Estimating Risk Factor Time Paths Among People With Type 2 Diabetes And QALY Gains From Risk Factor Management

This version of the manuscript has been accepted for publication after peer review but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at https://doi.org/10.1007/s40273-024-01398-4.

Running title: Type 2 Diabetes Risk Factor Time Paths

Word count (excluding abstract, references, figure legends, tables, supplementary materials): 4073

Ni Gao, MBBS, PhD,[1,2] Helen A. Dakin, DPhil,[1] Rury R. Holman, FRCP[3], Lee-Ling Lim, MBBS, PhD[4-6], José Leal, DPhil,[1*] Philip Clarke, PhD [1*]

* These authors contributed equally

[1] Health Economics Research Centre, University of Oxford, Oxford, UK

[2] Centre for Health Economics, University of York, York, UK

[3] Diabetes Trials Unit, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[4] Department of Medicine, Faculty of Medicine University of Malaya, Kuala Lumpur, Malaysia

[5] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR

[6] Asia Diabetes Foundation, Hong Kong, SAR

ORCID for each author:

Ni Gao, MBBS, PhD https://orcid.org/0000-0003-2099-0112

Helen A. Dakin, DPhil https://orcid.org/0000-0003-3255-748X

Rury R. Holman, FRCP https://orcid.org/0000-0002-1256-874X

Lee-Ling Lim, MBBS, PhD https://orcid.org/0000-0002-6214-6924

José Leal, DPhil

Philip Clarke, PhD

Contact details for corresponding author:

Helen Dakin, Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Old Road Campus, Headington, Oxford, OX3 7LF, UK. Email: helen.dakin@dph.ox.ac.uk; Tel: +44(0)1865 289422. http://orcid.org/0000-0003-3255-748X

Author contributions

Concept and design: Gao, Dakin, Leal, Clarke

Acquisition of data: Holman

Analysis and interpretation of data: Gao, Dakin, Leal, Holman, Lim, Clarke

Drafting of the manuscript: Gao, Dakin, Leal, Clarke

Critical revision of the paper for important intellectual content: Gao, Dakin, Leal, Holman, Lim, Clarke

Obtaining funding: Leal, Holman, Lim, Clarke

Supervision: Dakin, Leal, Clarke

Funding

This work was funded by supported by the Medical Research Council (MR/T018593/1). The project was supported also by the NIHR Oxford Biomedical Research Centre and the UK-Malaysia Joint Partnership on Non-Communicable Diseases under the Malaysia Partnership and Alliances in Research (MyPAiR), funded by the Ministry of Education, Malaysia (Grant number: IF076-2019). HD was partly funded by an NIHR Senior Research Fellowship through the Oxford Biomedical Research Centre at the time the research was conducted. JL acknowledges support from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115881 (RHAPSODY). PC is partly supported by funding from the NIHR Oxford Biomedical Research Centre (BRC) and the Health Foundation. EXSCEL (Exenatide Study of Cardiovascular Event Lowering) was sponsored and funded by Amylin Pharmaceuticals, Inc., a wholly owned subsidiary of AstraZeneca. TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) was funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interest statements

All authors have completed the ICMJE uniform disclosure form. HD, JL, RRH and PC are involved in the ongoing development of the UKPDS-OM, which is licensed by University of

Oxford. LLL reported receiving grants and/or honoraria for giving lectures and consultancy from Abbott, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk, Pfizer, Procter & Gamble Health, Roche, Sanofi, Servier, and Zuellig Pharma. HD and JL have received a research grant from AstraZeneca outside the submitted work. RRH reports research support from AstraZeneca, Bayer and Merck Sharp & Dohme, and personal fees from Anji Pharmaceuticals, AstraZeneca, Novartis and Novo Nordisk outside the submitted work. Other authors declare that they have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements:

We would like to thank Frauke Becker, Edward Gregg and Laurence Roope for their role in the acquisition of funding and the EXSCEL and TECOS Publications Committees for permission to use the clinical trial data.

We thank patients who participated in EXSCEL and TECOS clinical trials.

For the purpose of open access, the authors have applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising.

Data sharing:

Requests for data access and proposals for analyses of EXSCEL and TECOS data can be submitted to the respective study Publications Committee using instructions found at https://www.dtu.ox.ac.uk/exscel/ and https://www.dtu.ox.ac.uk/TECOS/.

Abstract

Objectives: Most type 2 diabetes simulation models utilise equations mapping out lifetime trajectories of risk factors (e.g. glycated haemoglobin [HbA_{1c}]). Existing equations, using historic data or assuming constant risk factors, frequently underestimate or overestimate complication rates. Updated risk factor time path equations are needed for simulation models to more accurately predict complication rates.

Aims: (i) Update United Kingdom Prospective Diabetes Study Outcomes Model (UKPDS-OM2) risk factor time path equations; (ii) Compare quality-adjusted life-years (QALYs) using original and updated equations; iii) Compare QALY gains for reference case simulations using different risk factor equations.

Methods: Using pooled contemporary data from two randomised trials EXSCEL and TECOS (n=28,608), we estimated: dynamic panel models of seven continuous risk factors (HDL-cholesterol, LDL-cholesterol, HbA_{1c}, haemoglobin, heart rate, blood pressure and body mass index); two-step models of estimated glomerular filtration rate; and survival analyses of peripheral arterial disease, atrial fibrillation and albuminuria. UKPDS-OM2-derived lifetime QALYs were extrapolated over 70 years using historical and the new risk factor equations.

Results: All new risk factor equation predictions were within 95% confidence intervals of observed values, displaying good agreement between observed and estimated values. Historical risk factor time path equations predicted trial participants would accrue 9.84 QALYs, increasing to 10.98 QALYs using contemporary equations.

Discussion: Incorporating updated risk factor time path equations into diabetes simulation models could give more accurate predictions of long-term health, costs, QALYs and cost-effectiveness

estimates, as well as a more precise understanding of the impact of diabetes on patients' health, expenditure and quality of life.

Trial registration: ClinicalTrials.gov NCT01144338 and NCT00790205

Key Words: Type 2 diabetes, quality-adjusted life years gained, patient-level simulation, risk modelling, complications, glycaemia, prognostic model, risk factor progression equations.

Key points

- We present updated time paths for 11 diabetes risk factors using data on more than 80,000 patient-years of follow up from contemporary multinational clinical outcome trials.
- Our results suggest that improvements in risk factor management over the last two decades have gained the average person with type 2 diabetes 1.13 QALYs.
- These updated time path equations can be used in diabetes simulation models to better inform economic evaluations and health technology assessments

1. Introduction

Health economic computer simulation models are now widely used to project health outcomes and costs among individuals with type 2 diabetes and to inform the cost-effectiveness of novel interventions [1]. Such models are used to predict a variety of diabetes-related complications and death to estimate outcomes, such as quality-adjusted life years (QALYs), life expectancy and lifetime costs [2]. One of the most widely-used diabetes simulation models is the United Kingdom Prospective Diabetes Study Outcomes Model (UKPDS-OM) [3]. UKPDS-OM is a multi-application model that has been used in a wide variety of applications, including cost-effectiveness analyses [4-6], prediction of life expectancy [7, 8], as well as informing diabetes guidelines of health technology assessment organisations such as NICE [9]. In a recent Mount Hood Diabetes Challenge, 10 of 12 health economic diabetes simulation models used UKPDS-OM risk equations [10].

Most diabetes simulation models comprise two main components: i) event risk equations predicting death and diabetes-related complications, such as myocardial infarction and stroke, conditional on risk factor values and history of complications; and ii) trajectories of risk factors (e.g. glycated haemoglobin [HbA_{1c}], blood pressure) over the simulation period. Risk factor time path equations have been developed [11-13] that allow risk factor trajectories to be projected over a lifetime, which enables treatment effects on risk factors to be translated into differences in mortality and complications [3, 12]. By contrast, assuming constant risk factors or a constant annual increment or decrement throughout the whole simulation period is likely to underestimate complication rates [11].

Time path equations have been estimated for 13 clinical risk factors using data from the UKPDS trial collected between 1977 and 2002 [14]. While such equations provide useful historical

information, there have been important changes in both the types of therapies available for treating type 2 diabetes [15] and patterns of clinical prescribing [16, 17]. Therefore, there is a need to re-estimate risk factor time path equations using more contemporary data that can be used to evaluate new therapies and technologies and inform decisions about regulatory approval and health technology assessment. These time paths are intended to extrapolate risk factors after the initial impact of the treatments being compared in the analysis; the time paths may include the effect of concomitant medications.

We used patient-level information from two large contemporary multinational randomised trials to develop new risk factor time path equations compatible with the UKPDS-OM2 and other diabetes models. Our study comprises four discrete steps: (i) estimating new time path equations to predict risk factors over time; (ii) internal validation of risk factor time path equations; (iii) comparing the predictions of new models with the published equations [11] to quantify the QALY gains from improvements in risk factor control that have occurred over the last two decades; and (iv) updating diabetes model reference case simulations [2] to assess how incorporating these new risk factor-path equations will affect predicted outcomes for a variety of hypothetical interventions.

2. Methods

2.1 EXSCEL and TECOS data

We pooled data from two randomised, placebo-controlled clinical cardiovascular outcome trials in people with type 2 diabetes: i) the Exenatide Study of Cardiovascular Event Lowering [18, 19] (EXSCEL ClinicalTrials.gov NCT01144338), with 14,752 participants conducted 2010-2017; and ii) the Trial Evaluating Cardiovascular Outcomes With Sitagliptin [20] (TECOS ClinicalTrials.gov, NCT00790205), with 14,671 participants conducted 2009-2014. Both trials

were pragmatic and allowed any concomitant medications (other than the drug class under investigation) to be used at the discretion of the usual care physician. See Supplementary Material Tables A1-A2 for comparison between these trials.

Data from both arms of the two trials were combined to maximise generalisability and use all available data. Risk factor measurements performed <6 months after starting randomised treatment were excluded from the analysis to exclude the initial effect of treatment. Within analyses for each risk factor, we excluded: i) participants who did not provide any information on that risk factor at randomisation; ii) those who had information on that risk factor at the randomisation visit but not at follow-up visits; iii) those who withdrew from the study on the day of their randomisation visit; iv) and those who had missing data on ethnicity.

2.2 Risk factors

Our study focused on 11 risk factors: high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); systolic blood pressure (SBP); HbA_{1c}; heart rate; haemoglobin; body mass index (BMI); estimated glomerular filter rate (eGFR); and whether the patient had been diagnosed with peripheral vascular disease (PVD), atrial fibrillation (AF) or micro- or macroalbuminuria (ALB). Neither trial measured white blood cell count or post-randomisation smoking status, which are included in the UKPDS-OM2 [3].

Risk factors were analysed on a yearly basis, taking the average across the measurements in that year was used. Values outside predefined ranges [21] were omitted from the analysis.

2.2.1 Equations for continuous risk factors

We applied linear dynamic model to estimate the time paths for HDL-C, LDL-C, HbA_{1c}, haemoglobin, heart rate, SBP and BMI. Linear dynamic model in this study refers to the inclusion of the value of the risk factors in the previous period to capture the dynamic feature that previous

values of risk factors affect current ones [11]. We used this model with random effects because it gave good predictions of risk factor values (within 95% confidence interval [CI] of observed values).[1]

The risk factor value for individual *i* in year *t* (y_{it}) was:

$$y_{it} = \phi_0 + \phi_1 y_{it-1} + \phi_2 y_{i,0} + \phi_3 sex_i + \phi_4 ethnic_{ij} + \phi_5 age_i +$$

$$\phi_6 \ln(duration\ of\ diabetes_{it}) + \mu_i + \epsilon_{it} \quad (1)$$

where $y_{i,t-1}$ was the previous year's risk factor value; $y_{i,0}$ was the first post-randomisation risk factor value and captured effect of the initial risk factors values on the subsequent time-path [11]; $ethnic_{ij}$ was a series of dummy variables, with '1' indicating White, Black, or Asian (oriental, Indian or other), and a baseline category of 'other' (Hispanic, Australian Aboriginal, Maori, Native Hawaiian, Pacific Islander, American Indian or Alaska Native); and age was age at randomisation. The natural log of $duration\ of\ diabetes_{it}$ was used as this was previously found to improve model fit [11]. The model included random effects by patient (μ_i), reflecting unobserved time-invariant characteristics, and an error component (ϵ_{it}).

2.2.2 Risk- factor equations for PVD, AF, ALB and eGFR

We applied multivariable parametric proportional hazard survival models to estimate the risk of developing PVD, AF, ALB and progressing to eGFR <60 ml/min/1.73m^2. The underlying assumption is that once an individual progresses to one of these health states they can never leave.

[1] We did not use linear dynamic model with fixed effects because they are not able to estimate time-invariant variables such as gender and ethnicity. We did not use system generalised method of moments (GMM) models because they are sensitive to the correct specification of temporal lags (how many lagged values of risk factors (e.g. values of risk factors in previous one year or two years should be included). Particularly, even slight alterations in temporal lags lead to different coefficients and even changes in the significance of the coefficients. Given that prediction of risk factors is the primary objective of our current study, we opted for a parsimonious model over GMM model, to ensure the stability of coefficients.

Several of the equations predicting diabetic events in UKPDS-OM2 incorporate eGFR as a spline variable with a knot at 60 ml/min/1.73m^2. Hence, to ensure robust predictions, the eGFR predictions have to accurately represent not only the time paths of eGFR values but also the proportion of the population below the knot value (60 ml/min/1.73m^2).

We therefore modelled eGFR time paths with a two-part model, predicting whether eGFR was <60 ml/min/1.73m^2 this year and then the exact eGFR value, conditional on covariates that included last year's values. Monte Carlo simulation was used to convert probability predictions for individual patients into binary events (see Supplementary Material 2). To predict a continuous eGFR value conditional on the eGFR<60 ml/min/1.73m^2 prediction, we used two additional multivariable random effects Tobit autoregressive models of order one for eGFR values above or below 60. In the two separate Tobit models, we included the same covariates as the other continuous risk factors, and an upper limit of 60 ml/min/1.73m^2 and a lower limit of 0 for eGFR <60 ml/min/1.73m^2, and a lower limit of 60 for eGFR ≥60 ml/min/1.73m^2. This two-step approach to predicting eGFR values has previously been shown to give the most accurate predictions of eGFR and events within UKPDS-OM2 [11].

For PVD, AF, ALB and the binary variable indicating eGFR <60 ml/min/1.73m^2 (and '0' otherwise), the parametric form (Weibull, exponential and Gompertz) was examined graphically and model choice was based on AIC. For all four outcomes, we selected a Weibull distribution. The proportional hazards assumption was tested by plotting Schoenfeld residuals and Cox–Snell semi-log graphs [22].

2.3 Selection of predictors

For all risk factor equations, we selected predictors based on two criteria: i) as suggested by previous evidence [23], parsimonious models with fewer predictors were preferred over models

with more predictors; and ii) a good agreement between observed and predicted risk factor values (predicted values should be within 95% CI of observed values).

For the continuous risk equations, we included all covariates shown in equation 1 regardless of their statistical significance if they were shown to improve agreement between observed and predicted risk factor values. This ensured a parsimonious model informed by the covariates most likely to be available to other users.

For eGFR and the equations estimating time to PVD, AF and ALB, we followed the same approach as in the UKPDS-OM2 and Leal et al [11]. The set of candidate covariates was initially informed by the literature and expert opinion and included time-invariant factors (sex, age at diagnosis, ethnicity, smoking at baseline) and time varying clinical risk factors (SBP, HbA1c, BMI, HDL, heart rate and LDL). The multivariable models were initially fitted with all covariates; backwards stepwise regression at $p<0.05$ was then used to select the significant covariates in the final models.

We explicitly excluded trial treatment allocation as a covariate in all risk equation models because the time path equations are intended to be applied to risk factor values from any diabetes dataset and any treatment. In sensitivity analysis, we re-estimated separate equations for each trial (TECOS and EXSCEL) and evaluated the impact of treatment allocation.

2.2.4 Mapping out risk factor trajectories

For all risk factors, predicted and observed time paths were plotted for the combined datasets to assess prediction accuracy and internal validity. We considered time paths to have good prediction accuracy if the predicted values lay within the 95% CI of observed values. Duration of diabetes was used as the time scale rather than time from randomisation, which allowed combining data on patients with different durations of diabetes together (similar to period life tables). For PVD, AF,

and ALB, we assessed calibration by plotting the observed cumulative incidence using the Kaplan-Meier estimator and comparing it with the predicted risk [24].

2.5 QALY gains using current and previous risk equations

To estimate the health gains from improvements in risk factor management, pre-randomisation data for the *placebo arms* from both trials were extrapolated to 70 years using UKPDS-OM2. This analysis only included patients with non-missing data for all risk factors at both baseline and Year 1 (n=2579). Using coefficients estimated from equation (1), we first calculated values of risk factors in year 1 from pre-randomisation values and then simulated values from year 2 onwards. The same data were extrapolated using the time paths estimated by Leal et al [11] and the difference in QALYs between the two simulations was estimated.

A bespoke version of UKPDS-OM2 was used which enabled the coefficients for binary risk factors to be modified. Baseline white blood cell count was imputed using a published algorithm [21]. Baseline data on smoking and white blood cell counts were extrapolated using the equations estimated by Leal et al [11] in both scenarios, since these were not re-estimated in the current study. Default values for utilities and other parameters were used within these analyses and we ran 100,000 loops and no bootstraps. Supplementary Material 3 gives further details.

2.6 Reference simulation

Following recommendations of the Mount Hood Diabetes Challenge Network, we replicated the reference case simulations for the UKPDS-OM2 that were registered on the Mount Hood website (https://www.mthooddiabeteschallenge.com/registry) [25]. The registry includes a set of reference simulations that are intended to enable comparisons of models and increase model transparency [2].

