6,421*	Alva 2015(17)
MI	\$64,912	Ward 2014 (15)	£2,211-£8,004*	Alva 2015(17)
Stroke	\$48,437	Ward 2014 (15)	£4,964-£7,674*	Alva 2015(17)
In subsequent years§				
IHD	\$2,189	Ward 2014 (15)	£1,526-£4,770*	Alva 2015(17)
MI	\$2,189	Ward 2014 (15)	£1,498-£4,575*	Alva 2015(17)
Heart failure	\$2,189	Ward 2014 (15)	£2,075-£5,539*	Alva 2015(17)
Stroke	\$17,872	Ward 2014 (15)	£1,567-£4,755*	Alva 2015(17)
Amputation	0	Ward 2014 (15)	£3,031-£6,550*	Alva 2015(17)
Blindness	\$3,291	Ward 2014 (15)	£1,037-£3,000*	Alva 2015(17)
Renal failure	\$82,472	Ward 2014 (15)	£20,578	NHS Blood and Transplant 2009 (20)
Ulcer	\$2,469	Ward 2014 (15)	£1,072	Kerr 2014 (19)

†US costs include medications, outpatient consultations, emergency department visits and inpatient stays(15). UK costs include non-inpatient contacts (e.g. general practitioner, nurse, hospital eye clinic, etc.) and inpatient stay(17). ‡ US diabetes management costs obtained from ADA 2018 excluding costs of complications. UK diabetes management costs obtained from UKPDS and concern costs in the absence of complications(17). IGT costs estimated by applying ratio of IGT and diabetes costs per individual from Khan 2007(23) for the US setting (0.74) and DPP(22) for the UK setting (0.77).

§ In the US analysis, IGT/diabetes management costs (\$6,762/\$9,158) were added to costs of non-fatal events in the year of the event and in subsequent years. In the UK analysis, management costs were already included in the costs of complications and no further costs were added to them.

* Costs varied by sex and age group (up to 50, 51-60, 61-70, 71-80, 81+).

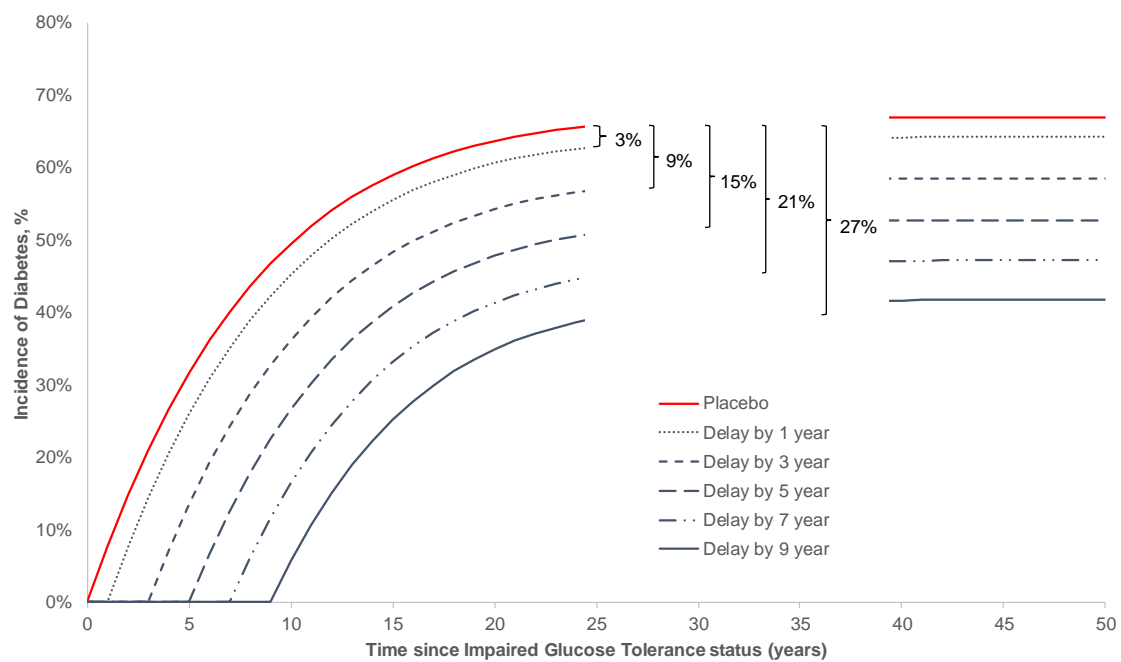
Benchmarking the cost-effectiveness of interventions delaying diabetes

