



Benchmarking the Cost-Effectiveness of Interventions Delaying Diabetes: A Simulation Study Based on NAVIGATOR Data

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OBJECTIVE

To estimate using the UK 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 (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) study.

RESEARCH DESIGN AND METHODS

We simulated the impact of delaying diabetes onset by 1–9 years, utilizing data from the 3,058 of 9,306 NAVIGATOR trial participants who developed type 2 diabetes. Costs and utility weights associated with diabetes and diabetes-related complications were obtained for the U.S. and U.K. settings, with costs expressed in 2017 values. We estimated discounted lifetime costs and quality-adjusted life years (QALYs) with 95% CIs.

RESULTS

Gains in QALYs increased from 0.02 (U.S. setting, 95% CI 0.01, 0.03) to 0.15 (U.S. setting, 95% CI 0.10, 0.21) as the imposed time to diabetes onset was increased from 1 to 9 years, respectively. Savings in complication costs increased from \$1,388 (95% CI \$1,092, \$1,669) for a 1-year delay to \$8,437 (95% CI \$6,611, \$10,197) for a delay of 9 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 U.S. and U.K., respectively, as the modeled delay in diabetes onset was increased from 1 to 9 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 (DPP) (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

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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 favorable conclusions (10,11).

Rather than evaluate a specific intervention in a specific setting, we have taken a different approach by using simulation modeling of a contemporaneous population to address the following question: What is the maximum annual cost and minimum delay in diabetes onset needed for an intervention to be cost-effective in the U.S. and U.K. settings? We used data from the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial (12,13), specifically the characteristics of the 3,058 of 9,306 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 while remaining cost-effective in the U.S. and U.K. settings.

RESEARCH DESIGN AND METHODS

Patient Sample

NAVIGATOR was a double-blind, randomized 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 160 mg daily) or placebo, and nateglinide (up to 60 mg three times daily) or placebo, in a 2-by-2 factorial design. These were given in addition to participation in a structured program of lifestyle modification. Participants were followed-up for a median of 5.0 years for the type 2 diabetes onset end point and a median of 6.5 years for the mortality end point (12,13).

IGT was defined as a fasting plasma glucose (FPG) level of ≥ 5.3 but < 7.0 mmol/L and a 2-h 75-g oral glucose tolerance test (OGTT) of ≥ 7.8 but < 11.1 mmol/L. New-onset diabetes was defined as a FPG of ≥ 7 mmol/L or a 2-h OGTT of ≥ 11.1 mmol/L on two consecutive valid glycemic 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 randomized treatment assignments, adjudicated cases in which diabetes was diagnosed by other means.

Data required for the UK Prospective Diabetes Study Outcomes Model version 2 (UKPDS-OM2), i.e., HbA_{1c}, systolic blood pressure, smoking status, total cholesterol, and HDL cholesterol, were available for 3,058 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 population of patients who were newly diagnosed with type 2 diabetes 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 1,000 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 population of patients at risk of diabetes 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 population at risk of diabetes by 1–9 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 Supplementary Table 1.

The UKPDS-OM2 predicts an individual's absolute probability of experiencing any of eight complications (first and second myocardial infarction, first and second stroke, heart failure, ischemic heart disease, first and second amputation, renal failure, 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, 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 history of complications. Duration of diabetes can also increase the absolute risk of some complications, such as ischemic 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 Supplementary Table 2), holding everything else constant (14).

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

Costs and Health Utilities in U.S. and U.K.

We obtained costs and utilities associated with diabetes management and diabetes-related complications (15–21) for the U.S. and U.K. settings (Supplementary Table 3, for more details). Diabetes-related costs comprised noninpatient costs (e.g., physician/outpatient visits, emergency department visit, and medications) 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 population of patients at risk of diabetes. The management costs of IGT (excluding complications) in the U.S. and U.K. were estimated by applying the ratio of IGT and diabetes

costs reported in Khan et al. (22) (0.74) and the DPP trial (0.77) (23), respectively, 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 (Supplementary Fig. 1).

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

We estimated mortality, costs, life years, and QALYs for the health states of being at risk of diabetes and having diabetes in any given year by using the 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 population with newly diagnosed diabetes 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 the state of having diabetes 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 to 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 onward allowing the model to update age, event histories, and diabetes duration. Lifetime costs and health outcomes were discounted at 3%

(U.S. setting) (24) and 3.5% (U.K. setting) (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 U.S. (26) or £20,000 per QALY in the U.K. (25). Using the base case rate of progression (80.4 per 1,000 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 Supplementary Material for details). We report discounted mean costs and QALYs estimates with 95% CIs.