The registry simulations were replicated using last observation carried forward (LOCF), trajectories estimated by Leal et al [11] and those from Tables 1-2. Supplementary Material 4 gives further details.

Except where otherwise stated, all analyses were conducted using Stata version 17 (StataCorp, College Station, TX).

3. Results

3.1 Sample

In total, 28,608 participants (14,551 from EXSCEL and 14,057 from TECOS) were eligible for analysis. The average participant was 64 years old at randomisation and had lived with diabetes for around 16 years. The number of observations (person-years) that were available for analysis ranged from 41,928 (haemoglobin) to 94,068 (AF; Supplementary Material Tables A2-A3).

3.2 Estimation of risk factor time path equations

For continuous risk factors, both one-year lagged risk factors and first recorded post-randomisation risk factor values had significant and positive effects on current values of risk factors in all risk equations ($p<0.01$; Table 1). Older participants had significantly higher values of HDL-C and SBP, and lower values of LDL-C, HbA_{1c}, haemoglobin, heart rate and BMI. Women had significantly higher values for all risk factors except haemoglobin, holding all else constant. Patients with higher first recorded values and lagged values of eGFR were less likely to develop eGFR <60 ml/min/1.73m^2 (Table 2). SBP and duration of diabetes were significant and negatively correlated with eGFR in Tobit models.

Older patients were more likely to be diagnosed with AF, ALB and PVD, whilst women were less likely to be diagnosed with AF and ALB (Table 2). The probability of being diagnosed with AF was significantly affected by smoking, black or white ethnicity and one-year lagged

values of BMI. The probability of being diagnosed with ALB was significantly affected by white ethnicity, lagged values of BMI, SBP and HbA_{1c}. The probability of being diagnosed with PVD was significantly affected by smoking at baseline and HbA_{1c}. For users interested in trial-specific risk factor trajectories, we report separate equations for each trial in the supplementary materials (Tables A5-A6). Finally, Supplemental Material 2 describes how the equations are to be used to predict risk factor progression.

3.3 Internal and cross-validation of risk factor time path equations

The predicted values of continuous risk factors were within the 95% CIs of the observed values for each risk factor (Figure 1), suggesting a good agreement between observed and modelled risk factors. HDL-C and HbA_{1c} increased slightly with duration of diabetes whilst SBP and BMI were relatively stable. LDL-C, haemoglobin and heart rate showed downward trends.

The coefficients estimated on the pooled dataset (Table 1) perform well for both TECOS and EXSCEL for all risk factors, except HbA_{1c} (Supplementary Materials Figure A1). Time paths of predicted and observed risk factor values were further compared by quintiles based on the first observed risk factors value (Supplementary Materials Figure A2, Table A4). In general, predicted risk factor values were within 95% CIs of observed values in each quintile.

Predicted time paths of risk factors using coefficients from Leal et al. [11] were compared graphically with those from the current study (Figure 1). Except for BMI and haemoglobin, time paths using previous risk equations showed poor agreement with observed risk factor time paths. The predicted cumulative incidence of AF, ALB and PVD was consistent with observed events: both among the full sample, and the EXSCEL and TECOS samples separately (Figure 2). Cross-validation suggested that for the models of LDL, HDL, SBP, haemoglobin, heart rate and BMI predictions based on coefficients estimated on the EXSCEL trial lie within the 95% CI of observed

outcomes for TECOS patients (vice versa; Figure A4). However, for HbA1c, values predicted based on the other study lay outside the 95% CI, with EXSCEL coefficients predicting HbA1c values to be 0.1% higher than those from TECOS. Sensitivity analyses suggested that exenatide may affect SBP and heart rate trajectories while sitagliptin may affect HbA1c trajectories (Supplementary Materials 5).

3.4 QALY gains using updated risk equations and previous ones

UKPDS-OM2 was used to simulate QALYs over 70 years using both the risk factor trajectories equations in the current study and those of Leal et al. [11]. On average, the cohort was predicted to accrue 9.84 (standard deviation 4.64) QALYs using risk factor equations estimated on the UKPDS sample [11], compared with 10.98 (standard deviation 5.14) QALYs using the risk factor equations estimated in the current paper (Figure 3). This equates to a gain of 1.13 (95% CI: 0.90, 1.36) QALYs per patient (12%; $p<0.001$ in paired t-test).

3.5 Mount Hood reference case simulations

With LOCF, the model used in our simulation produced results for this reference simulation that were identical to those reported in the Mount Hood registry on 5 October 2018 [25] other than Monte Carlo error. Compared with LOCF, applying risk factor trajectories reduced the QALYs accrued by all reference patients and increased the QALYs gains from reducing HbA_{1c}, blood pressure, LDL-C and BMI by the fixed increments specified for the reference case simulation [25] (Table A10, Figure 4). The QALYs gains were smaller for the risk factor trajectories estimated in the current study than the trajectories estimated by Leal et al. [11]: reducing men's HbA_{1c}, blood pressure, LDL-C and BMI together gained 0.75 QALYs with trajectories from Leal et al. [11] and 0.50 QALYs with trajectories from the current study and 0.51 QALYs using LOCF.

4. Discussion

We estimated a set of contemporary risk factor time path equations for type 2 diabetes. These equations were derived from two large clinical trials covering 48 countries with >80,000 person-years of follow-up. We show the equations and predictions to be clinically plausible and internally-valid within and between the trials. Furthermore, we show gains of 1.13 QALYs associated with improvements in risk factor trajectories relative to the UKDPS time period.

The equations have been estimated so that they can be integrated into the UKPDS-OM2 and other diabetes simulation models, to facilitate predictions of diabetes-related complications and death consistent with contemporary diabetes populations. Internal validation of the updated equations gave much better predictions than those estimated on historical UKPDS data [11]. In particular, the older equations predicted markedly higher HbA1c levels than the observed values or new equations. However, the older models continued to give reasonable predictions for BMI and haemoglobin, which may suggest that these risk factor time paths have improved less over time than for other risk factors. Earlier studies omitted important risk factors (e.g. eGFR) and more recent trends in metabolic control [13]. With our multinational data, we also estimated coefficients for more ethnic groups than previous studies [11]. Simple risk factor equations mean that the covariates within our models are likely to be available in other datasets.

Although the equations are relatively parsimonious, they showed good fit within the two trials. Between-trial cross-validity was good for LDL, HDL, SBP, haemoglobin, heart rate and BMI, suggesting that the coefficients estimated on the pooled dataset are most informative. For HbA_{1c}, the observed trajectory differed between EXSCEL and TECOS and cross-validity was not as good. This is likely the result of differences between trial protocols: the TECOS trial was designed to optimise the likelihood of achieving glycaemic equipoise [26], whereas in EXSCEL,

this was not a requirement [19]. Hence, we also provide trial-specific equations for those interested in replicating the trajectories observed in a given trial or a clinical setting.

These equations can inform economic evaluations of diabetes management strategies, which will improve risk stratification for guiding healthcare resource allocation and targeting treatment approaches. Current health economic diabetes simulation models typically capture treatment effects via changes in ≥1 risk factor. For example, the effect of glucose-lowering drugs are usually simulated through changes in HbA_{1c} relative to the trajectory observed in usual care. To remove any changes in risk factor values related to study interventions or study participation, we excluded data on the first six months of the trial when estimating our models and focused on estimating subsequent trajectories. We also controlled for lagged values of risk factors and demographic factors such as sex, age and ethnicity. Decision modellers are encouraged to use their own data on treatment effect in the first year and then use our estimated models afterwards (see Supplementary Material 2). Our risk factor time path equations are intended to simulate background time-paths that could be applied to patients on any stable treatment. The time paths reflect the natural history of risk factors and contemporary patterns of disease management and concomitant medication. Most risk factors were not affected by treatment allocation; treatment-specific models are presented for those that may be sensitive (Supplementary Materials, Table A11).

Although models, such as UKPDS-OM2, have performed reasonably well on external validation, they appear to overestimate mortality and myocardial infarction rates [21]. Updating risk factor time paths may go some way to improving the prediction accuracy of diabetes simulation models, further research may also be needed to update event equations.

The reference case simulations highlight the impact of time path equations on decision-making in diabetes. Our contemporary time-paths increased incremental QALYs by 10-20% compared with the previous reference simulation, which assumed LOCF, but decreased incremental QALYs compared with historic risk factor trajectories [11]. These QALY gains exclude the impact of changes in smoking cessation rates. Although we estimated these QALY gains using a common patient sample and used similar methods to Leal et al. [11], it is possible that part of the difference in trajectories could be attributable to differences in methodology or inclusion criteria. The QALY gains reinforce the importance of using contemporary risk factor time path equations in economic evaluation that are relevant to the target diabetes population. Furthermore, as the standards of diabetes care are likely to continue to improve there is a strong case for updating the equations periodically to reflect changes in clinical practice. While we found that region dummies worsened prediction accuracy, future research should further explore variation in these time-path equations in different settings, populations and regions. Estimating future equations using a similar approach to that adopted here would facilitate comparison across different estimates and allow easy integration into existing diabetes simulation models that are based on the UKPDS-OM2 structure.

Our analysis has a number of limitations. First, the trials used provided only six years' follow-up; however, the wide variation in diabetes duration at baseline allowed us to estimate risk factor trajectories over 40 years after diagnosis. Second, the trajectories described by these equations represent the outcome of a mixture of treatments and natural history over time in EXSCEL and TECOS. Analysing the impact of specific treatments on risk factors was beyond the scope of the current study, especially for newer agents such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists that deliver cardiovascular and renal risk

reductions by mechanisms other than improving conventional risk factor values [27, 28]. Further research is needed to assess whether risk factor trajectories beyond the first year of treatment are different in populations receiving the newer drugs: especially for BMI and HbA1c. Third, the observed trajectory of some risk factors may not be representative of a typical diabetes patient given the potentially more intense management in the trials. However, both EXCSEL and TECOS both used highly pragmatic designs with few restrictions on concomitant medications, little additional monitoring over usual care and wide-ranging eligibility criteria [19, 26]. There is a shortage of long-term studies collecting regular data on all risk factors and the early years of follow-up in long studies are unavoidably historical. Fourth, all TECOS participants [26] and 73% of EXSCEL participants [29] had cardiovascular disease at baseline; in principle this could affect risk factor trajectories, although we are not aware of any evidence for this. Further research externally validating our equations in other contemporary cohorts is recommended, following the Mount Hood tradition of extensive external validation [30]. Finally, white blood cell counts and post-baseline data on smoking status were not collected in EXSCEL or TECOS. As a result, UKPDS-OM2 users will continue to rely on older equations for these two risk factors based on the UKPDS data [11].

5. Conclusion

Our new equations give modellers and the wider research community a useful additional tool to simulate the long-term effects of type 2 diabetes and its therapies. The parsimonious estimation approach encourages their replication across datasets and populations facilitating the sharing and comparison of knowledge across researchers.

References

1. Hua X, Lung TW-C, Palmer A, Si L, Herman WH, Clarke P. How consistent is the relationship between improved glucose control and modelled health outcomes for people with type 2 diabetes mellitus? A systematic review. Pharmacoeconomics. 2017;35:319-29.

2. Kent S, Becker F, Feenstra T, Tran-Duy A, Schlackow I, Tew M, et al. The Challenge of Transparency and Validation in Health Economic Decision Modelling: A View from Mount Hood. Pharmacoeconomics. 2019;37:1305-12. https://doi.org/10.1007/s40273-019-00825-1.

3. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona. 2013;56:1925-33. https://doi.org/10.1007/s00125-013-2940-y.

4. Becker F, Dakin HA, Reed SD, Li Y, Leal J, Gustavson SM, et al. Lifetime cost-effectiveness simulation of once-weekly exenatide in type 2 diabetes: A cost-utility analysis based on the EXSCEL trial. Diabetes research and clinical practice. 2022;183:109152.

5. Leal J, Reed SD, Patel R, Rivero-Arias O, Li Y, Schulman KA, et al. Benchmarking the cost-effectiveness of interventions delaying diabetes: a simulation study based on NAVIGATOR data. Diabetes Care. 2020;43:2485-92.

6. Clarke PM, Gray AM, Briggs A, Stevens RJ, Matthews DR, Holman RR, Study UUKPD. Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona. 2005;48:868-77. https://doi.org/10.1007/s00125-005-1717-3.

7. Keng MJ, Tsiachristas A, Leal J, Gray A, Mihaylova B. Impact of achieving primary care targets in type 2 diabetes on health outcomes and healthcare costs. Diabetes, Obesity and Metabolism. 2019;21:2405-12.

8. Leal J, Gray AM, Clarke PM. Development of life-expectancy tables for people with type 2 diabetes. European Heart Journal. 2009;30:834-9.

9. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management. NICE guideline NG28 2015 (updated 2022). www.nice.org.uk/guidance/ng28. Accessed 5 December 2022.

10. Tew M, Willis M, Asseburg C, Bennett H, Brennan A, Feenstra T, et al. Exploring structural uncertainty and impact of health state utility values on lifetime outcomes in diabetes economic simulation models: Findings from the Ninth Mount Hood Diabetes Quality-of-Life Challenge. Medical Decision Making. 2022;42:599-611.

11. Leal J, Alva M, Gregory V, Hayes A, Mihaylova B, Gray AM, et al. Estimating risk factor progression equations for the UKPDS Outcomes Model 2 (UKPDS 90). Diabet Med. 2021:e14656. https://doi.org/10.1111/dme.14656.

12. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona. 2004;47:1747-59. https://doi.org/10.1007/s00125-004-1527-z.

13. Ahmad Kiadaliri A, Clarke PM, Gerdtham U-G, Nilsson P, Eliasson B, Gudbjörnsdottir S, Steen Carlsson K. Predicting Changes in Cardiovascular Risk Factors in Type 2 Diabetes in

the Post-UKPDS Era: Longitudinal Analysis of the Swedish National Diabetes Register. Journal of Diabetes Research. 2013;2013:241347. https://doi.org/10.1155/2013/241347.

14. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89. https://doi.org/10.1056/NEJMoa0806470.

15. White Jr JR. A brief history of the development of diabetes medications. Diabetes spectrum: a publication of the American Diabetes Association. 2014;27:82.

16. Higgins V, Piercy J, Roughley A, Milligan G, Leith A, Siddall J, Benford M. Trends in medication use in patients with type 2 diabetes mellitus: a long-term view of real-world treatment between 2000 and 2015. Diabetes, metabolic syndrome and obesity: targets and therapy. 2016;9:371.

17. Brennan MB, Huang ES, Lobo JM, Kang H, Guihan M, Basu A, Sohn M-W. Longitudinal trends and predictors of statin use among patients with diabetes. Journal of Diabetes and its Complications. 2018;32:27-33.

18. Holman RR, Bethel MA, George J, Sourij H, Doran Z, Keenan J, et al. Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. Am Heart J. 2016;174:103-10. https://doi.org/10.1016/j.ahj.2015.12.009.

19. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017;377:1228-39. https://doi.org/10.1056/NEJMoa1612917.

20. Green JB, Bethel MA, Paul SK, Ring A, Kaufman KD, Shapiro DR, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes

with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American Heart Journal. 2013;166:983-9. e7. https://doi.org/10.1016/j.ahj.2013.09.003.

21. Pagano E, Konings SRA, Di Cuonzo D, Rosato R, Bruno G, van der Heijden AA, et al. Prediction of mortality and major cardiovascular complications in type 2 diabetes: External validation of UK Prospective Diabetes Study outcomes model version 2 in two European observational cohorts. Diabetes Obes Metab. 2021;23:1084-91. https://doi.org/10.1111/dom.14311.

22. Cleves M, Gould W, Gould WW, Gutierrez R, Marchenko Y. An introduction to survival analysis using Stata: Stata press; 2008.

23. Bedogni G, TSYBAkOV A, Berlin S. Clinical prediction models—a practical approach to development, validation and updating. development. 2009;18:53-99.

24. McLernon DJ, Giardiello D, Van Calster B, Wynants L, van Geloven N, van Smeden M, et al. Assessing Performance and Clinical Usefulness in Prediction Models With Survival Outcomes: Practical Guidance for Cox Proportional Hazards Models. Ann Intern Med. 2023;176:105-14. https://doi.org/10.7326/M22-0844.

25. Mount Hood Diabetes Challenge Network. Economics, simulation modelling & diabetes. https://www.mthooddiabeteschallenge.com/. Accessed 15 November 2021.

26. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015;373:232-42. https://doi.org/10.1056/NEJMoa1501352.

27. Coleman RL, Gray AM, Broedl Md UC, Fitchett D, George JT, Woerle HJ, et al. Can the cardiovascular risk reductions observed with empagliflozin in the EMPA-REG OUTCOME trial

be explained by concomitant changes seen in conventional cardiovascular risk factor levels? Diabetes Obes Metab. 2020;22:1151-6. https://doi.org/10.1111/dom.14017.

28. Konig M, Riddle MC, Colhoun HM, Branch KR, Atisso CM, Lakshmanan MC, et al. Exploring potential mediators of the cardiovascular benefit of dulaglutide in type 2 diabetes patients in REWIND. Cardiovasc Diabetol. 2021;20:194. https://doi.org/10.1186/s12933-021-01386-4.

29. Mentz RJ, Bethel MA, Gustavson S, Thompson VP, Pagidipati NJ, Buse JB, et al. Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL). Am Heart J. 2017;187:1-9. https://doi.org/10.1016/j.ahj.2017.02.005.

30. Palmer AJ, Si L, Tew M, Hua X, Willis MS, Asseburg C, et al. Computer Modeling of Diabetes and Its Transparency: A Report on the Eighth Mount Hood Challenge. Value Health. 2018;21:724-31. https://doi.org/10.1016/j.jval.2018.02.002.