Figure A.2: Simulated incremental complication costs and incremental quality-adjusted life years (QALYs) gained of postponing versus no postponing for different annual postponement in US and UK setting*



* Excluding costs of intervention and assuming rate of diabetes progression of 80.4 per 1000 person years.

Figure A.3. Simulating impact of delaying onset of diabetes in at risk population*



*Simulated cumulative incidence of diabetes among individuals with IGT using the observed rate from NAVIGATOR (placebo arm in Nateglinide comparison, 80.4 per 1000 person years) allowing for death as a competing risk. The relative effectiveness of each hypothetical intervention was modelled by shifting the onset of diabetes delay by 1, 3, 5, 7 and 9 years for all individuals.

Benchmarking the cost-effectiveness of interventions delaying diabetes

Table A.4. Outcomes of population at risk of diabetes progression (80.4 per 1000 person years) with relative effectiveness of each hypothetical intervention modelled by shifting the onset of diabetes by 1, 3, 5, 7 and 9 years for all individuals.

Outcomes (over 50 years)	No delay	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
Cumulative incidence of diabetes, %	67.0	64.2	58.5	52.8	47.2	41.7
Hazard ratio vs no delay	-	0.93	0.79	0.68	0.58	0.49
US setting*						
Life years	11.90 (11.65-12.13)	11.94 (11.72-12.15)	12.01 (11.82-12.18)	12.06 (11.91-12.20)	12.11 (11.99-12.22)	12.15 (12.06-12.24)
QALYs	9.51 (9.32-9.68)	9.55 (9.38-9.71)	9.61 (9.47-9.74)	9.66 (9.55-9.77)	9.71 (9.62-9.79)	9.75 (9.67-9.82)
Costs (excluding intervention)	\$161,457 (156792-166367)	\$159,629 (155250-164380)	\$155,972 (152056-160414)	\$152,838 (149144-157007)	\$150,169 (146453-154398)	\$147,918 (144201-152244)
Δ Life years vs no delay	-	0.04 (0.02 to 0.06)	0.11 (0.05 to 0.15)	0.16 (0.07 to 0.25)	0.21 (0.10 to 0.32)	0.25 (0.12 to 0.38)
Δ QALY vs no delay	-	0.04 (0.02 to 0.06)	0.10 (0.05 to 0.15)	0.16 (0.09 to 0.23)	0.21 (0.12 to 0.30)	0.25 (0.15 to 0.36)
Δ Costs vs no delay (excluding intervention)	-	-\$1,828 (-2423 to -1262)	-\$5,485 (-7075 to -3987)	-\$8,620 (-10994 to -6443)	-\$11,288 (-14272 to -8569)	-\$13,539 (-16993 to -10361)
Max annual cost of intervention to be cost-effective at \$100,000/QALY	-	\$864 (764-964)	\$2,004 (1733-2275)	\$2,797 (2389-3206)	\$3,370 (2848-3892)	\$3,795 (3176-4413)
UK setting**						
Life years	11.43 (11.19-11.64)	11.47 (11.25-11.66)	11.53 (11.35-11.68)	11.58 (11.43-11.70)	11.62 (11.51-11.72)	11.65 (11.56-11.73)
QALYs	9.13 (8.94-9.30)	9.17 (9.00-9.32)	9.23 (9.10-9.35)	9.28 (9.17-9.37)	9.32 (9.23-9.40)	9.35 (9.28-9.42)
Costs (excluding intervention)	£38,321 (37208-39470)	£38,078 (37057-39146)	£37,549 (36638-38471)	£37,088 (36344-37922)	£36,689 (36034-37426)	£36,348 (35746-37040)
Δ Life years vs no delay	-	0.04 (0.02 to 0.06)	0.10 (0.04 to 0.16)	0.15 (0.06 to 0.25)	0.20 (0.08 to 0.31)	0.23 (0.09 to 0.36)
Δ QALY vs no delay	-	0.04 (0.02 to 0.06)	0.10 (0.05 to 0.15)	0.15 (0.08 to 0.22)	0.19 (0.10 to 0.28)	0.22 (0.12 to 0.33)
Δ Costs vs no delay (excluding intervention)	-	-£242 (-385 to -107)	-£772 (-1166 to -395)	-£1,233 (-1817 to -659)	-£1,631 (-2361 to -899)	-£1,973 (-2813 to -1141)
Max annual cost of intervention to be cost-effective at £20,000/QALY	-	£478 (384-573)	£982 (762-1202)	£1,262 (963-1560)	£1,433 (1082-1784)	£1,533 (1143-1922)