In the sensitivity analysis, we explored the impact of varying the diabetes incidence rate per 1,000 patient-years between 45.5, which was obtained from a meta-analysis of observational IGT cohorts (27), translating to a 4% annual probability of developing diabetes ($1 - \exp[-0.0455]$); 114.3, which was obtained from placebo group in DPP trial (23) with

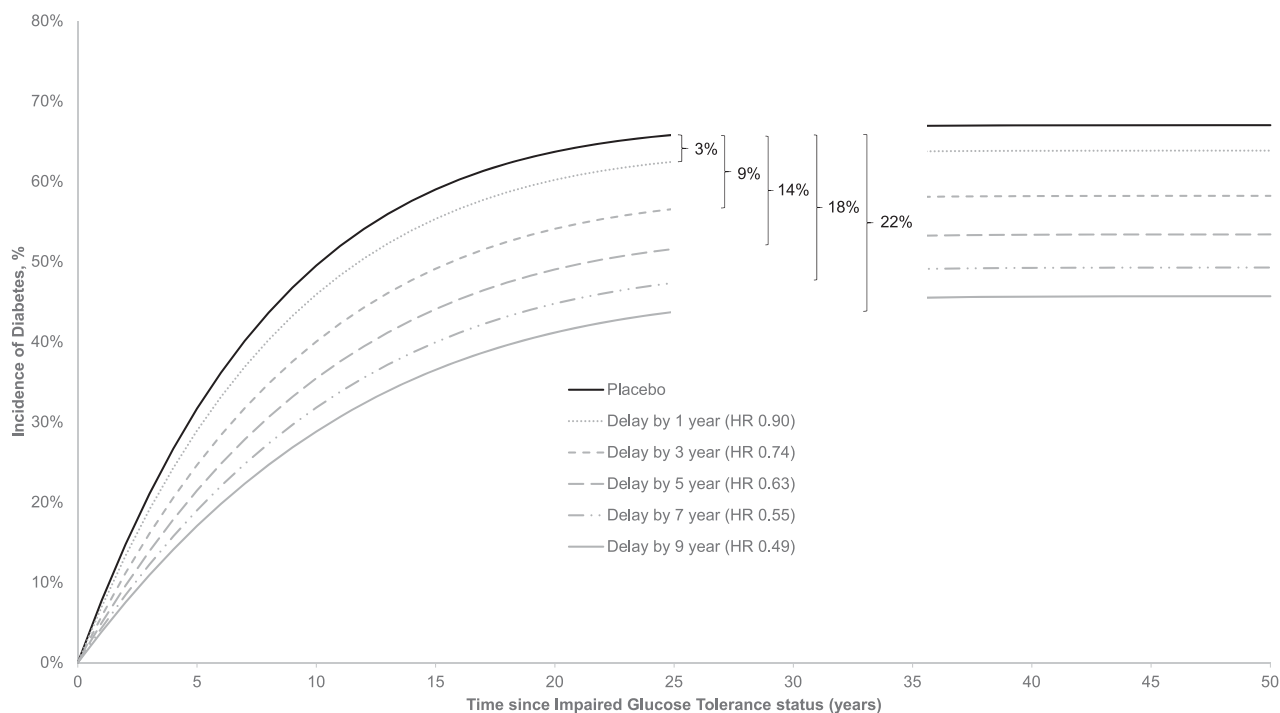


Figure 1—Simulating the impact of delaying the onset of diabetes in an at-risk population. The simulated cumulative incidence of diabetes among individuals with IGT is given using the observed rate from NAVIGATOR (placebo arm, 80.4 per 1,000 person-years) allowing for death as a competing risk. The relative effectiveness of each hypothetical intervention was modeled as a HR 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).

an 11% annual probability of developing diabetes; 288, which assumes a 25% annual probability of developing diabetes ($1 - \exp[-0.288]$); and 693, which assumes a 50% annual probability of developing diabetes ($1 - \exp[-0.693]$). We also explored the impact of modeling 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 U.S. setting). In the U.S. setting, we evaluated the impact of changing the trajectories of risk factors over time by exploring two scenarios: 1) individuals' risk factors were predicted annually from baseline onward regardless of diabetes onset; and 2) individuals' risk factors were held constant up to diabetes onset and then predicted annually from that point onward (see Supplementary Material for details). Finally, we estimated the maximum annual cost of the intervention in the U.S. setting varying the rate of progression to diabetes and adopting cost-effectiveness thresholds of \$50,000 and \$200,000 per QALY (26).