Table 1. Coefficients for linear dynamic models with autoregression first order predicting annual risk factor values of continuous variables. Supplemental Material 2 describes how to use these coefficients to predict risk factors for individual patients, with examples.

	HDL-C	LDL-C	SBP	HbA1c	Haemoglobin	Heart rate	BMI
Value of Y in previous year	0.238***	0.295***	0.271***	0.456***	0.329***	0.283***	0.684***
	(0.018)	(0.011)	(0.006)	(0.009)	(0.016)	(0.007)	(0.023)
First recorded post-randomisation value of Y (>6 months after treatment start)	0.506***	0.383***	0.291***	0.243***	0.462***	0.346***	0.289***
	(0.021)	(0.012)	(0.007)	(0.009)	(0.017)	(0.007)	(0.023)
ln(duration of diabetes)	-0.001	-0.037***	0.034	0.083***	-0.096***	-0.186**	0.000
	(0.002)	(0.008)	(0.122)	(0.009)	(0.015)	(0.075)	(0.013)
Age at randomisation	0.001***	-0.004***	0.027***	-0.012***	-0.010***	-0.059***	-0.008***
	(0.000)	(0.001)	(0.008)	(0.001)	(0.001)	(0.005)	(0.001)
Female	0.055***	0.100***	0.356***	0.031***	-0.177***	0.560***	0.039**
	(0.003)	(0.009)	(0.136)	(0.010)	(0.018)	(0.085)	(0.015)
Ethnicity (reference group: other§)							
White ethnicity	0.019***	-0.001	0.365	-0.082***	-0.037	0.316**	0.022
	(0.005)	(0.019)	(0.271)	(0.021)	(0.037)	(0.155)	(0.028)
Black ethnicity	0.045***	0.032	0.780*	0.065*	-0.208***	0.376	-0.079*
	(0.008)	(0.027)	(0.442)	(0.035)	(0.049)	(0.261)	(0.044)
Asian (oriental and other) ethnicity	0.015**	-0.037*	-0.416	-0.091***	-0.081*	1.389***	-0.078***
	(0.006)	(0.020)	(0.307)	(0.023)	(0.042)	(0.184)	(0.030)
Constant	0.188***	1.027***	56.461***	2.945***	3.698***	30.755***	1.219***
	(0.014)	(0.044)	(0.850)	(0.064)	(0.149)	(0.563)	(0.094)
R^2	0.60	0.51	0.30	0.50	0.65	0.40	0.95
Observations	37,792	35,554	54,790	51,453	22,657	53,928	53,885
Number of individuals	18,499	17,523	24,115	22,741	12,116	23,867	23,747

§ Reference group for ethnicity is Hispanic, Aboriginal (Australia), Maori (New Zealand), Native Hawaiian or Other Pacific Islander, Indian (American) or Alaska Native). Coefficient values with a larger number of decimal places and using white ethnicity as the reference group are available from the corresponding author on request.

Robust standard errors in parentheses; *** p<0.01, ** p<0.05, * p<0.1

Abbreviations: BMI, body mass index; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Table 2. Sample size, functional form, parameters and beta coefficients (SE) for equations estimating probability of binary variables and eGFR values. Coefficient values with a larger number of decimal places and using white ethnicity as the reference group are available from the corresponding author on request. Supplemental Material 2 describes how to use these coefficients to predict risk factors for individual patients, with examples.

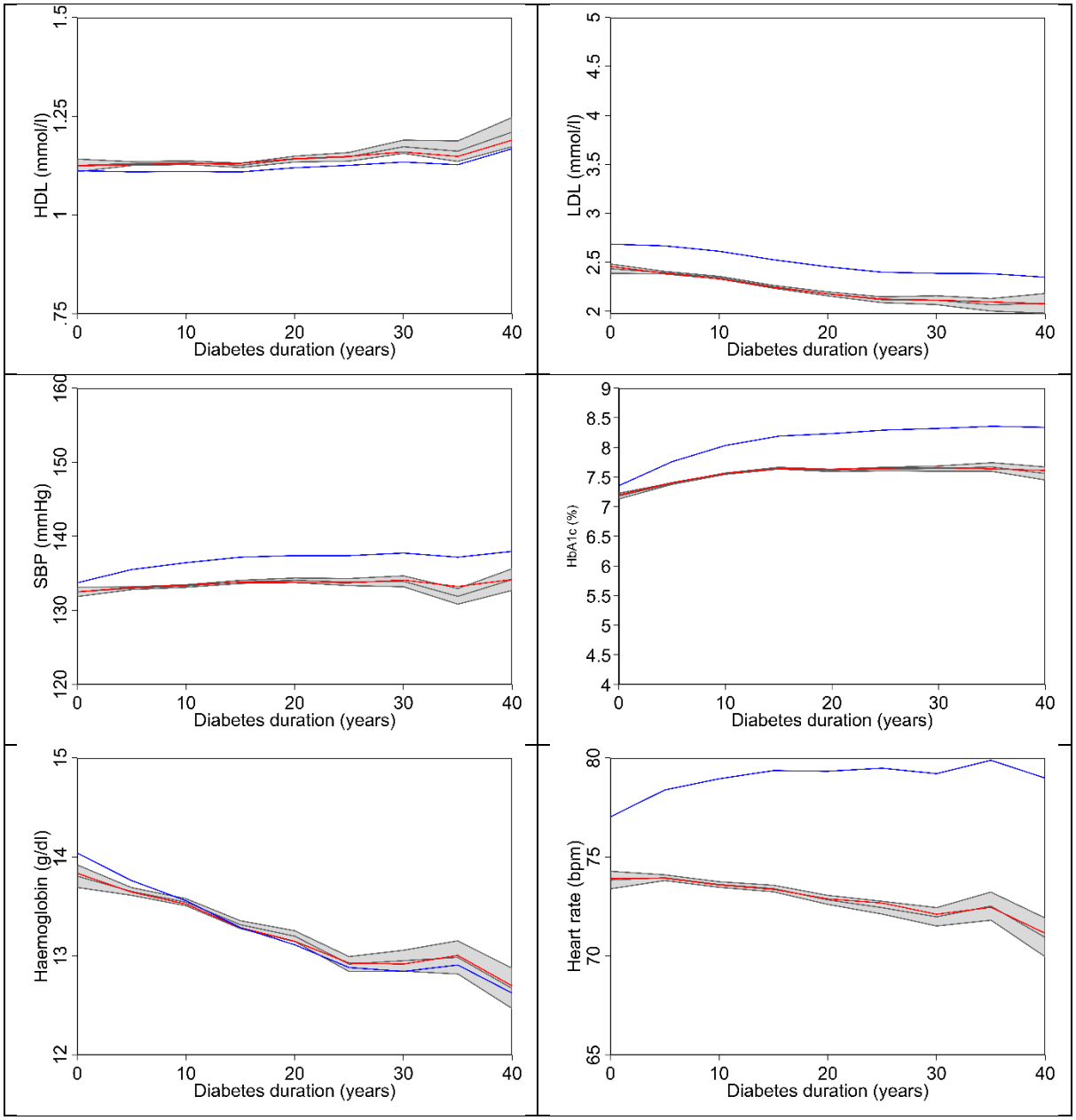
Variables	**AF**	**ALB**	**PVD**	**eGFR<60 (binary)**	**eGFR<60 (continuous)**	**eGFR≥60 (continuous)**
Function Form	Weibull	Weibull	Weibull	Weibull	Tobit model	Tobit model
Age at randomisation	0.060***	0.011**	0.030***		-0.100***	-0.230***
	(0.006)	(0.005)	(0.008)		(0.016)	(0.011)
Female	-0.576***	-0.298***				
	(0.124)	(0.092)				
White ethnicity	1.073***	0.291***	1.120***			
	(0.198)	(0.104)	(0.216)			
Black ethnicity	1.150***					
	(0.303)					
Smoking at randomisation			0.465***			
			(0.124)			
BMI last year	0.058***	0.028***				
	(0.007)	(0.006)				
First recorded value of eGFR				-0.037***	0.232***	0.446***
				(0.002)	(0.015)	(0.010)
eGFR last year				-0.032***	0.459***	0.303***
				(0.003)	(0.016)	(0.011)
SBP last year		0.011***			-0.025***	-0.011**
		(0.003)			(0.007)	(0.005)
Lag HDL last year	-0.487***					
	(0.176)					
HbA_{1c} last year		0.102***	0.151***			
		(0.034)	(0.054)			
Ln(duration of diabetes)					-1.335***	-0.753***
					(0.228)	(0.164)
Constant	-11.269***	-8.590***	-11.596***	0.706**	36.058***	36.317***

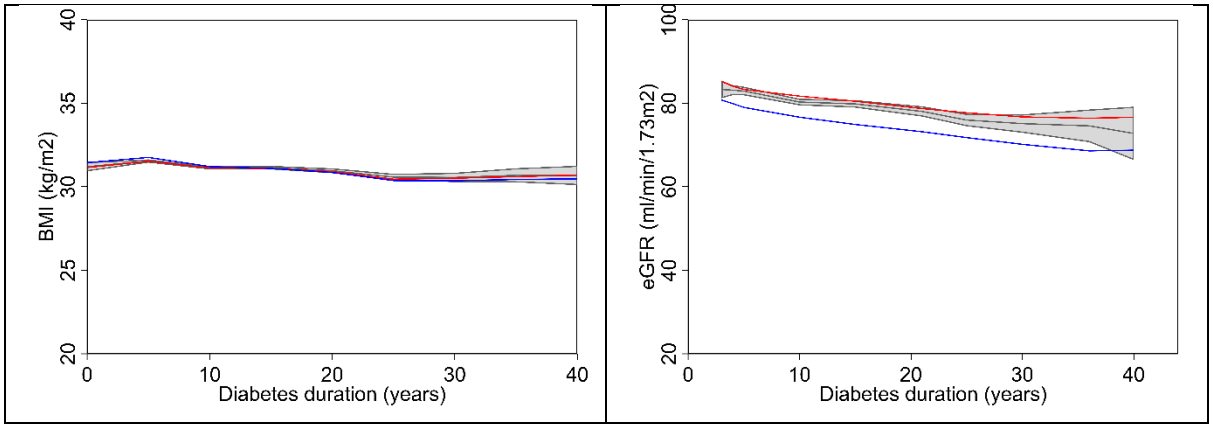
Variables	**AF**	**ALB**	**PVD**	**eGFR<60 (binary)**	**eGFR<60 (continuous)**	**eGFR≥60 (continuous)**
	(0.572)	(0.614)	(0.803)	(0.299)	(1.611)	(1.108)
ln(Γ)	0.191**	0.204***	0.443***	0.078		
	(0.076)	(0.060)	(0.090)	(0.060)		
Sigma: Standard error of the forecast (estimated using predict stdf, stdf)					11.888	13.839
Observations	46,281	34,627	52,412	53,765	37,997	37,997
Number of events	416	596	219	755	N/A	N/A

Robust standard errors in parentheses; *** p<0.01, ** p<0.05, * p<0.1

Abbreviations: AF, whether the patient has been diagnosed with atrial fibrillation; ALB, whether the patient has been diagnosed with micro- or macro-albuminuria; BMI, body mass index; eGFR, estimated glomerular filter rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; PVD, peripheral vascular disease; SBP, systolic blood pressure. The baseline category for ethnicity is any non-white, non-black ethnicity.

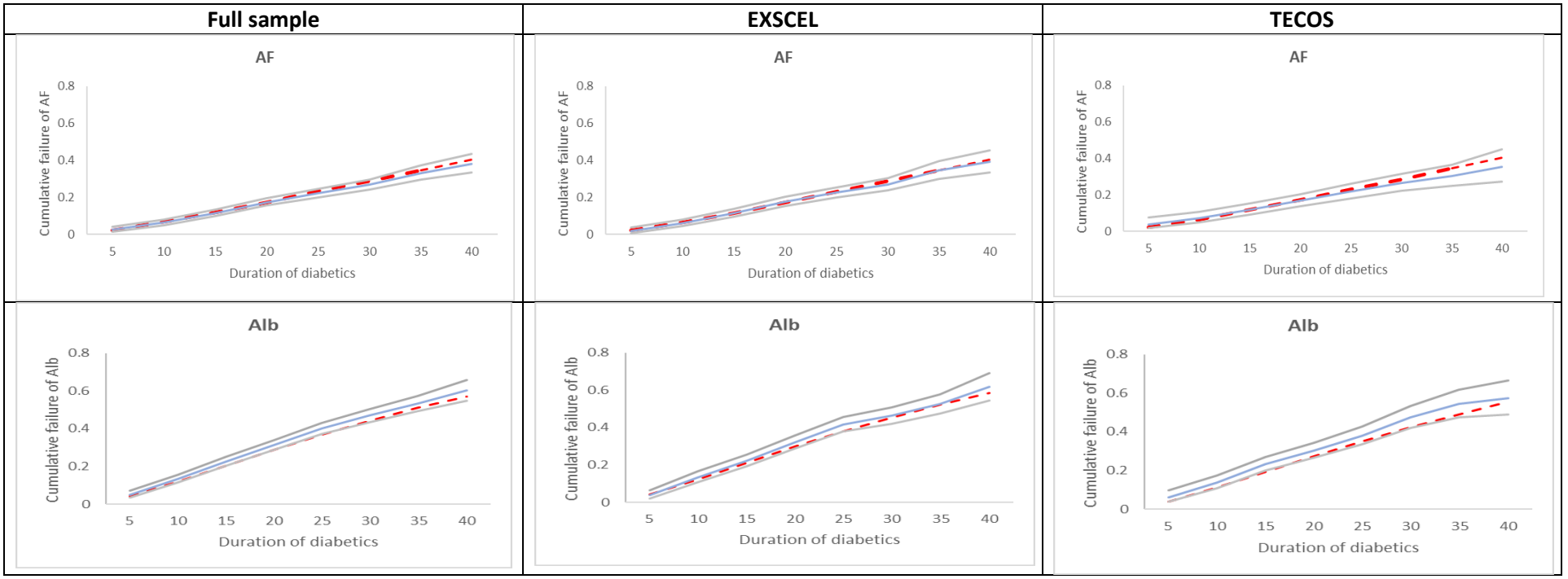
Figure 1. Observed values with 95% confidence intervals (grey area) and simulated time paths for continuous risk factors estimated in the current study (red line) and by Leal et al [11] (blue line). Each patient was followed for up to six years and patients are combined to plot risk factors by diabetes duration.

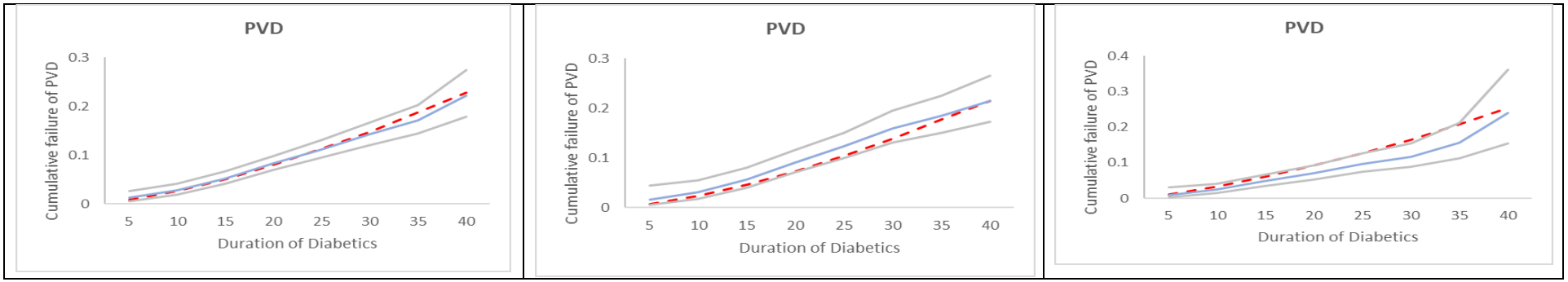




Abbreviations: BMI, body mass index (BMI); eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

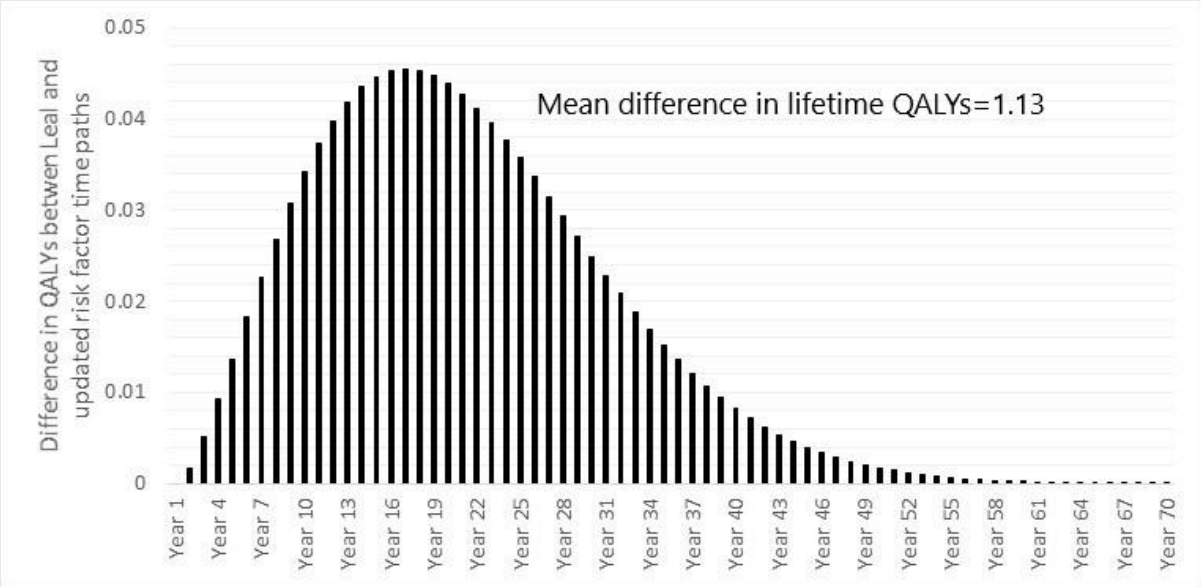
Figure 2. Kaplan-Meier estimates of observed (blue line) and simulated* (red line) cumulative failure of AF, ALB and PVD. Observed 95% confidence intervals are represented using grey lines. Each patient was followed for up to six years and patients were combined to plot risk factors by diabetes duration.