*discounted at 3%; **discounted at 3.5%

Benchmarking the cost-effectiveness of interventions delaying diabetes

Table A.5: Maximum annual cost of intervention in the US and UK for intervention to be cost-effective relative to no delay by varying the rate of progression to diabetes with relative effectiveness of each hypothetical intervention modelled by shifting the onset of diabetes by 1, 3, 5, 7 and 9 years for all individuals.

Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
US setting*					
45.5	\$490	\$1,208	\$1,749	\$2,162	\$2,480
80.4 (base case)	\$864	\$2,004	\$2,797	\$3,370	\$3,795
114.3	\$1,225	\$2,684	\$3,632	\$4,286	\$4,756
288	\$3,049	\$5,225	\$6,306	\$6,951	\$7,380
693	\$7,050	\$8,378	\$8,899	\$9,183	\$9,381
UK setting**					
45.5	£248	£561	£764	£901	£989
80.4 (base case)	£478	£982	£1262	£1433	£1533
114.3	£704	£1332	£1643	£1821	£1918
288	£1689	£2429	£2694	£2825	£2882
693	£3091	£3362	£3459	£3506	£3512

*discounted at 3% and using \$100,000 per QALY threshold; **discounted at 3.5% and using £20,000 per QALY threshold

Benchmarking the cost-effectiveness of interventions delaying diabetes

Table A.6. Outcomes of US and UK population at risk of diabetes (80.4 per 1000 person years) conditional on effectiveness of hypothetical intervention and assuming IGT management costs to be the same as diabetes management costs (\$9,158 and £827-£2,792 per year)