Data and Resource Availability

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

RESULTS

In the base case analysis, we evaluated the lifetime costs and QALYs 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 a 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 46%, 40%, 35%, 32%, and 29%, respectively, by year 10 and 62%, 57%, 52%, 47%, and 44%, respectively, 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 1,000 patient-years. The hypothetical intervention resulted in gains in QALYs and savings in costs of complications in both the U.S. and U.K. settings. In the U.S. setting, the gains in QALYs (discounted at 3%) increased from 0.02 (95% CI 0.01–0.03) to 0.15 (95% CI 0.10–0.21) 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 1-year delay and −\$8,437 for a delay of 9 years). In the U.K. setting, the longer the delay in progression to diabetes the greater the savings in diabetes costs (e.g., −£205 for a delay of 1 year and −£1,257 for a delay of 9 years). The savings were considerably lower in the U.K. setting due to lower management costs of the disease compared with the U.S. setting.

The maximum annual cost, which the intervention could reach while remaining below the cost-effectiveness thresholds (\$100,000/QALY for U.S. and £20,000/QALY for U.K.), 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 U.S. setting and £201 (1-year delay, 95% CI £151–£250) and £947 (9-year delay, 95% CI £699–£1,195) in the U.K. 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.

Supplementary Fig. 2 reports the impact of parameter uncertainty on incremental costs (excluding intervention costs) and QALYs associated with a delay of diabetes onset compared with no delay in diabetes onset. In both U.S. and U.K. settings, the interventions were significantly more effective compared with no delay. In the U.S. setting compared with the U.K. setting, 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 U.S. and £20,000 per QALY in the U.K., 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 the U.S. and U.K. settings while remaining cost-effective. For example, if 25% of individuals were predicted to develop diabetes in year 1 (288 per 1,000 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 U.S. and U.K., respectively. In contrast, if progression to diabetes was lower than the base case (45.5 per 1,000 person-years), the intervention could cost a maximum of \$225 (U.S.) and £79 (U.K.) if it delayed diabetes onset by a single year.

We also modeled the effectiveness of the hypothetical intervention by shifting diabetes onset for all individuals by 1, 3, 5, 7, or 9 years (see Supplementary Fig. 3). Supplementary Table 4 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 the U.S. and U.K. settings. Cost savings increased in the U.S. and U.K. 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 1-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 U.S. setting and £478 (1-year delay, 95% CI £384–£573) and £1,533 (9-year delay, 95% CI £1,143–£1,922) in the U.K. setting (Supplementary Tables 4 and 5).

We modeled the management costs of IGT to be the same as for diabetes. Supplementary Table 6 reports the incremental QALYs and costs running this scenario in the U.S. and U.K. settings. In both settings, we estimated lower cost savings for any given delay scenario compared with the base case. For example, in the U.S. setting, we observed estimated savings of −\$436 compared with −\$1,388 for a delay of 1 year and −\$2,672 compared with −\$8,437 for a delay of 9 years. In the U.S. and U.K. settings, the intervention could support lower annual costs relative to the base case for each effectiveness and rate of progression scenario examined (Supplementary Tables 6 and 7).

Table 1—Outcomes of U.S. and U.K. population at risk for diabetes conditional on the effectiveness of hypothetical intervention