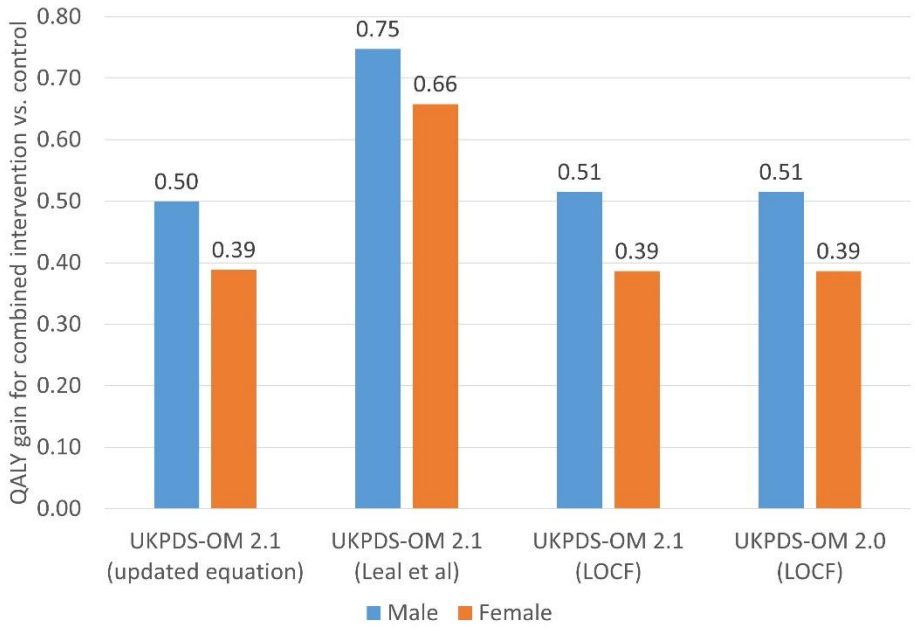
Cumulative incidence is 1 minus Kaplan-Meier. Abbreviations: AF, whether the patient has been diagnosed with atrial fibrillation; ALB, whether the patient has been diagnosed with micro- or macro-albuminuria; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; PVD, peripheral vascular disease; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

Figure 3. Mean QALY gains per year using current and previous risk equations for the 2,563 patients randomised to placebo who had complete data on all risk factors at randomisation and in the first year post-randomisation. The graph plots the difference in QALYs using updated risk equations and previous ones by Leal et al [11] at each time point.



Abbreviations: QALY, quality-adjusted life-year.

Figure 4. Results of the Mount Hood reference case simulation for: UKPDS-OM version 2.0 assuming: last observation carried forward (LOCF); UKPDS-OM version 2.2 using updated risk factor trajectories estimated in the current paper; UKPDS-OM version 2.2 using risk factor trajectories estimated by Leal et al [11]; and UKPDS-OM version 2.2 assuming LOCF. This shows the difference in QALYs between the hypothetical 'combined' intervention (simultaneously reducing HbA_{1c} by 0.5%, systolic blood pressure by 10 mmHg, low-density lipoprotein by 0.5mmol/l and body mass index by one unit) compared with control, for the Mount Hood registry reference patients [25].



Abbreviations: HbA1c glycated haemoglobin; LOCF, last observation carried forward; QALY, quality-adjusted life-year; UKPDS-OM, United Kingdom Prospective Diabetes Study Outcomes Model.

Electronic Supplementary Material

Estimating Risk Factor Time Paths Among People With Type 2 Diabetes And QALY Gains From Risk Factor Management

Pharmacoeconomics 2024 https://doi.org/10.1007/s40273-024-01398-4

Ni Gao, MBBS, PhD,[1,2] Helen A. Dakin, DPhil,[1] Rury R. Holman, FRCP[3], Lee-Ling Lim, MBBS, PhD[4-6], José Leal, DPhil,[1*] Philip Clarke, PhD [1*]
* These authors contributed equally

[1] Health Economics Research Centre, University of Oxford, Oxford, UK
[2] Centre for Health Economics, University of York, York, UK
[3] Diabetes Trials Unit, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
[4] Department of Medicine, Faculty of Medicine University of Malaya, Kuala Lumpur, Malaysia
[5] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR
[6] Asia Diabetes Foundation, Hong Kong, SAR

Corresponding author: Helen Dakin, helen.dakin@dph.ox.ac.uk

Supplementary material 1: Additional results

Table A1. Comparison of the trials used in the study

Study Name	EXSCEL [1, 2]	TECOS [3]
Study Calendar Time	2010-2017	2009-2014
Target Population	Type 2 diabetes with a glycated haemoglobin (HbA_{1c}) between ≥7.0% and ≤10.0% on stable dose of oral antihyperglycemic agents for at least 3 months. eGFR ≥30 mL/min/1.73 m^2 with approximately 70% having previous cardiovascular disease	Type 2 diabetes with HbA_{1c} between ≥6.5% and ≤8.0% on stable dose of metformin, pioglitazone, or a sulfonylurea (either monotherapy or dual combination therapy) for at least 3 months. eGFR ≥30 mL/min/1.73 m^2.
Duration of diabetes	13.1 (standard deviation 8.3) years	11.6 (standard deviation 8.1) years
Number of participants	14,752	14,671
Median follow up	3.2 (maximum 6.8) years	3.0 (maximum 5.7) years
Method for estimating eGFR	Modification of Diet in Renal Disease (MDRD) method	Modification of Diet in Renal Disease (MDRD) method

Abbreviations: eGFR, estimated glomerular filter rate; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

Table A2. Summary of risk factors averaged over all years. Patient characteristics for each trial at randomisation have been reported[4,5] previously [4, 5].

	EXSCEL mean (SD) / %(n)	TECOS mean (SD) / %(n)	Pooled sample mean (SD) / %(n)	Pooled sample Number of Individuals	Pooled sample Number of observations
HDL-C (mmol/l)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	24420	64371
LDL-C (mmol/l)	2.4 (1.0)	2.3 (0.9)	2.3 (0.9)	23623	61387
SBP (mmHg)	133.5 (15.2)	133.5 (16.6)	133.5 (15.9)	27182	83422
HbA_{1c} (%)	7.8 (1.4)	7.3 (1.1)	7.5 (1.7)	26192	79248
Haemoglobin (g/dL)	13.6 (1.6)	13.1 (1.9)	13.4 (1.7)	17758	41928
Heart rate (bpm)	74.7 (9.9)	72.3 (10.7)	73.5 (10.4)	27085	82550
BMI (kg/m^2)	32.4 (6.3)	30.0 (5.6)	31.2 (6.1)	26905	82312
eGFR ($ml/min/1.73m^2$)	75.9 (23.5)	72.8 (21.4)	74.3 (22.5)	26957	78658
PVD	0.28%	0.33%	0.23%	23608	84633
AF	0.71%	0.51%	0.62%	26222	94068
ALB	1.20%	1.08%	1.14%	16691	59114

Abbreviations: AF, whether the patient has been diagnosed with atrial fibrillation; ALB, whether the patient has been diagnosed with micro- or macroalbuminuria; BMI, body mass index (BMI); eGFR, estimated glomerular filtration rate; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PVD, peripheral vascular disease; SBP, systolic blood pressure; SD, standard deviation; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin.

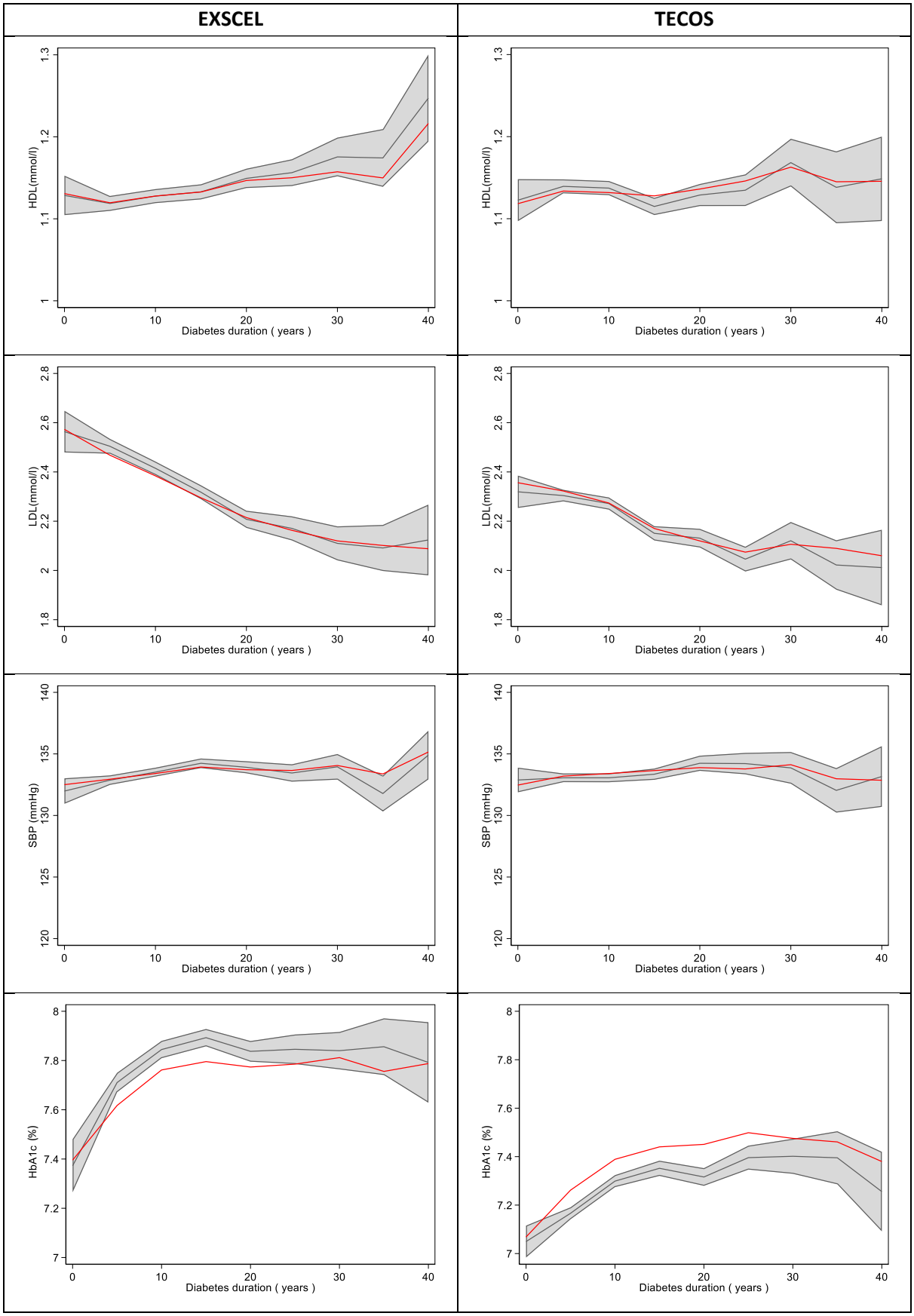
Table A3. Mean, SD and number of individuals (N) for each continuous risk factor during six follow-up years

		Follow-up years					
Risk factors		**1**	**2**	**3**	**4**	**5**	**6**
HDL (mmol/l)	N	19,546	19,846	13,971	7,914	2,667	427
	Mean	1.13	1.13	1.13	1.14	1.15	1.17
	SD	0.32	0.31	0.32	0.32	0.32	0.33
LDL (mmol/l)	N	18,556	18,900	13,323	7,578	2,610	420
	Mean	2.35	2.31	2.29	2.31	2.29	2.18
	SD	0.96	0.94	0.92	0.95	0.97	0.83
SBP (mmHg)	N	26,818	24,398	17,802	10,175	3,664	565
	Mean	133.55	133.88	133.59	133.23	131.97	129.29
	SD	15.92	16.03	15.89	15.75	15.73	14.97
HbA_{1c} (%)	N	24,933	23,360	17,082	9,873	3,474	526
	Mean	7.47	7.54	7.53	7.55	7.50	7.74
	SD	1.22	1.26	1.27	1.31	1.27	1.51
Haemoglobin (g/dL)	N	12,518	13,146	9,040	5,143	1,763	318
	Mean	13.51	13.41	13.35	13.35	13.35	13.36
	SD	1.71	1.76	1.76	1.73	1.69	1.80
Heart rate (bpm)	N	11,046	24,141	17,624	10,076	3,629	554
	Mean	74.89	73.40	73.29	73.37	73.52	74.80
	SD	11.15	10.42	10.48	10.35	10.29	10.49
BMI (kg/m^2)	N	26,473	24,023	17,567	10,060	3,635	554
	Mean	31.30	31.27	31.06	31.05	30.95	33.66
	SD	6.06	6.06	6.02	6.08	6.23	6.75
eGFR ($ml/min/1.73m^2$)	N	23,481	23,699	17,463	10,028	3,471	516
	Mean	75.72	74.31	73.71	72.72	72.49	74.32
	SD	22.60	22.22	22.54	22.69	22.96	24.08

Table A4. Mean and SD for each fifth of the population (first observed value post randomisation) of the continuous risk factors

Risk factors	Quintile	Mean	SD	N
HDL (mmol/l)	1	0.76	0.10	25281
	2	0.95	0.04	25562
	3	1.08	0.04	26160
	4	1.24	0.05	25768
	5	1.61	0.29	25737
LDL (mmol/l)	1	1.23	0.24	24497
	2	1.76	0.12	24820
	3	2.17	0.12	24482
	4	2.69	0.19	25214
	5	3.82	0.77	24754
SBP (mmHg)	1	110.90	6.79	23796
	2	124.06	3.10	33945
	3	132.35	2.18	31776
	4	140.18	2.06	27210
	5	155.56	10.37	32647
HbA_{1c} (%)	1	6.05	0.36	25644
	2	6.72	0.14	27240
	3	7.25	0.17	32678
	4	7.91	0.22	28341
	5	9.43	1.05	29024
Haemoglobin (g/dL)	1	10.87	1.25	17631
	2	12.70	0.28	17785
	3	13.56	0.23	18977
	4	14.39	0.26	18642
	5	15.70	0.74	18719
Heart rate (bpm)	1	60.12	4.35	29697
	2	68.37	1.41	27368
	3	73.06	1.36	29926
	4	78.37	1.72	31780
	5	88.53	6.59	29852
BMI (kg/m^2)	1	24.07	1.84	29544
	2	27.88	0.83	29547
	3	30.61	0.80	29545
	4	33.79	1.10	29547
	5	40.63	4.70	29547
eGFR ($ml/min/1.73m^2$)	1	56.07	9.17	14968
	2	70.17	2.74	14580
	3	79.61	2.85	15373
	4	90.16	3.35	14886
	5	111.61	14.03	15065

Figure A1. Continuous risk factor values for the EXSCEL and TECOS study populations separately, using the time path models that were estimated on the pooled dataset (coefficients in Table 1). Observed values (black line) are shown with 95% confidence intervals (grey area) and simulated (red line) time paths.