Outcomes (over 50 years)	No delay	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
Cumulative incidence of diabetes, %	67.0	63.8	58.2	53.4	49.3	45.7
Hazard ratio vs no delay	-	0.92	0.79	0.69	0.61	0.55
US setting*						
Life years	11.90 (11.67-12.13)	11.92 (11.70-12.14)	11.97 (11.77-12.17)	12.00 (11.82-12.18)	12.03 (11.86-12.20)	12.05 (11.89-12.21)
QALYs	9.51 (9.33-9.69)	9.53 (9.36-9.71)	9.57 (9.42-9.73)	9.60 (9.46-9.75)	9.63 (9.50-9.77)	9.65 (9.53-9.78)
Costs (excluding intervention)	\$176,734 (172008-181632)	\$176,298 (171699-180942)	\$175,562 (171237-179815)	\$174,966 (170823-179155)	\$174,475 (170483-178626)	\$174,062 (170109-178180)
Δ Life years vs no delay	-	0.03 (0.01 to 0.04)	0.07 (0.04 to 0.10)	0.10 (0.05 to 0.15)	0.13 (0.07 to 0.19)	0.15 (0.08 to 0.22)
Δ QALY vs no delay	-	0.02 (0.01 to 0.03)	0.07 (0.04 to 0.09)	0.10 (0.06 to 0.13)	0.13 (0.08 to 0.17)	0.15 (0.09 to 0.20)
Δ Costs vs no delay	-	-\$436 (-720 to -184)	-\$1,172 (-1937 to -494)	-\$1,768 (-2924 to -744)	-\$2,260 (-3739 to -950)	-\$2,672 (-4423 to -1123)
Max annual cost of intervention to be cost-effective at \$100,000/QALY	-	\$427 (350-503)	\$1,045 (854-1236)	\$1,469 (1197-1741)	\$1,778 (1445-2111)	\$2,013 (1632-2393)
UK setting**						
Life years	11.43 (11.21-11.63)	11.45 (11.25-11.64)	11.49 (11.30-11.67)	11.52 (11.35-11.68)	11.54 (11.38-11.69)	11.56 (11.41-11.70)
QALYs	9.13 (8.97-9.29)	9.15 (9.00-9.31)	9.19 (9.05-9.33)	9.22 (9.09-9.35)	9.24 (9.12-9.37)	9.26 (9.15-9.38)
Costs (excluding intervention)	£40,223 (39089-41366)	£40,139 (39054-41236)	£39,998 (38986-41014)	£39,884 (38934-40830)	£39,790 (38891-40676)	£39,711 (38856-40562)
Δ Life years vs no delay	-	0.02 (0.01 to 0.03)	0.06 (0.04 to 0.09)	0.09 (0.05 to 0.13)	0.11 (0.07 to 0.17)	0.13 (0.08 to 0.20)
Δ QALY vs no delay	-	0.02 (0.01 to 0.03)	0.06 (0.04 to 0.08)	0.09 (0.06 to 0.12)	0.11 (0.08 to 0.16)	0.13 (0.09 to 0.18)
Δ Costs vs no delay (excluding intervention)	-	-£84 (-148 to -21)	-£225 (-403 to -55)	-£339 (-611 to -83)	-£433 (-781 to -105)	-£512 (-924 to -124)
Max annual cost of intervention to be cost-effective at £20,000/QALY	-	£182 (151-214)	£446 (367-525)	£627 (513-740)	£758 (619-897)	£858 (698-1017)