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
HR versus no delay	—	0.92	0.79	0.69	0.61	0.55
U.S. setting*						
Life years	11.90 (11.64–12.14)	11.92 (11.68–12.15)	11.97 (11.79–12.17)	12.00 (11.79–12.19)	12.03 (11.83–12.21)	12.05 (11.87–12.22)
Quality-adjusted life expectancy (QALYs)	9.51 (9.29–9.69)	9.53 (9.33–9.71)	9.57 (9.39–9.74)	9.60 (9.43–9.76)	9.63 (9.47–9.77)	9.65 (9.50–9.78)
Costs, excluding intervention (£)	161,457 (156,721–166,781)	160,069 (155,468–165,305)	157,737 (153,347–162,816)	155,856 (151,640–160,803)	154,311 (150,239–158,942)	153,020 (149,068–157,321)
Δ Life years versus no delay	—	0.03 (0.01–0.04)	0.07 (0.04–0.10)	0.10 (0.06–0.15)	0.13 (0.07–0.19)	0.15 (0.08–0.22)
Δ QALY versus no delay	—	0.02 (0.01–0.03)	0.07 (0.04–0.09)	0.10 (0.07–0.14)	0.13 (0.08–0.18)	0.15 (0.10–0.21)
Δ Costs versus no delay, excluding intervention (£)	—	–1,388 (–1,669 to –1,092)	–3,721 (–4,483 to –2,923)	–5,601 (–6,757 to –4,395)	–7,146 (–8,630 to –5,603)	–8,437 (–10,197 to –6,611)
Maximum annual cost of intervention to be cost-effective at \$100,000/QALY (\$)	—	567 (462–672)	1,389 (1,126–1,652)	1,954 (1,578–2,331)	2,367 (1,904–2,829)	2,680 (2,150–3,210)
U.K. 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 (37,181–39,450)	38,116 (37,021–39,200)	37,769 (36,756–38,780)	37,489 (36,545–38,436)	37,257 (36,371–38,149)	37,063 (36,226–37,944)
Δ Life years versus no delay	—	0.02 (0.01–0.03)	0.06 (0.04–0.09)	0.09 (0.05–0.13)	0.11 (0.07–0.17)	0.13 (0.08–0.20)
Δ QALY versus no delay	—	0.02 (0.01–0.03)	0.06 (0.04–0.08)	0.09 (0.06–0.12)	0.11 (0.08–0.16)	0.13 (0.09–0.18)
Δ Costs versus no delay, excluding intervention (£)	—	–205 (–269 to –145)	–552 (–727 to –389)	–832 (–1,098 to –585)	–1,064 (–1,404 to –745)	–1,257 (–1,660 to –878)
Maximum annual cost of intervention to be cost-effective at £20,000/QALY (£)	—	201 (151–250)	491 (367–616)	691 (513–868)	836 (619–1,054)	947 (699–1,195)

Data are mean (95% CI). *Discounted at 3% and using a cost-effectiveness threshold of \$100,000 per QALY. †Discounted at 3.5% and using a cost-effectiveness threshold of £20,000 per QALY; Δ incremental.

Table 2—Maximum annual cost of intervention in the U.S. and U.K. for intervention to be cost-effective relative to no delay by varying the rate of progression to diabetes

Annual rate of progression (per 1,000 person-years)	1-year delay	3-year delay	5-year delay	7-year delay	9-year delay
U.S. 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
U.K. 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.

Using the base case rate of progression (80.4 per 1,000 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 U.S. setting. In the U.K. 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 modeled risk factors to change over time for the U.S. setting (Supplementary Table 8 and Supplementary Fig. 4). 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 1,000 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 1,000 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 U.S. 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) (Supplementary Table 9).

CONCLUSIONS

As the worldwide prevalence of type 2 diabetes 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 they have typically been trial-based analyses or computer simulation studies (7–11,23). These studies have been based directly or indirectly either on the STOP-NIDDM (Study to Prevent NIDDM) trial (7,8) or the DPP, and have reported the within-trial or lifetime cost-effectiveness of the trial results (23), 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, posing the question of how effective an intervention would have to be and at what cost in order 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 centers 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 U.S. and for the U.K., 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 U.S. and U.K. settings. For example, this will be of use to researchers deciding on which novel agent or biomarker to invest time and resources translating from laboratory 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 U.S. and £201 and £947 per year in the U.K. are cost-effective at \$100,000 per QALY and £20,000 per QALY if diabetes onset is delayed by 1 and 9 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 U.S. setting. Higher rates of diabetes progression translated into a higher annual ceiling costs for preventative interventions in both the U.K. and U.S. settings. However, the U.S. can accommodate higher ceiling costs because the costs of diabetes and its complications are considerably higher than in the U.K.

A number of previous studies have reported quite substantial delays in the 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 (23). In comparison, 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-to-9-year range examined in our study therefore seems reasonable.

Similarly, the DPP group reported that the incremental costs compared with placebo were ~\$400 to \$1,200 annually for a lifestyle intervention and \$500 to \$1,200 for a metformin intervention (22), while the STOP-NIDDM group reported an additional cost of approximately \$2000 per patient over 40 months in the acarbose group compared with placebo, or around \$70 (\$606) 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 the patients at risk of diabetes and in patients with type 2 diabetes. Therefore, we assumed the risk of complications in individuals at risk of diabetes to be the same as that of patients newly diagnosed with diabetes (with the same characteristics, risk factor values, and history of events). This was due to the following: 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 onward because of a 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 related to diabetes 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 modeling strategies used to estimate their value for money.

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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., R.R.H., and A.M.G. designed the study. S.D.R. provided U.S. 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 U.K. 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 data set used for analysis in this manuscript, and reviewed the manuscript. K.A.S., R.M.C., and R.R.H. interpreted the findings and reviewed and edited the manuscript. R.M.C. was the clinical investigator in the NAVIGATOR trial. 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.

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