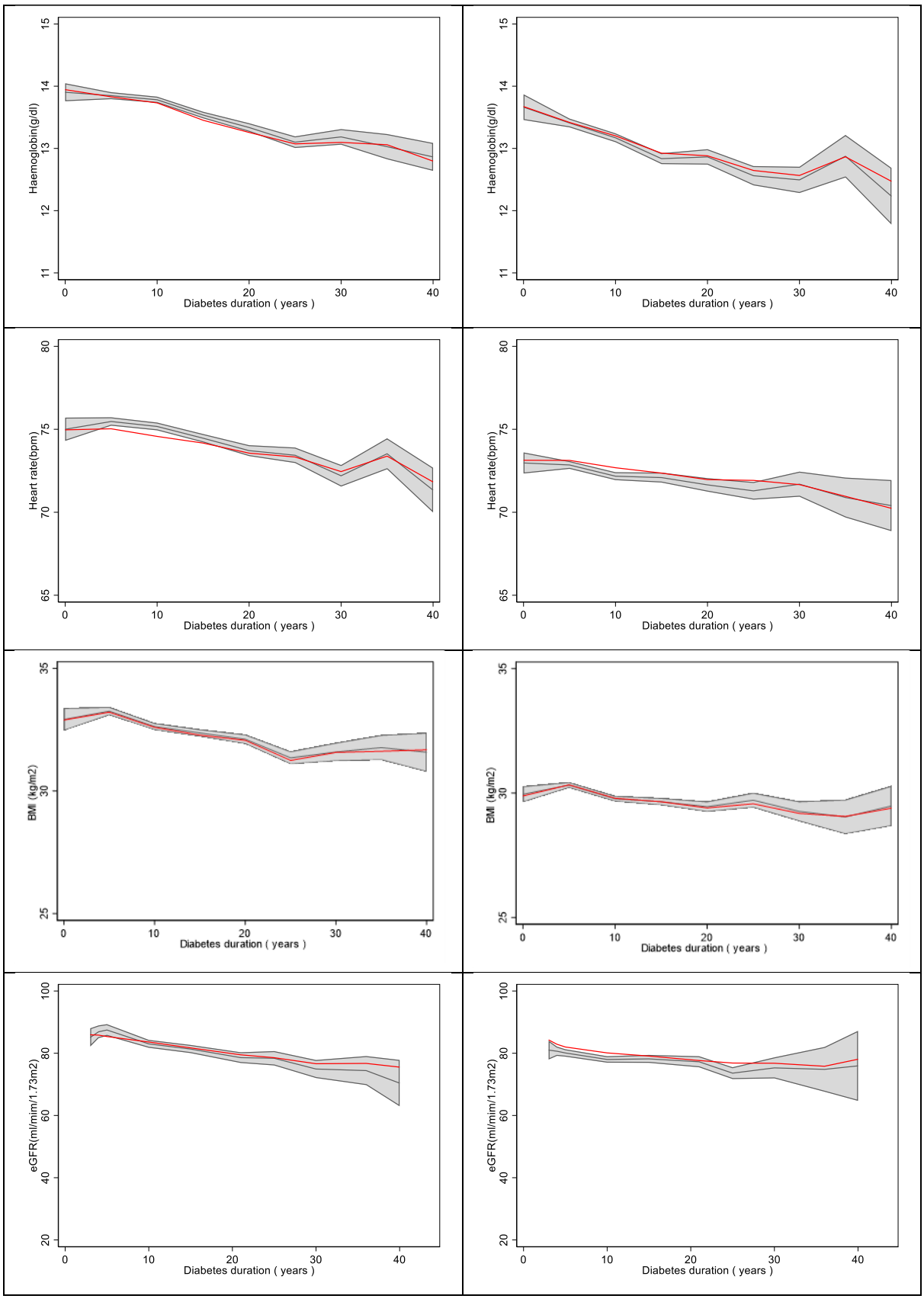

Haemoglobin(g/dl)
11
12
13
14
15
0
10
20
30
40
Diabetes duration (years)
Haemoglobin(g/dl)
11
12
13
14
15
0
10
20
30
40
Diabetes duration (years)
Heart rate(bpm)
65
70
75
80
0
10
20
30
40
Diabetes duration (years)
Heart rate(bpm)
65
70
75
80
0
10
20
30
40
Diabetes duration (years)
BMI (kg/m2)
25
30
35
0
10
20
30
40
Diabetes duration (years)
BMI (kg/m2)
25
30
35
0
10
20
30
40
Diabetes duration (years)
eGFR(ml/mim/1.73m2)
20
40
60
80
100
0
10
20
30
40
Diabetes duration (years)
eGFR(ml/mim/1.73m2)
20
40
60
80
100
0
10
20
30
40
Diabetes duration (years)

Figure A2. Observed values with 95% confidence intervals (grey area) and simulated* (red line) time paths by quintile of continuous risk factors

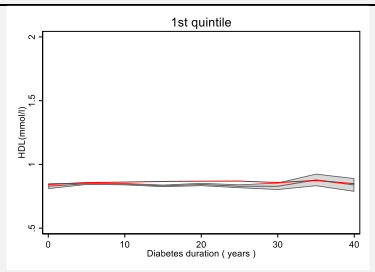
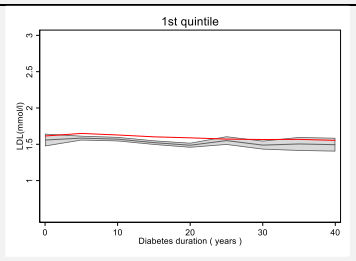
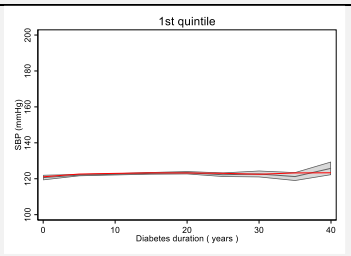
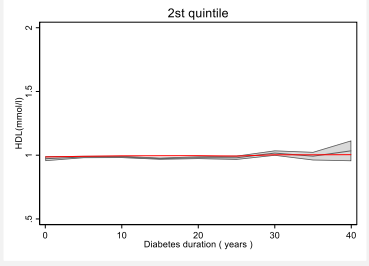
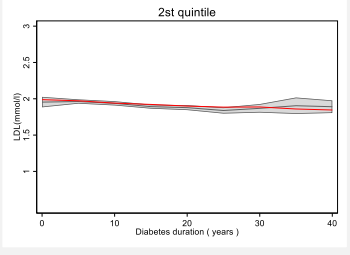
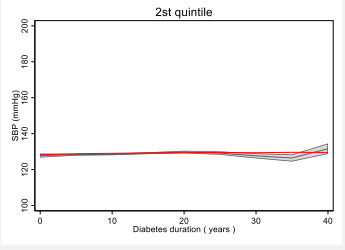
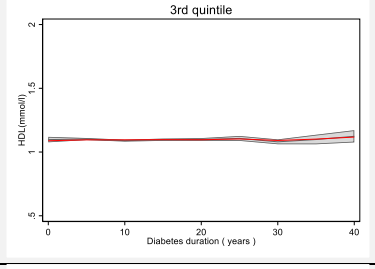
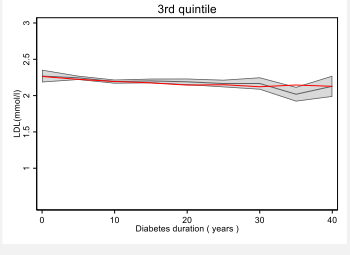
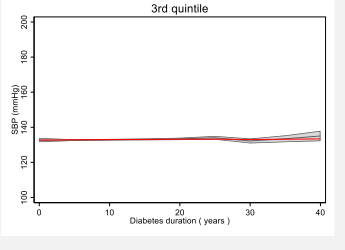
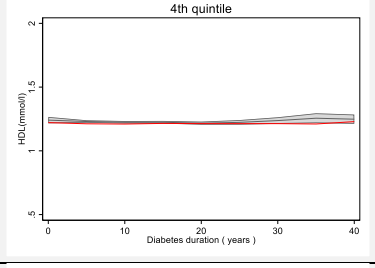
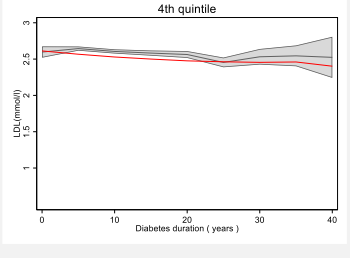
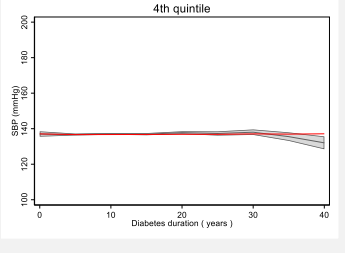
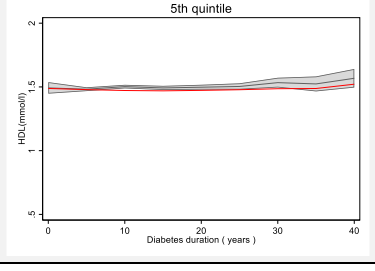
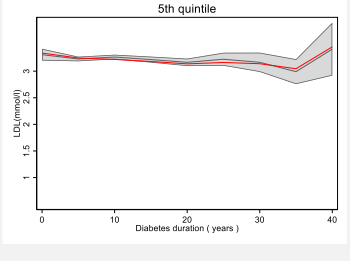
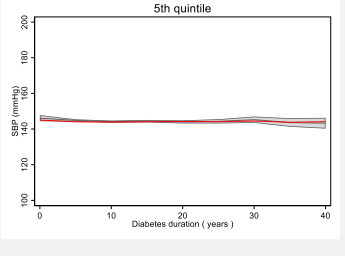
Q	HDL	LDL	SBP
1			
2			
3			
4			
5			

Figure A2. Observed values with 95% confidence intervals (grey area) and simulated* (red line) time paths by quintile of continuous risk factors (continued)

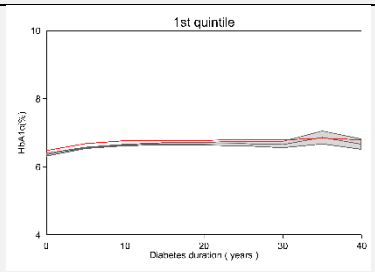
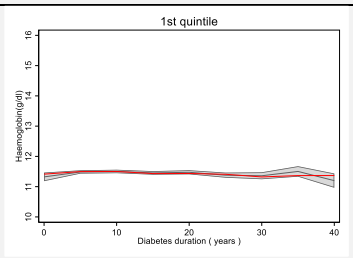
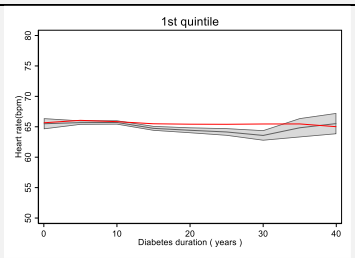
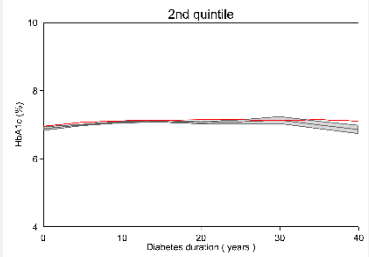
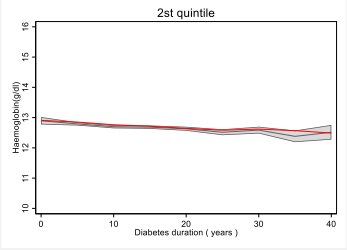
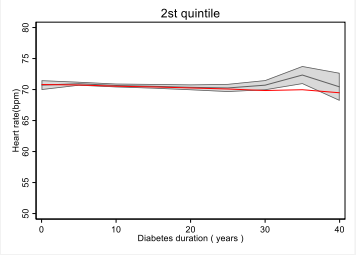
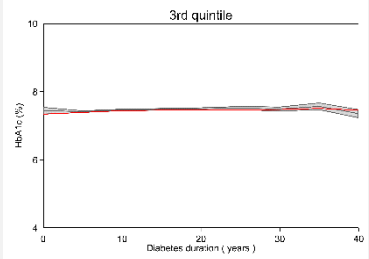
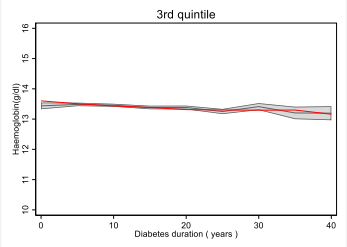
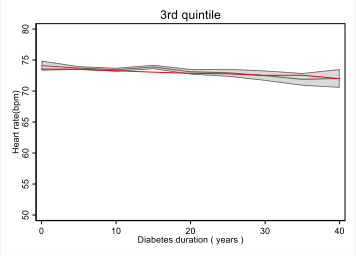
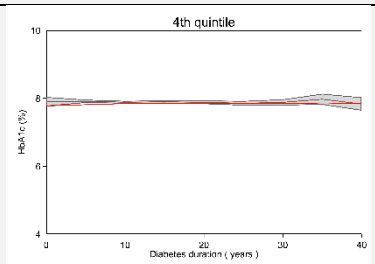
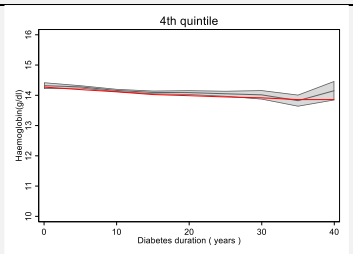
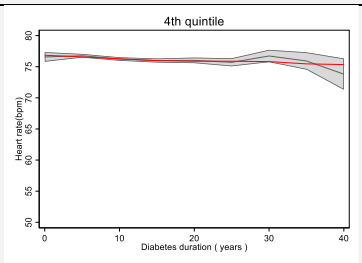
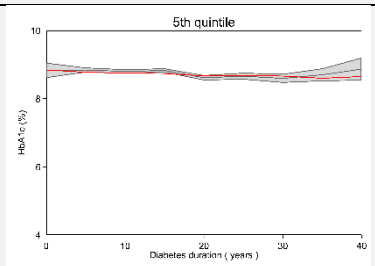
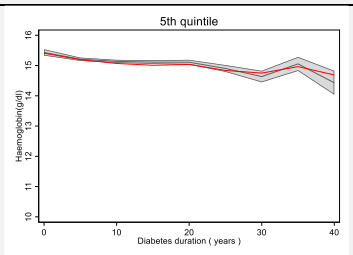
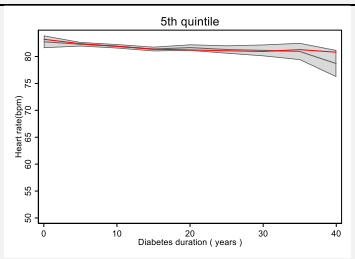
Q	HbA1c	Haemoglobin	Heart rate
1			
2			
3			
4			
5			

Figure A2. Observed values with 95% confidence intervals (grey area) and simulated* (red line) time paths by quintile of continuous risk factors (continued)

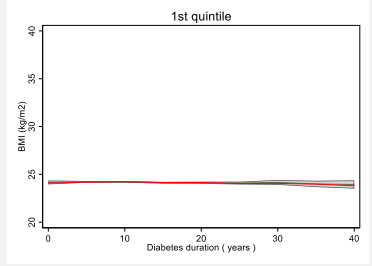
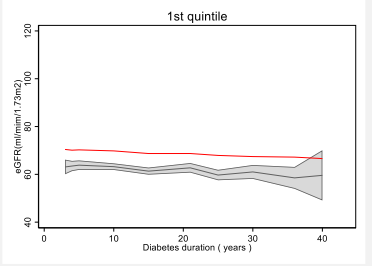
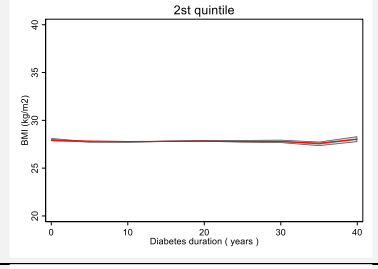
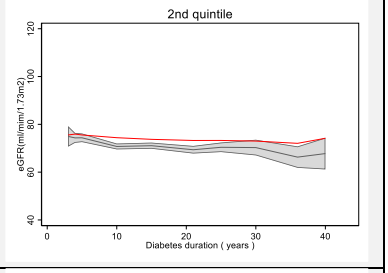
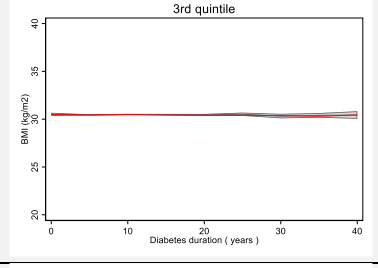
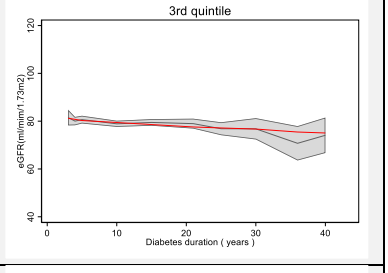
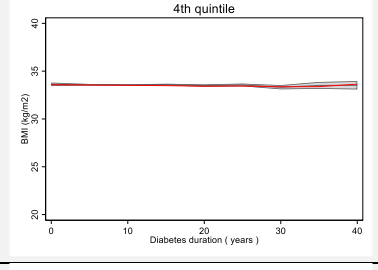
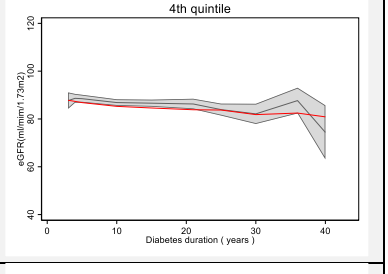
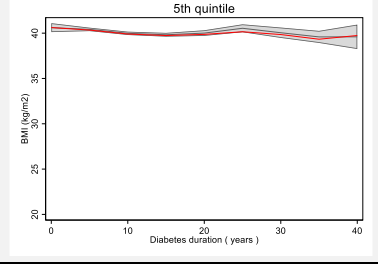
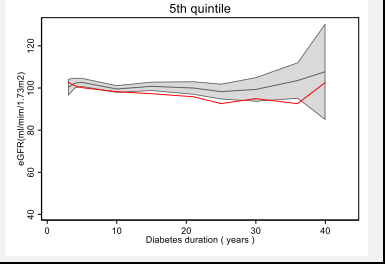
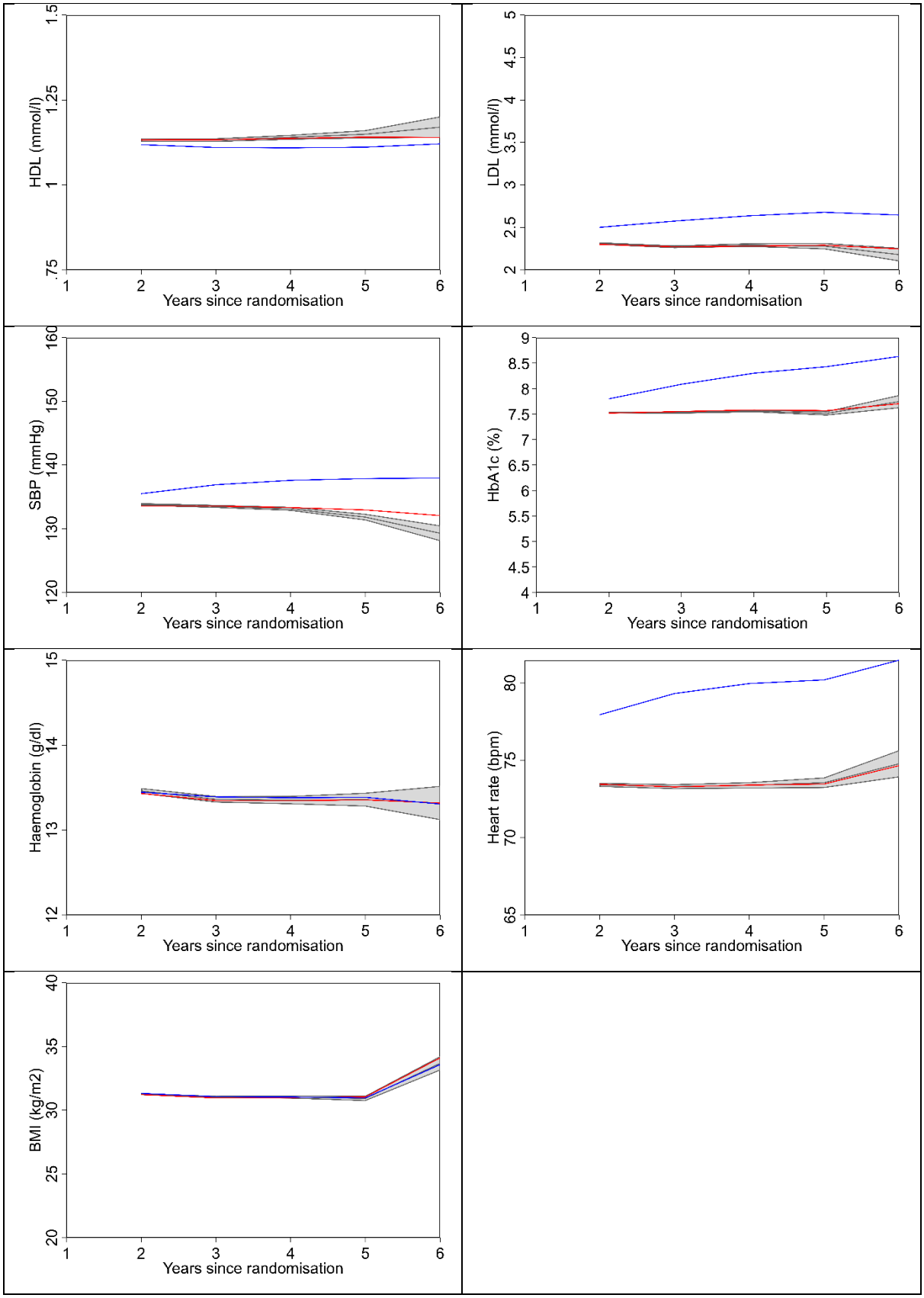
Q	BMI	eGFR
1		
2		
3		
4		
5		