*discounted at 3%; **discounted at 3.5%

Benchmarking the cost-effectiveness of interventions delaying diabetes

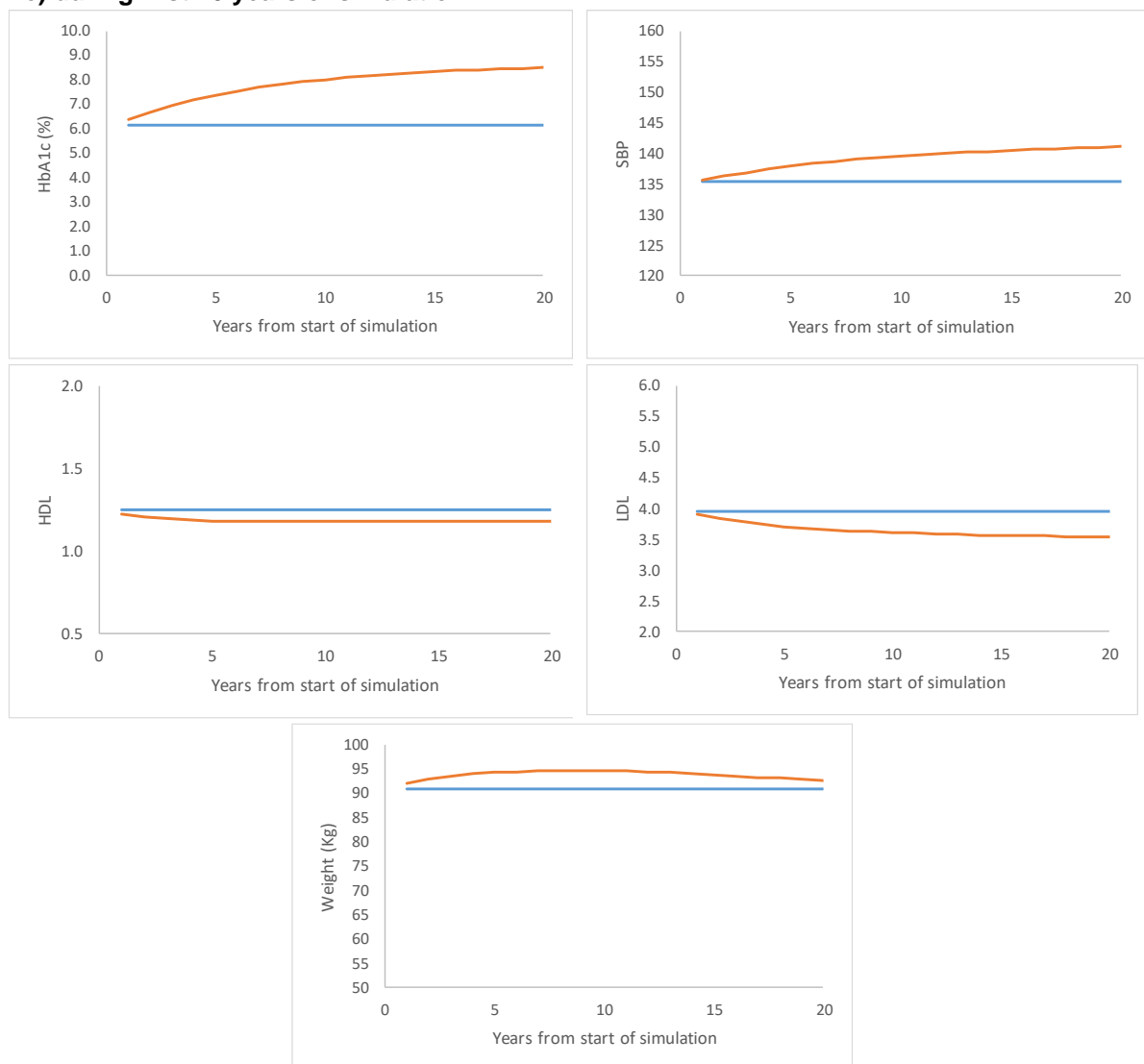
Table A.7: Maximum annual cost of intervention in the US and UK for intervention to be cost-effective relative to no delay by varying the rate of progression to diabetes and assuming IGT management costs to be the same as diabetes management costs (\$9,158 and £827-£2,792 per year)

Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
US setting*					
45.5	\$168	\$447	\$667	\$846	\$993
80.4 (base case)	\$427	\$1,045	\$1,469	\$1,778	\$2,013
114.3	\$716	\$1,637	\$2,202	\$2,583	\$2,855
288	\$2,204	\$3,938	\$4,660	\$5,050	\$5,292
693	\$4,945	\$6,468	\$6,855	\$7,026	\$7,119
UK setting**					
45.5	£71	£189	£282	£358	£420
80.4 (base case)	£182	£446	£627	£758	£858
114.3	£307	£702	£944	£1,107	£1,223
288	£961	£1,714	£2,026	£2,194	£2,297
693	£2,165	£2,835	£3,003	£3,076	£3,114

*discounted at 3% and using \$100,000 per QALY threshold; **discounted at 3.5% and using £20,000 per QALY threshold

Benchmarking the cost-effectiveness of interventions delaying diabetes

Figure A.4. Average risk factor trajectories held constant (blue line) and predicted annually from baseline onwards regardless of diabetes onset using UKPDS-based equations (orange line) during first 20 years of simulation



Benchmarking the cost-effectiveness of interventions delaying diabetes

Table A.8: Maximum annual cost of intervention in the US for intervention to be cost-effective relative to no delay by varying the rate of progression to diabetes and allowing risk factors to change over time (scenario 1 and 2)*

Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
Base case: risk factors held constant					
45.5	\$225	\$596	\$891	\$1,129	\$1,327
80.4 (base case)	\$567	\$1,389	\$1,954	\$2,367	\$2,680
114.3	\$947	\$2,170	\$2,921	\$3,428	\$3,792
288	\$2,857	\$5,144	\$6,110	\$6,636	\$6,964
693	\$6,144	\$8,238	\$8,818	\$9,085	\$9,235
Scenario 1: risk factors were predicted annually from baseline onwards regardless of diabetes onset					
45.5	\$239	\$633	\$946	\$1,200	\$1,410
80.4 (base case)	\$599	\$1,468	\$2,068	\$2,506	\$2,839
114.3	\$995	\$2,285	\$3,081	\$3,620	\$4,007
288	\$2,946	\$5,342	\$6,370	\$6,936	\$7,293
693	\$6,201	\$8,426	\$9,085	\$9,399	\$9,582
Scenario 2: risk factors were held constant up to diabetes onset and then predicted annually from that point onwards					
45.5	\$245	\$651	\$972	\$1,232	\$1,447
80.4 (base case)	\$619	\$1,515	\$2,132	\$2,582	\$2,923
114.3	\$1,033	\$2,367	\$3,187	\$3,740	\$4,137
288	\$3,115	\$5,611	\$6,665	\$7,239	\$7,597
693	\$6,664	\$8,962	\$9,602	\$9,896	\$10,062

*discounted at 3% and using \$100,000 per QALY threshold

Benchmarking the cost-effectiveness of interventions delaying diabetes

Table A.9: Maximum annual cost of intervention in the US for intervention to be cost-effective relative to no delay using \$50,000 and \$200,000 per QALY threshold and varying the rate of progression to diabetes (mean and 95%CI)

Annual rate of progression (per 1000 person years)	1 year delay	3 year delay	5 year delay	7 year delay	9 year delay
Using \$50,000 per QALY*					
45.5	\$154 (134-173)	\$408 (355-461)	\$610 (530-689)	\$773 (672-875)	\$909 (789-1029)
80.4 (base case)	\$386 (342-430)	\$946 (835-1056)	\$1,332 (1173-1490)	\$1,613 (1419-1808)	\$1,828 (1605-2051)
114.3	\$642 (575-709)	\$1,473 (1313-1632)	\$1,985 (1764-2205)	\$2,331 (2067-2595)	\$2,580 (2283-2877)
288	\$1,913 (1766-2060)	\$3,460 (3166-3755)	\$4,119 (3745-4493)	\$4,480 (4055-4905)	\$4,707 (4246-5168)
693	\$3,992 (3766-4218)	\$5,450 (5073-5826)	\$5,871 (5419-6324)	\$6,069 (5569-6570)	\$6,184 (5649-6718)
Using \$200,000 per QALY*					
45.5	\$367 (266-468)	\$973 (702-1244)	\$1,453 (1044-1861)	\$1,841 (1320-2362)	\$2,163 (1547-2778)
80.4 (base case)	\$930 (703-1156)	\$2,276 (1708-2843)	\$3,200 (2387-4013)	\$3,873 (2874-4872)	\$4,383 (3239-5527)
114.3	\$1,557 (1214-1899)	\$3,564 (2747-4380)	\$4,794 (3664-5925)	\$5,623 (4268-6977)	\$6,216 (4693-7739)
288	\$4,743 (3998-5488)	\$8,513 (7014-10012)	\$10,091 (8185-11998)	\$10,946 (8777-13116)	\$11,478 (9123-13832)
693	\$10,448 (9321-11575)	\$13,813 (11914-15712)	\$14,712 (12421-17003)	\$15,115 (12573-17657)	\$15,338 (12620-18057)

*discounted at 3%