Figure A3. Observed values with 95% confidence intervals (grey area) and simulated time paths for continuous risk factors estimated in the current study (red line) and by Leal et al [6] (blue line), relative to randomisation.



Abbreviations: BMI, body mass index (BMI); HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Table A5. Coefficients for the models estimating annual risk factor values of continuous variables using solely EXSCEL data

VARIABLES	HDL	LDL	SBP	HbA1c	Haemoglobin	Heart rate	BMI
Value Y in previous year	0.187***	0.304***	0.257***	0.440***	0.325***	0.258***	0.766***
	(0.028)	(0.015)	(0.010)	(0.012)	(0.021)	(0.010)	(0.011)
First recorded value Y	0.578***	0.410***	0.384***	0.273***	0.443***	0.426***	0.211***
	(0.031)	(0.016)	(0.011)	(0.013)	(0.023)	(0.011)	(0.012)
ln(duration of diabetes)	0.004	-0.041***	-0.053	0.066***	-0.093***	-0.366***	-0.025
	(0.003)	(0.011)	(0.165)	(0.014)	(0.020)	(0.105)	(0.018)
age at baseline	0.001***	-0.003***	0.027***	-0.011***	-0.009***	-0.044***	-0.004***
	(0.000)	(0.001)	(0.010)	(0.001)	(0.001)	(0.007)	(0.001)
female	0.053***	0.086***	0.193	0.018	-0.186***	0.408***	0.017
	(0.005)	(0.012)	(0.179)	(0.015)	(0.024)	(0.112)	(0.020)
White	0.020***	0.036	0.294	-0.070**	-0.052	0.487**	0.061
	(0.007)	(0.025)	(0.343)	(0.033)	(0.056)	(0.199)	(0.038)
Black	0.050***	0.069**	1.107**	0.083	-0.271***	0.202	-0.044
	(0.011)	(0.034)	(0.529)	(0.051)	(0.068)	(0.315)	(0.055)
Asia	0.017*	-0.028	0.660	-0.068	-0.009	1.422***	-0.040
	(0.009)	(0.030)	(0.445)	(0.042)	(0.071)	(0.280)	(0.043)
Constant	0.156***	0.908***	46.211***	2.898***	4.015***	26.363***	0.898***
	(0.017)	(0.056)	(1.110)	(0.091)	(0.207)	(0.728)	(0.105)
Observations	20,323	19,164	27,081	24,963	14,303	26,902	26,651
Number of id	9,673	9,211	12,311	11,431	7,321	12,263	12,134

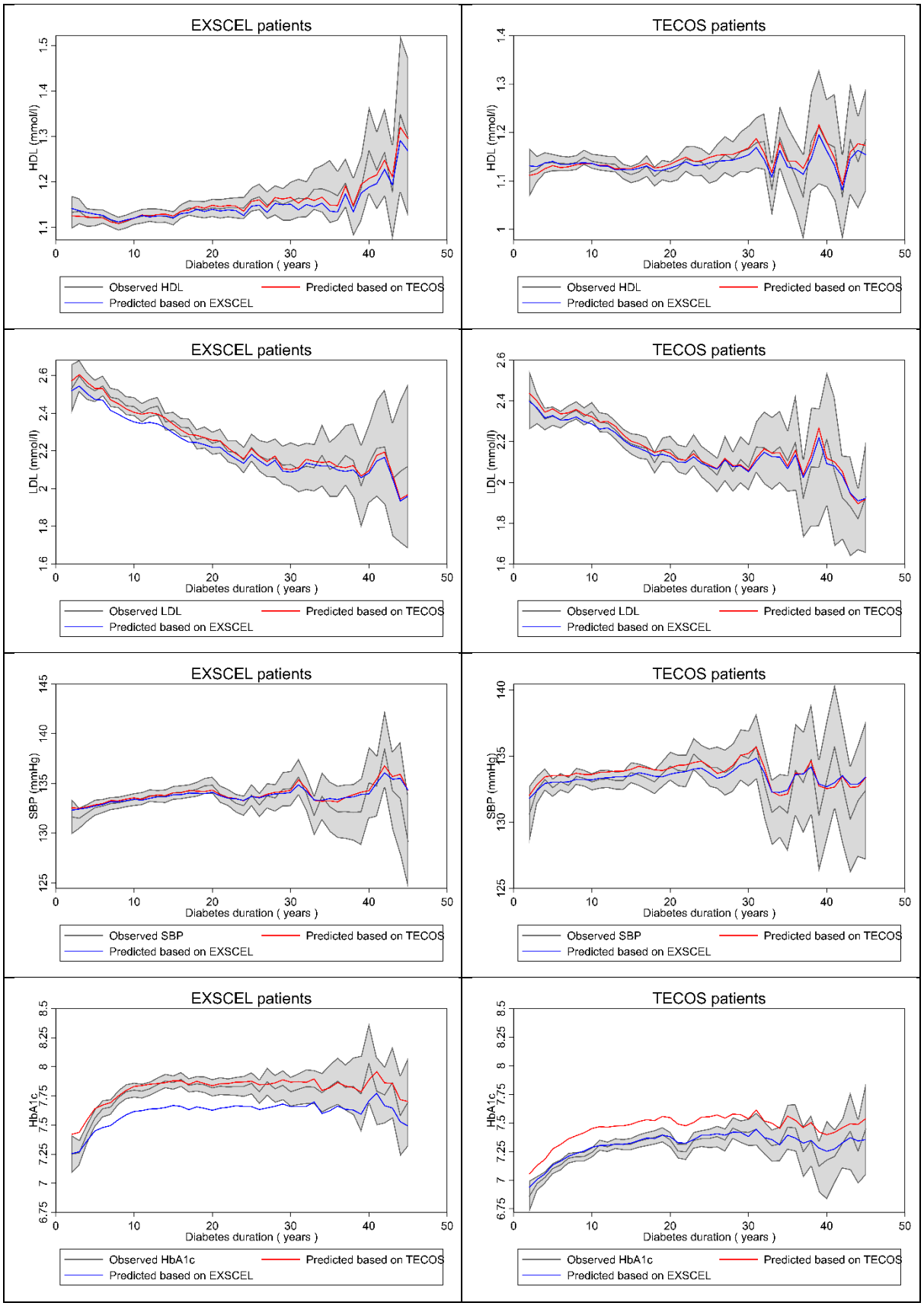
Robust standard errors in parentheses; *** p<0.01, ** p<0.05, * p<0.1

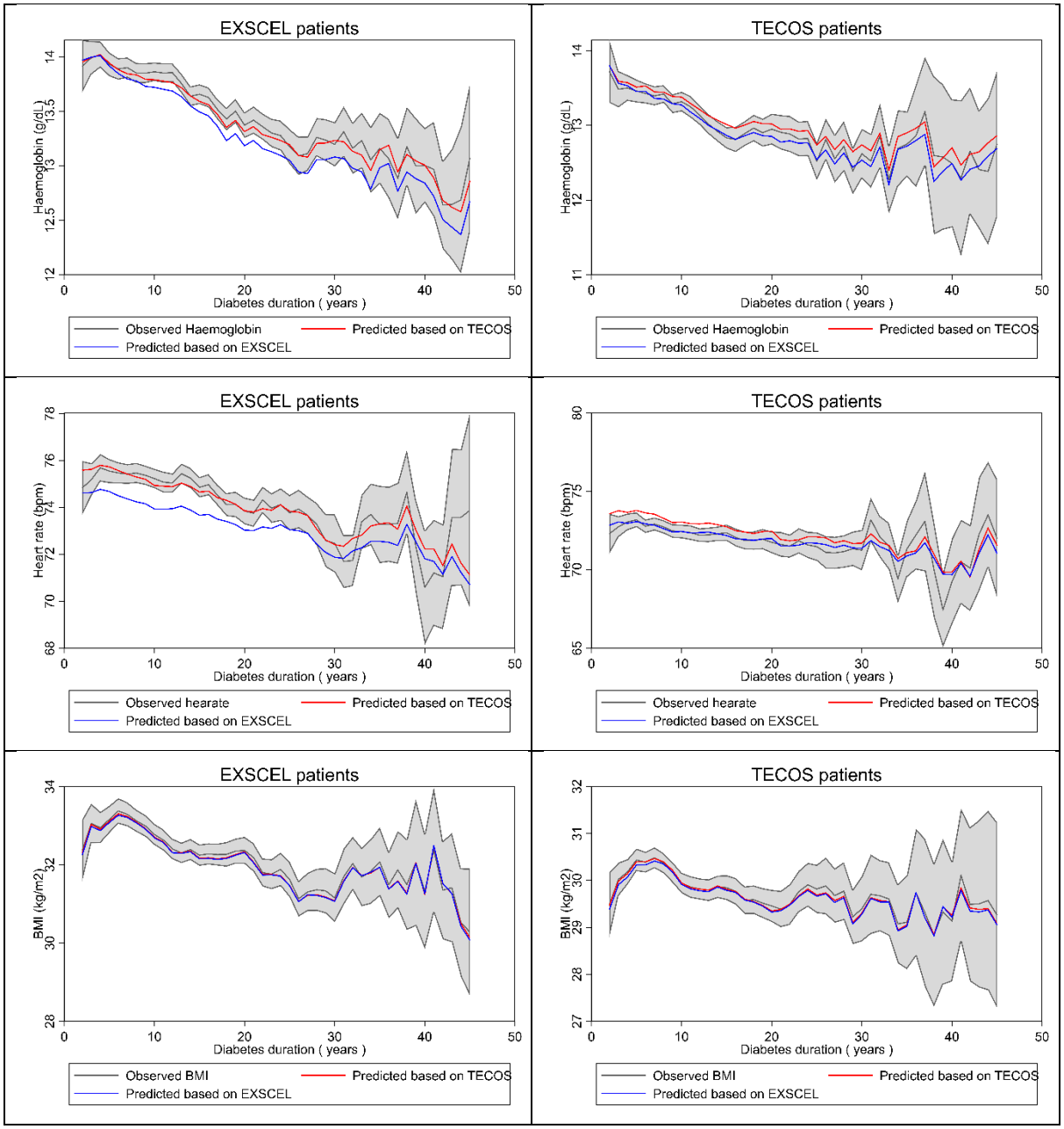
Table A6. Coefficients for the models estimating annual risk factor values of continuous variables using solely TECOS data

VARIABLES	HDL	LDL	SBP	HbA1c	Haemoglobin	Heart rate	BMI
Value Y in previous year	0.297***	0.274***	0.282***	0.516***	0.321***	0.303***	0.605***
	(0.021)	(0.018)	(0.008)	(0.013)	(0.023)	(0.009)	(0.037)
First recorded value Y	0.427***	0.354***	0.226***	0.153***	0.484***	0.277***	0.361***
	(0.025)	(0.018)	(0.008)	(0.013)	(0.025)	(0.010)	(0.037)
ln(duration of diabetes)	-0.007**	-0.042***	0.062	0.063***	-0.139***	-0.233**	0.014
	(0.003)	(0.010)	(0.180)	(0.010)	(0.024)	(0.107)	(0.019)
age at baseline	0.001***	-0.003***	0.026**	-0.009***	-0.009***	-0.046***	-0.012***
	(0.000)	(0.001)	(0.013)	(0.001)	(0.002)	(0.008)	(0.001)
female	0.054***	0.109***	0.558***	0.019	-0.210***	0.612***	0.067***
	(0.005)	(0.014)	(0.210)	(0.012)	(0.030)	(0.129)	(0.024)
White	0.017**	-0.060**	0.177	-0.112***	-0.067	-0.039	-0.045
	(0.007)	(0.030)	(0.423)	(0.026)	(0.051)	(0.240)	(0.042)
Black	0.035***	-0.046	0.039	0.004	-0.138*	0.516	-0.133*
	(0.013)	(0.045)	(0.765)	(0.045)	(0.081)	(0.460)	(0.074)
Asia	0.012	-0.064**	-1.054**	-0.056**	-0.079	1.558***	-0.159***
	(0.008)	(0.030)	(0.450)	(0.028)	(0.053)	(0.264)	(0.045)
Constant	0.215***	1.134***	63.672***	2.926***	3.525***	33.435***	1.710***
	(0.021)	(0.068)	(1.307)	(0.085)	(0.226)	(0.846)	(0.172)
Observations	17,469	16,390	27,709	26,490	8,354	27,026	27,234
Number of id	8,826	8,312	11,804	11,310	4,795	11,604	11,613

Robust standard errors in parentheses; *** p<0.01, ** p<0.05, * p<0.1

Figure A4. Cross-validation analyses comparing the performance of models fitted on EXSCEL data (Table A5) and models fitted on TECOS data (Table A6) against observed data from either EXSCEL or TECOS.





Abbreviations: BMI, body mass index (BMI); HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Supplementary material 2: Instructions on how to use the coefficients to predict risk factors

Tables 1 and 2 in the manuscript provide coefficients for the estimation of the continuous and binary risk factors of an individual patient for each year of simulation, based on their predicted risk factor value in the previous year and their risk factor value at the start of the simulation. The values at the start of the simulation may represent the last recorded value in a randomised trial.

This supplementary material describes how these coefficients should be applied, using a hypothetical individual who had the risk factor values shown in Table A7 at the start of the simulation. The methods for applying these coefficients are similar to those for Leal et al 2021 [6].

Table A7. Risk factor values for hypothetical individual at the start of the simulation. These are based on the Mount Hood reference case simulation [7]

Risk factor	Value at start of simulation
Sex	Male
Ethnicity	White*
Smoker	No
Age, years	66
Duration of diabetes, years	8
Age at diagnosis	58
HbA1c, %	7.5
Height (m)	1.7
Weight (kg)	80.92
BMI, kg/m^2	28.69
LDL, mmol/l	3.0
HDL, mmol/l	1.3
SBP, mmHg	145
eGFR, $ml/min/1.73m^2$	70
Heart rate, bpm	79
Haemoglobin, g/dl	14
White blood cell count $x10^9/l$	7
PVD	No
Atrial fibrillation	No
Albuminuria	No

* Assumed for the purposes of this simulation: not specified in the Mount Hood reference.

Estimating predictions for continuous risk factors

As described in the Methods, continuous risk factors, such as HbA1c are predicted as

$y_{it} = \phi_0 + \phi_1 y_{it-1} + \phi_2 y_{i,0} + \phi_3 sex_i + \phi_4 ethnic_{ij} + \phi_5 age_i + \phi_6 \ln(duration\ of\ diabetes_{it})$

where y_{it} is the value of risk factor for individual *i* in year *t*. $y_{i,t-1}$ is the previous year's risk factor value; $y_{i,0}$ is the risk factor value at start of simulation[6] and $ethnic_{ij}$ is a series of dummy variables for ethnicity, with '1' indicating White for $ethnic_{i1}$, Black for $ethnic_{i2}$, or Asian (oriental, Indian or other) for $ethnic_{i1}$. The baseline ethnicity category is other (Hispanic, Aboriginal (Australia), Maori, Native Hawaiian, Pacific Islander, Indian (American) or Alaska Native). Finally, age_i is age at the start of the simulation.

We can insert the coefficient values from Table 1 to estimate predictions for HbA1c for the hypothetical individual shown in Table A7 12 months after the start of the simulation (9 years of duration of diabetes) as:

$HbA1c_{Person1Year1} = 2.945 + 0.456 * 7.5 + 0.243 * 7.5 + 0 * 0.031 - 0.082 - 0.012 * 66 + 0.083 * \ln(8 + 1) = 7.496$

In Year 2, we can insert the Year 1 HbA1c as the HbA1c last year and increase the duration of diabetes by 1 to give:

$HbA1c_{Person1Year2} = 2.945 + 0.456 * \mathbf{7.496} + 0.243 * 7.5 + 0 * 0.031 - 0.082 - 0.012 * 66 + 0.083 * \ln(\mathbf{8 + 2}) = 7.503$

The same methods can be used to estimate predictions for other continuous risk factors using the coefficients in Table 1.

Estimating predictions for binary risk factors

Atrial fibrillation (AF), albuminuria (ALB), PVD and eGFR <60 ml/min/1.73m^2 were predicted based on Weibull proportional hazards models (Table 2). We assumed that once a patient has been diagnosed with one of these events, they will have it for the rest of their life. The unconditional probability of these events occurring in the interval *t* to *t+1* is:

$$1 - \exp(H(t|x_{jt}) - H(t+1|x_{jt}))$$

Where $H(t|x_{jt})$ is the integrated cumulative hazard at time *t* (years since diagnosis of diabetes) defined for the Weibull regression as

$$H(t|x_{jt}) = \exp(\beta_0 + \beta_j x_{tj}) t^{\gamma}$$

where x_{tj} is the vector of the covariates reported in Table A7 and β_j is the vector of their respective coefficients (Table 2).

Hence, the probability of atrial fibrillation (AF) 12 months after the start of the simulation for the individual outlined in Table A7 can be calculated as follows. First we estimate the cumulative hazards at time t and time t+1.

$$H_{AF}(t|x_{jt}) = \exp(\beta_0 + \beta_1 AgeAtRandomisation + \beta_2 Female + \beta_3 White + \beta_4 Black + \beta_5 BMIpreviousyear + \beta_6 HDLpreviousyear\ )t^{\Gamma}$$

Hence for $t_1 = 9$ (year 1 of the simulation, where duration of diabetes is 9 years)

$$H_{AF}(t_1|x_{j1}) = \exp(-11.269 + 0.060 * 66 - 0.576 * 0 + 1.073 * 1 + 1.150 * 0 + 0.058 * 28.69 - 0.487 * 1.3) * (8+1)^{1.210} = 0.07836$$

And $t_2 = 10$ (year 2 of the simulation, where duration of diabetes is 10 years [assuming for simplicity that BMI and LDL have remained unchanged])

$$H_{AF}(t_2|x_{j1}) = \exp(-11.269 + 0.060 * 66 - 0.576 * 0 + 1.073 * 1 + 1.150 * 0 + 0.058 * 28.69 - 0.487 * 1.14) * (8+2)^{1.210} = 0.09623$$

Where Γ =1.210 i.e. exp(ln(Γ)) in Table 2 of the manuscript.

Second, we estimate the probability of AF in the first year of the simulation to be 1.8% as,

$$ProbabilityAF = 1 - \exp(0.07836 - 0.09623) = 0.01771$$

This probability is then compared against a random draw from a uniform (0,1) distribution and, if it is higher, the individual develops AF.

The same approach is used to predict the probability of albuminuria, PVD and eGFR <60 ml/min/1.73m^2 conditional on the Weibull model covariates reported in Table 2. Smoking at randomisation was a significant predictor of PVD (Table 1); when predicting PVD, a dummy variable indicating whether the patient smoked at the start of the model simulation can be used in place of a dummy indicating whether the patient smoked at randomisation.

Predicting eGFR

A two-step approach was used to predict eGFR for each year of the UKPDS-OM2 simulation. The first step comprised a proportional hazard Weibull survival model predicting the probability that eGFR is <60 ml/min/1.73m^2 for each year of simulation. As with the other survival equations, once an individual progresses to eGFR<60 they remain in this health state for the rest of the simulation. The second step uses one of two Tobit models to predict the patient's eGFR value (as a continuous variable) conditional on whether they were predicted to have eGFR above or below 60 ml/min/1.73m^2 in the first step.

The Weibull model and Tobit models described in the main manuscript were used to predict eGFR for each patient one year at a time. For each patient with eGFR>60 ml/min/1.73m^2 in the previous year, in each loop of the UKPDS-OM simulation, the predicted probability of the Weibull model is compared with a random number to determine whether the patient progressed to eGFR<60 ml/min/1.73m^2 that year. Then, conditional on progression or not to eGFR<60

ml/min/1.73m^2, one of the Tobit models is used to predict that patient's eGFR value. For patients with eGFR<60 ml/min/1.73m^2 in the previous year, the patient is assumed to remain in the eGFR<60 ml/min/1.73m^2 health state and the Tobit model for eGFR<60 ml/min/1.73m^2 is used to predict eGFR for that year.

For the first step, the instructions for binary risk factors in the previous section can be followed to estimate the predicted probability that eGFR is <60 ml/min/1.73m^2 and determine whether the patient progresses to eGFR<60 ml/min/1.73m^2 that year (by comparing predicted probability against random draw from uniform distribution (0,1)).

If patient i is determined to have eGFR below 60 ml/min/1.73m^2, the conditional expected eGFR value is predicted as:

$$E(eGFR_i|0 < eGFR_i^* < 60) = \beta' x_i - \sigma\frac{\phi_{1i} - \phi_{2i}}{\Phi_{1i} - \Phi_{2i}}$$

Where: $\Phi_{1i} = \Phi(\frac{0-\beta' x_i}{\sigma})$ is the cumulative distribution function for a standard normal distribution using the lower limit (0 ml/min/1.73m^2); $\Phi_{2i} = \Phi(\frac{60-\beta' x_i}{\sigma})$ is the cumulative distribution function for a standard normal distribution using the upper limit (60 ml/min/1.73m^2); ϕ_{1i} and ϕ_{2i} are the corresponding density functions for the standard normal distribution; and σ is the sigma (standard error of the forecast) given in Table 2 (11.888).

$\beta' x_i$ is the linear predictor:

$$\beta' x_i = 36.058 + (-0.100) * ageatrandomisation - 0.025 * SBP + 0.232 * eGFRpreviousyear + 0.459 * eGFRatbaseline + (-1.335) * \ln(durationdiabetes)$$

For instance, for the hypothetical individual in Table A7 who was age 66 with eGFR of 70 ml/min/1.73m^2 and SBP of 145 mmHg at the start of the simulation, the linear predictor $\beta' x_i$ at the end of the first year of simulation (nine years after diagnosis of diabetes) can be calculated as follows if the first step predicts eGFR <60 ml/min/1.73m^2:

$\beta' x_i = 36.058 + (-0.100) * 66 - 0.025 * 145 + 0.232 * 70 + 0.459 * 70 + (-1.335) * \ln(8 + 1\ years) = 71.2697$

$\Phi_{1i} = \Phi\left(\frac{0-(71.2697)}{11.888}\right) = \Phi(-5.995) = 1.017 \times 10^{-9}$ and $\phi_{1i} = \phi(-5.995) = 6.257 \times 10^{-9}$

$\Phi_{2i} = \Phi\left(\frac{60-(71.2697)}{11.888}\right) = \Phi(-0.948) = 0.1716$ and $\phi_{2i} = \phi(-0.948) = 0.2545$

This patient will also be assumed to continue to have eGFR<60 ml/min/1.73m^2 for the rest of their life.

Then,

$E(eGFR_i|0 < eGFR_i^* < 60) = \beta' x_i - \sigma\frac{\phi_{1i}-\phi_{2i}}{\Phi_{1i}-\Phi_{2i}} = 71.2697 - 11.888 * \frac{6.257\times10^{-9}-0.2545}{1.017\times10^{-9}-0.1716} =$ 53.632 ml/min/1.73m^2

If patient i is determined to have eGFR above 60 ml/min/1.73m^2 in loop L, the conditional eGFR value is predicted as:

$$E(eGFR_i|eGFR_i^* \geq 60) = \beta' x_i + \sigma \frac{\phi_{1i}}{1 - \Phi_{1i}}$$

Where: $\Phi_{1i} = \Phi(\frac{60-\beta' x_i}{\sigma})$ is the cumulative distribution function for a standard normal distribution using the lower limit (60 ml/min/1.73m^2); ϕ_{1i} is the corresponding density functions for the standard normal distribution; σ is the sigma (standard error of the forecast) given in Table 2 (13.839).

For the same hypothetical individual in Table A7 who was age 66 with eGFR of 70 ml/min/1.73m^2 and SBP of 145 mmHg at the start of the simulation, the linear predictor $\beta' x_i$ at the end of the first year of simulation (nine years after diagnosis of diabetes) can be calculated as follows if the first step predicts eGFR ≥60 ml/min/1.73m^2 in loop L:
$\beta' x_i = 36.317 + (-0.230) * 66 - 0.011 * 145 + 0.446 * 70 + 0.303 * 70 +$
$(-0.753) * \ln(8 + 1\ years) = 70.3175$

$\Phi_{1i} = \Phi\left(\frac{60-(70.3175\ )}{13.839}\right) = \Phi(-0.746) = 0.228$ and $\phi_{1i} = \phi(-0.746) = 0.302$

Hence, $E(eGFR_i) = \beta' x_i + \sigma \frac{\phi_{1i}}{1-\Phi_{1i}} = 70.3175\ + 13.839 * \frac{0.302}{1-0.228} = 75.73$ ml/min/1.73m^2

If the patient did not progress to eGFR <60 ml/min/1.73m^2 in year 1, the eGFR predicted for that patient for year 1 in this loop was then used to predict the probability that this patient progressed to eGFR <60 ml/min/1.73m^2 the following year for the same loop. The eGFR for year 1 was also used to predict the exact eGFR value in the relevant Tobit model conditional on the prediction of the Weibull survival model. This was repeated for subsequent years for this patient in this loop and then repeated for multiple loops for the same patient, and then for other patients.

Notes regarding all time paths

Coefficients to more decimal places and those with an alternative ethnicity coding (which uses white as the baseline category, rather than other) are available from the corresponding author on request. A set of 5000 bootstrap estimates (with replacement) of all regression coefficients using this alternative ethnicity coding are also available on request, which could be used to propagate uncertainty around the risk that the trajectory equations within a model, such as UKPDS-OM2.

Since neither EXSCEL nor TECOS collected data on white blood cell count, or post-baseline smoking, the equations estimated by Leal et al could be used to project white blood cell count and smoking [6].

EXSCEL and TECOS were designed as glycaemic equipoise studies, i.e. "usual care physicians [were] encouraged to follow guidelines for care based on local and institutional practice

patterns and any relevant published practice guidelines" [2]. This differs considerably from previous diabetes trials where individuals were prescribed a placebo without usual care. See, for example, Bethel 2020 [8]. Both trials had a highly pragmatic design with very few restrictions on concomitant treatment and compared usual care plus study drug against usual care plus placebo. Hence, data from these trials are likely to be valid for contemporary populations that are similar to those in the trials.

In addition to the study medication evaluated in EXSCEL and TECOS, there have been many other new drugs and many changes to clinical management and secular trends since the UKPDS era (1977-2002) that will affect risk factor time paths. For example, HbA1c may be affected by increased use of metformin, lower blood glucose targets, patient education, introduction of long-acting insulins, glitazones, as well as the newer drugs (e.g. empagliflozin) that were introduced during EXSCEL and TECOS follow up. LDL will be affected by the introduction of statins and change of guidance recommending lower LDL targets, higher intensity statin regimens and use in a wider range of patients. People diagnosed with diabetes in 1977-1997 are also a different generation from most of those participating in EXSCEL and TECOS and may have been less active in old age and be more likely to have smoked.

For each patient, it is likely that any change in medication (whether this is exenatide/sitagliptin, or concomitant drug) will produce a step change in risk factors in the first 6-12 months after changing medication. While patients are on stable treatment, the change in risk factors is likely to be relatively stable but there may be changes due to concomitant medication, lifestyle factors and increasing duration of diabetes. For example, an individual EXSCEL study participant may initially receive exenatide plus metformin and have a gradual increase in HbA1c over time. If their HbA1c exceeds a target level two years later, their clinician may decide to add insulin, resulting in a reduction in HbA1c. After that fall, HbA1c levels may then gradually rise and their clinician may increase the insulin dose accordingly, resulting in another rapid fall and then a gradual rise. Other patients may stop medications (e.g. due to patient preference, hypoglycaemia or adverse events). However, many patients may have no change in glucose-lowering medication during the study period and may have relatively stable HbA1c. Across our cohorts, there will be patients starting or stopping many different medications at different times. Our time path equations aim to predict the average risk factor trend over time given the current package of interventions (and controlling for demographics and past risk factor levels).

Users of diabetes simulation models, such as UKPDS-OM2, will typically use our risk factor time paths to model how risk factors change over time after the effect of study interventions has been applied. For example, researchers may do a network meta-analysis of 48-week trials to estimate the reduction in HbA1c during the initial year of treatment. They may reduce HbA1c in year 1 of simulation based on the meta-analysis treatment effects and use our risk factor time paths to model how HbA1c changes over time from year 2 onwards. Researchers evaluating treat-to-target regimens may also assume that patients intensify treatment when our time path equations predict that patients' HbA1c has risen above a target level and may then apply an initial treatment effect, followed by a further period extrapolated using our time path equations.

Supplementary material 3: Methods for QALY gains using current and previous risk equations extrapolated using UKPDS-OM2

The impact of different risk factor trajectories on QALYs was by extrapolating risk factors for 2579 participants randomised to placebo in either EXSCEL or TECOS who had complete data on all risk factors at baseline.

For each participant, we took the pre-randomisation values of each risk factor and extrapolated using either the risk factor trajectories estimated in this paper, or those estimated by Leal et al. [6].

Since neither trial measured white blood cell count, baseline white blood cell count was imputed using a published algorithm estimated using the UKPDS trial dataset [9]. Post-baseline values for white blood cell count and for smoking (where there was no data post-baseline) were estimated from the baseline value using the trajectories estimated by Leal et al. [6]. Continuous risk factors were extrapolated in Stata version 17.0 and entered into the model directly as fixed values.

A bespoke version of UKPDS-OM version 2.2 was used, which incorporated risk factor time paths using the equations of Leal et al. [6] or those of the current paper. As described in Supplementary material 2, for binary risk factors (PVD, albuminuria, atrial fibrillation and smoking) and eGFR, accurate estimation of lifetime QALYs requires Monte Carlo simulation. For PVD, albuminuria, atrial fibrillation and eGFR <60 ml/min/173m^2, the survival models predict the rate at which patients will develop risk factors, whereas the UKPDS-OM requires binary inputs for whether the patient has or has not developed that risk factor at each time point. Similarly, the logistic regression for smoking reported by Leal et al [6] predicts whether patients are current smokers or not. In each loop of the model, the hazard (or log-odds) for developing each risk factor in the next year is estimated and this hazard (or log-odds) is compared against random numbers to decide whether or not the patient develops that risk factor that year. Outcomes for the following year are estimated conditional on whether the patient developed it previous year. This approach ensures that the patient will develop each risk factor in the correct proportion of loops and ensures that the mean QALYs for each patient reflect that patient's true risk. By contrast, other methods, such as the highest probability approach, would introduce bias [10].

Results were extrapolated for 70 years using 100,000 loops. No bootstraps were used since the aim was to compare point estimates. The default utility values, estimated from the UKPDS sample [11], were used to estimate QALYs. No discounting was applied.

Supplementary material 4: Methods and results of reference simulation

The 12 reference simulations set out in https://www.mthooddiabeteschallenge.com/registry were run using the same bespoke version of UKPDS-OM version 2.2. The simulation engine and QALY calculations in the model we used is identical to that of the publically available models of version 2.0 and 2.2 but enables extrapolation of risk factors using the time path equations presented in the current paper as well as those of Leal et al. [6].

In line with the original reference simulation for UKPDS-OM version 2.0, we assumed patients were white and 1.7 m tall. We ran 50 million loops and did not consider parameter uncertainty. Following the methods for the Mount Hood registry, no increments were applied at baseline (only from year 1 onwards). We extrapolated the baseline outcomes for the control patients using each of the three methods and then applied the increments to year 1 onwards, relative to the values for the control patient in that year (Tables A8 and A9).

Predicted risk factors from this simulation are plotted for the control patients in Figure A5.

Table A8. Baseline inputs for reference simulation. The columns for IHD, Heart failure, Amputation, Blindness, Renal failure, Stroke, MI and ulcer have missing values for all patients (indicating no history of these events at start of simulation).

		Demographic characteristics						Risk factor values at start of simulation											Discounting start year
ID	Group	Ethnicity	Gender	Age now	Duration of diabetes	Weight	Height	AF	PVD	Current smoker	Albuminuria	HDL	LDL	Systolic BP	HbA1c	Heart rate	WBC	Haemoglobin	eGFR	
Control male	1	1	M	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
Control female	2	1	F	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
0.5%-point reduction in HbA1c Male	3	1	M	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
0.5%-point reduction in HbA1c Female	4	1	F	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
10mm Hg reduction in SBP male	5	1	M	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
10mm Hg reduction in SBP female	6	1	F	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
0.5 mmol/l reduction in LDL male	7	1	M	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
0.5 mmol/l reduction in LDL female	8	1	F	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
1-unit reduction in BMI (kg/m2) male	9	1	M	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
1-unit reduction in BMI (kg/m2) female	10	1	F	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
All interventions combined male	11	1	M	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0
All interventions combined female	12	1	F	66	8	80.92	1.7	N	N	N	N	1.3	3	145	7.5	79	7	14	70	0

Table A9. Example of BMI inputs for reference simulation

	BMI trajectory LOCF					BMI trajectories from current paper				
ID	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Control male	80.92	80.92	80.92	80.92	80.92	80.80	80.71	80.65	80.61	80.59
Control female	80.92	80.92	80.92	80.92	80.92	80.91	80.90	80.90	80.89	80.89
0.5%-point reduction in HbA1c Male	80.92	80.92	80.92	80.92	80.92	80.80	80.71	80.65	80.61	80.59
0.5%-point reduction in HbA1c Female	80.92	80.92	80.92	80.92	80.92	80.91	80.90	80.90	80.89	80.89
10mm Hg reduction in SBP male	80.92	80.92	80.92	80.92	80.92	80.80	80.71	80.65	80.61	80.59
10mm Hg reduction in SBP female	80.92	80.92	80.92	80.92	80.92	80.91	80.90	80.90	80.89	80.89
0.5 mmol/l reduction in LDL male	80.92	80.92	80.92	80.92	80.92	80.80	80.71	80.65	80.61	80.59
0.5 mmol/l reduction in LDL female	80.92	80.92	80.92	80.92	80.92	80.91	80.90	80.90	80.89	80.89
1-unit reduction in BMI (kg/m2) male	78.03	78.03	78.03	78.03	78.03	77.91	77.82	77.76	77.72	77.70
1-unit reduction in BMI (kg/m2) female	78.03	78.03	78.03	78.03	78.03	78.02	78.01	78.01	78.00	78.00
All interventions combined male	78.03	78.03	78.03	78.03	78.03	77.91	77.82	77.76	77.72	77.70
All interventions combined female	78.03	78.03	78.03	78.03	78.03	78.02	78.01	78.01	78.00	78.00

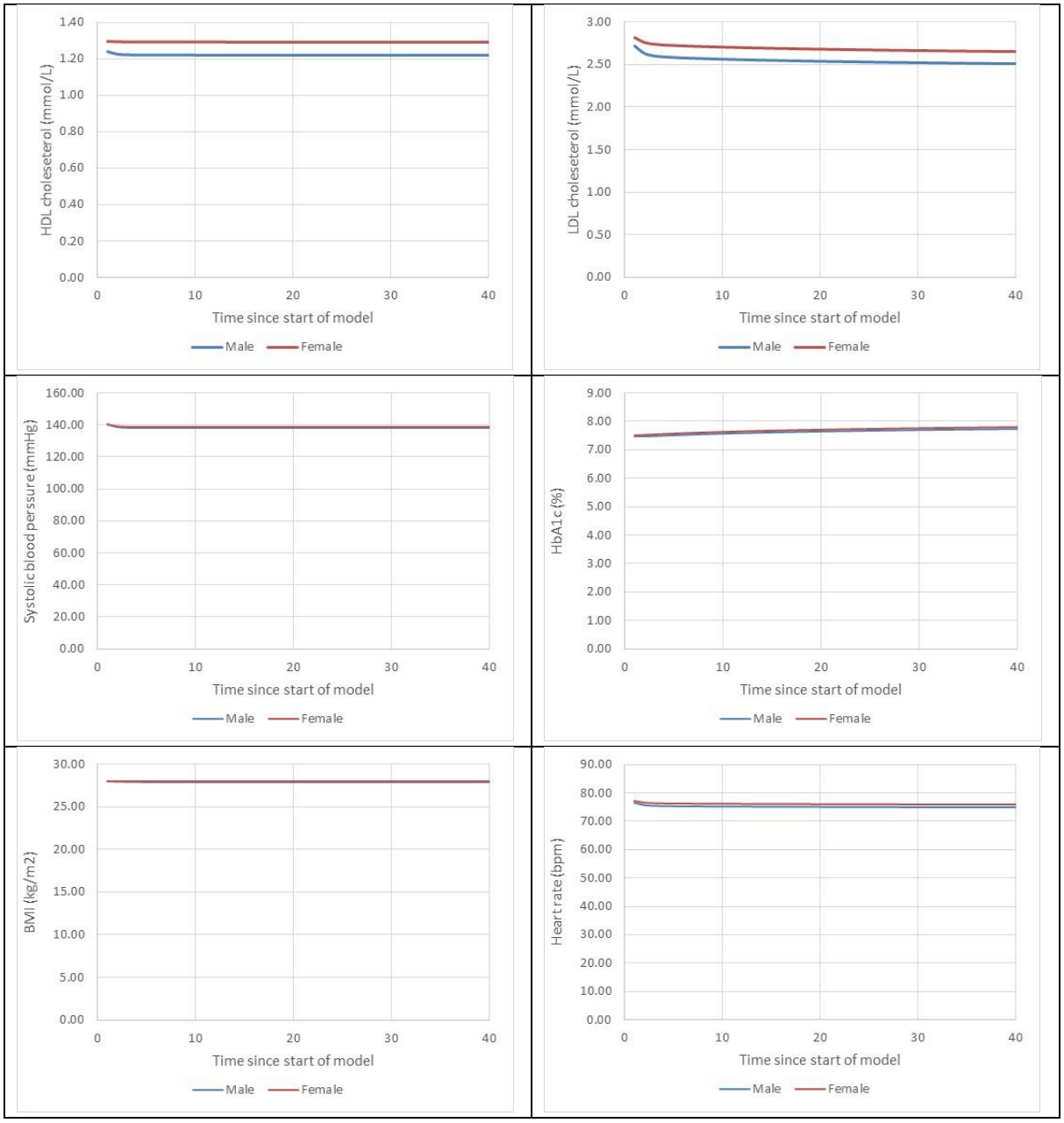
Table A10. Results of reference simulation: QALYs for each hypothetical individual defined in the Mount Hood reference. The results for the model we used (version 2.2 Global) and the 2.0 release version are negligible and result purely from Monte Carlo error.

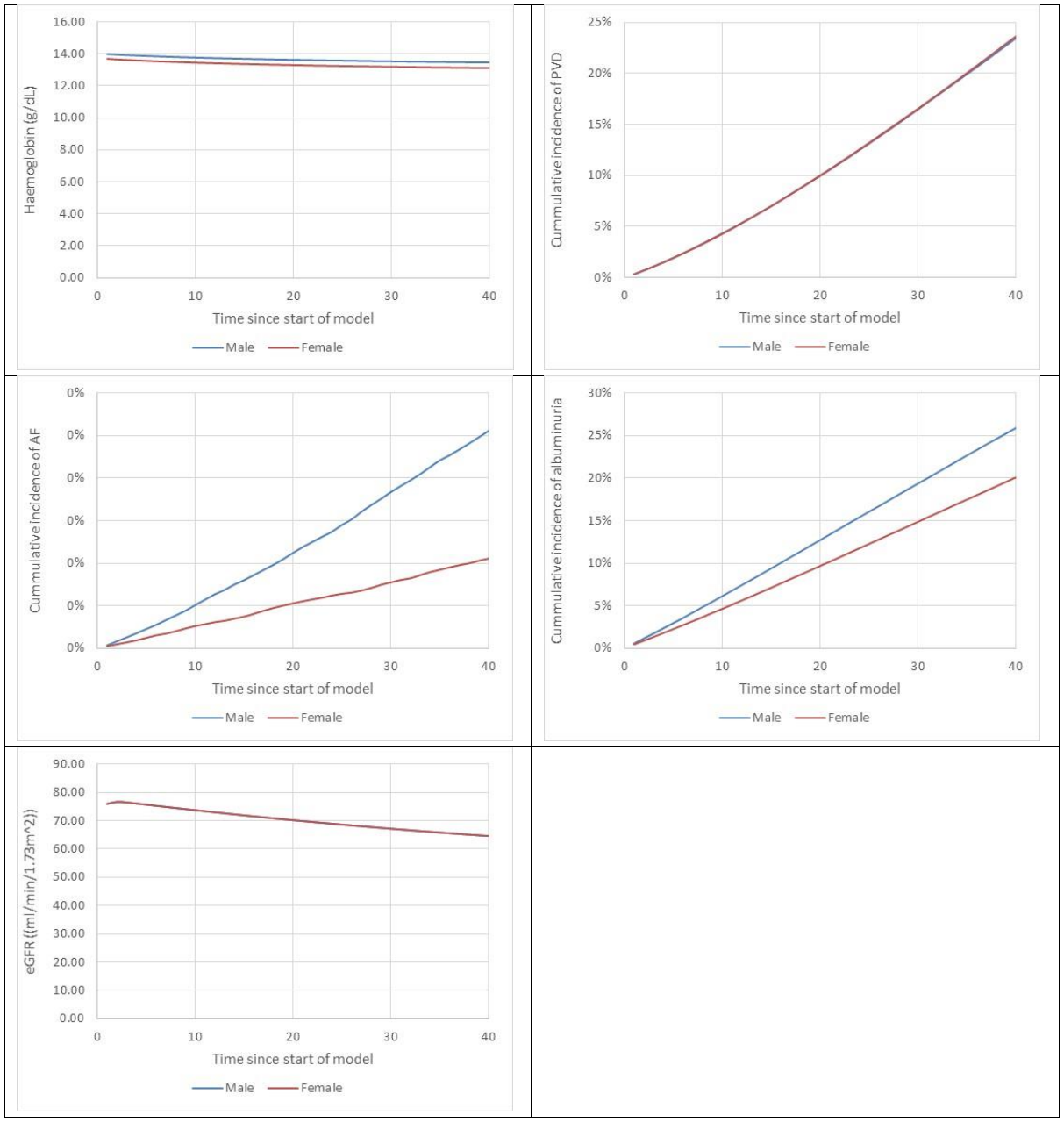
Model	Version	Extrapolation	Sex	Control	0.5% red. HbA1c	10mmHg in SBP	0.5mmol/l red. LDL	1-unit red BMI	All combined	Absolute QALY gain for all combined vs control	Date of simulation
UKPDS-OM	2.2 global 2023	Trajectories from current paper*	Male	11.97	12.07	12.15	12.19	12.00	12.47	0.50	12/09/2023
UKPDS-OM	2.2 global 2023		Female	13.47	13.56	13.64	13.59	13.50	13.86	0.39	12/09/2023
UKPDS-OM	2.2 global 2023	Leal et al [6] trajectories	Male	10.55	10.70	10.84	10.84	10.59	11.30	0.75	2/10/2023
UKPDS-OM	2.2 global 2023		Female	11.87	12.01	12.17	12.06	11.92	12.53	0.66	2/10/2023
UKPDS-OM	2.2 global 2023	LOCF	Male	11.90	11.99	12.09	12.13	11.92	12.41	0.51	13/09/2023
UKPDS-OM	2.2 global 2023		Female	13.56	13.64	13.74	13.69	13.59	13.95	0.39	13/09/2023
UKPDS-OM	2.0 release version	LOCF	Male	11.90	11.99	12.08	12.13	11.92	12.41	0.51	05/10/2018
UKPDS-OM	2.0 release version		Female	13.57	13.64	13.74	13.69	13.59	13.95	0.39	05/10/2018

LOCF, last observation carried forward (assuming no change in risk factors over 40 years, other than the increment applied at year one).

* Trajectories for smoking and WBC taken from Leal et al. [6].

Figure A5. Predicted risk factors for male (blue lines) and female (red lines) control patients defined by the Mount Hood Registry extrapolated over a lifetime using the time paths estimated in the current study. Values were estimated using a beta version of UKPDS-OM2; predicted cases of binary endpoints allow for death as a competing risk.





Abbreviations: AF, atrial fibrillation; BMI, body mass index (BMI); eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PVD, peripheral vascular disease; SBP, systolic blood pressure.

Supplementary material 5: Evaluating impact of randomised treatment group on time paths ≥12 months after start of treatment

Post hoc analyses were conducted to test whether randomised treatment allocation affected continuous risk factor time paths. These were conducted by replicating the study-specific models shown in Tables A5 and A6 with the addition of a dummy indicating treatment allocation.

Treatment allocation was statistically significant ($p<0.05$) for only three combinations of study/risk factor: exenatide allocation had a significant effect on time paths for systolic blood pressure ($p=0.012$) and heart rate ($p=0.014$) while sitagliptin affected time paths for HbA1c ($p=0.001$). However, it should be noted that this is a post hoc analysis including 14 statistical tests, so has a high risk of a type 1 error.

For the three risk factor/study combinations where a significant difference was observed, we present coefficients separately for each treatment group (Supplementary material Table A11).

Table A11. Coefficients for the models estimating annual risk factor values of continuous variables separately for individual study arms. For brevity, the table shows only those combinations of study and risk factor for which treatment allocation had a statistically significant effect (p<0.05) when added to the regression.

VARIABLES	SBP	SBP	Heart rate	Heart rate	HbA1c	HbA1c
Trial	EXSCEL	EXSCEL	EXSCEL	EXSCEL	TECOS	TECOS
Treatment allocation	Exenatide	Placebo	Exenatide	Placebo	Sitagliptin	Placebo
Value Y in previous year	0.241** (0.013)	0.273** (0.014)	0.275** (0.015)	0.236** (0.014)	0.535** (0.018)	0.494** (0.019)
First recorded value Y	0.410** (0.015)	0.357** (0.015)	0.384** (0.016)	0.468** (0.016)	0.146** (0.017)	0.157** (0.019)
ln(duration of diabetes)	0.089 (0.227)	-0.209 (0.238)	-0.303** (0.149)	-0.411** (0.147)	0.061** (0.014)	0.066** (0.015)
Age at baseline	0.018 (0.014)	0.035** (0.015)	-0.045** (0.009)	-0.043** (0.009)	-0.010** (0.001)	-0.008** (0.001)
Female	0.134 (0.251)	0.233 (0.253)	0.319** (0.156)	0.477** (0.162)	0.023 (0.017)	0.015 (0.018)
White	0.480 (0.491)	0.092 (0.48)	0.437 (0.288)	0.536** (0.273)	-0.110** (0.036)	-0.113** (0.039)
Black	0.568 (0.762)	1.679** (0.732)	0.249 (0.427)	0.163 (0.468)	-0.014 (0.066)	0.021 (0.061)
Asian	0.209 (0.624)	1.066 (0.632)	1.333** (0.414)	1.567** (0.376)	-0.093** (0.038)	-0.012 (0.041)
Constant	44.754** (1.604)	47.886** (1.546)	28.375** (1.033)	24.726** (1.06)	2.906** (0.116)	3.002** (0.126)
Sigma_u	5.510	5.097	3.337	3.656	0.222	0.240
Sigma_e	9.660	10.028	6.005	5.821	0.601	0.626
rho	0.245	0.205	0.236	0.283	0.120	0.128
Observations	13,791	13,290	13,693	13,209	13,355	13,135
Number of id	6,188	6,123	6,156	6,107	5,683	5,627

Robust standard errors in parentheses** p<0.05

References for supplementary material

1. Holman RR, Bethel MA, George J, Sourij H, Doran Z, Keenan J, et al. Rationale and design of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial. Am Heart J. 2016;174:103-10. https://doi.org/10.1016/j.ahj.2015.12.009.
2. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017;377:1228-39. https://doi.org/10.1056/NEJMoa1612917.
3. Green JB, Bethel MA, Paul SK, Ring A, Kaufman KD, Shapiro DR, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American Heart Journal. 2013;166:983-9. e7. https://doi.org/10.1016/j.ahj.2013.09.003.
4. Mentz RJ, Bethel MA, Gustavson S, Thompson VP, Pagidipati NJ, Buse JB, et al. Baseline characteristics of patients enrolled in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL). Am Heart J. 2017;187:1-9. https://doi.org/10.1016/j.ahj.2017.02.005.
5. Bethel MA, Green JB, Milton J, Tajar A, Engel SS, Califf RM, et al. Regional, age and sex differences in baseline characteristics of patients enrolled in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Obes Metab. 2015;17:395-402. https://doi.org/10.1111/dom.12441.
6. Leal J, Alva M, Gregory V, Hayes A, Mihaylova B, Gray AM, et al. Estimating risk factor progression equations for the UKPDS Outcomes Model 2 (UKPDS 90). Diabet Med. 2021:e14656. https://doi.org/10.1111/dme.14656.
7. Kent S, Becker F, Feenstra T, Tran-Duy A, Schlackow I, Tew M, et al. The Challenge of Transparency and Validation in Health Economic Decision Modelling: A View from Mount Hood. Pharmacoeconomics. 2019;37:1305-12. https://doi.org/10.1007/s40273-019-00825-1.
8. Bethel MA, Stevens SR, Buse JB, Choi J, Gustavson SM, Iqbal N, et al. Exploring the Possible Impact of Unbalanced Open-Label Drop-In of Glucose-Lowering Medications on EXSCEL Outcomes. Circulation. 2020;141:1360-70. https://doi.org/10.1161/CIRCULATIONAHA.119.043353.
9. Pagano E, Konings SRA, Di Cuonzo D, Rosato R, Bruno G, van der Heijden AA, et al. Prediction of mortality and major cardiovascular complications in type 2 diabetes: External validation of UK Prospective Diabetes Study outcomes model version 2 in two European observational cohorts. Diabetes Obes Metab. 2021;23:1084-91. https://doi.org/10.1111/dom.14311.
10. Ramos-Goñi J, Rivero-Arias O, Dakin H. Response mapping to translate health outcomes into the generic health-related quality of life instrument EQ-5D: Introducing the mrs2eq and oks2eq commands. Stata Journal. 2013;13:474-91.
11. Alva M, Gray A, Mihaylova B, Clarke P. The effect of diabetes complications on health-related quality of life: the importance of longitudinal data to address patient heterogeneity. Health Econ. 2014;23:487-500. https://doi.org/10.1002/hec.2930.