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ORIGINAL ARTICLE

Lifetime and 10-year cardiovascular risk prediction in individuals with type 1 diabetes: The LIFE-T1D model

Marga A. G. Helmink MD[1] | Steven H. J. Hageman PhD[1] | Björn Eliasson PhD[2] | Naveed Sattar PhD[3] | Frank L. J. Visseren PhD[1] | Jannick A. N. Dorresteijn PhD[1] | Katie Harris PhD[4] | Sanne A. E. Peters PhD[4,5,6] | Mark Woodward PhD[4,6] | Péter Szentkúti MSc[7] | Kurt Højlund PhD[8] | Jan Erik Henriksen PhD[8] | Henrik Toft Sørensen PhD[7] | Erik H. Serné PhD[9] | Thomas T. van Sloten PhD[1] | Reimar W. Thomsen PhD[7] | Jan Westerink PhD[1,10]

[1]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

[2]Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

[3]School of Cardiovascular and Metabolic Sciences, University of Glasgow, Glasgow, UK

[4]The George Institute for Global Health, University of New South Wales, Sydney, Australia

[5]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

[6]The George Institute for Global Health, Imperial College London, London, UK

[7]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

[8]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[9]Department of Vascular Medicine, Amsterdam University Medical Center, Location AMC, Amsterdam, The Netherlands

[10]Department of Internal Medicine, Isala, Zwolle, The Netherlands

Correspondence
Frank L. J. Visseren, Department of Vascular Medicine, University Medical Center Utrecht, PO Box 85500, 3508 GA, Utrecht, The Netherlands.
Email: f.l.j.visseren@umcutrecht.nl

Abstract

Aims: To develop and externally validate the LIFE-T1D model for the estimation of lifetime and 10-year risk of cardiovascular disease (CVD) in individuals with type 1 diabetes.

Materials and Methods: A sex-specific competing risk-adjusted Cox proportional hazards model was derived in individuals with type 1 diabetes without prior CVD from the Swedish National Diabetes Register (NDR), using age as the time axis. Predictors included age at diabetes onset, smoking status, body mass index, systolic blood pressure, glycated haemoglobin level, estimated glomerular filtration rate, non-high-density lipoprotein cholesterol, albuminuria and retinopathy. The model was externally validated in the Danish Funen Diabetes Database (FDDB) and the UK Biobank.

Results: During a median follow-up of 11.8 years (interquartile interval 6.1–17.1 years), 4608 CVD events and 1316 non-CVD deaths were observed in the NDR ($n = 39\,756$). The internal validation c-statistic was 0.85 (95% confidence interval [CI] 0.84–0.85) and the external validation c-statistics were 0.77 (95% CI 0.74–0.81) for the FDDB ($n = 2709$) and 0.73 (95% CI 0.70–0.77) for the UK Biobank ($n = 1022$). Predicted risks were consistent with the observed incidence in the derivation and both validation cohorts.

Conclusions: The LIFE-T1D model can estimate lifetime risk of CVD and CVD-free life expectancy in individuals with type 1 diabetes without previous CVD. This model can facilitate individualized CVD prevention among individuals with type 1 diabetes. Validation in additional cohorts will improve future clinical implementation.

KEYWORDS
cardiovascular disease, diabetes complications, macrovascular disease, type 1 diabetes

1 | INTRODUCTION

Individuals with type 1 diabetes have an increased risk of developing cardiovascular disease (CVD, defined as myocardial infarction, stroke and fatal CVD) compared to the general population, with risks elevated 2.3-fold in women and threefold in men.[1,2] The first signs of accelerated vascular harm have been shown to already appear during adolescence in individuals with type 1 diabetes.[3] Efforts to mitigate risk factor exposure, including glycaemic control, should ideally start early in life, as supported by data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study.[4] Current guidelines for individuals with type 1 diabetes, including the recently published 2023 European Society of Cardiology (ESC) guideline for the management of CVD in patients with diabetes, are largely based on extrapolations from studies in type 2 diabetes,[5,6] despite the differences in the underlying pathophysiology and the longer duration of hyperglycaemia in type 1 compared to type 2 diabetes.[7]

Currently available prediction models for CVD in individuals with type 1 diabetes are hampered by the relatively limited prediction horizons of those models, which are often a maximum of 10 years,[8–13] or by the lack of external validation.[14] Since the risk of CVD is mainly driven by age, the short-term risk in young people is usually very low. Hence, based on models with a relatively short prediction horizon, young people living with type 1 diabetes will often not qualify for preventive therapy, even if their long-term risk is high and they could potentially benefit from lifelong risk factor reduction. A lifetime risk assessment, which estimates the risk over the remainder of an individual's lifespan from the time of assessment, allows the identification of individuals that would benefit most from long-term preventive treatment options, and could motivate them to make lifestyle changes and accept or adhere to preventive medication. In addition, most of the existing models were developed without considering potential sex-specific variations in the effect of cardiovascular risk factors, despite evidence of differences between males and females.[15] The aim of the present study, therefore, was to develop and externally validate the competing risk-adjusted sex-specific LIFE-T1D model for the estimation of lifetime risk, in addition to 10-year risk, of incident CVD in individuals with type 1 diabetes without established CVD.

2 | MATERIALS AND METHODS

2.1 | Study populations

The target population consisted of individuals with type 1 diabetes, aged 18 to 80 years, without established CVD (defined as no previous record of coronary heart disease, cerebrovascular disease and peripheral artery disease). Model development and internal validation were conducted in the Swedish National Diabetes Register (NDR),[16] which is classified as a moderate-risk region according to the 2021 ESC prevention guidelines.[17] The NDR was initiated in 1996 and contains information on clinical characteristics, risk factors, medication use and complications of diabetes in patients aged 18 years and older. Virtually all patients with type 1 diabetes in Sweden are treated in hospital outpatient clinics. All these hospital outpatient clinics regularly report data on individuals with type 1 diabetes to the NDR, which covers ~98% of all adults with type 1 diabetes in Sweden.[18] Type 1 diabetes was defined by a diabetes diagnosis at the age of 30 years or younger in combination with treatment with insulin only. This definition has been validated to be accurate in 97% of the patients in the register.[19] For the present study, follow-up started 2 years after registration in the NDR for all participants. These 2 years were used to collect baseline variables. For every variable, the value closest to the start of follow-up was selected. Participants whose follow-up started between January 1998 and January 2020 were included in the present study (Figure S1).

External validation was performed with data from the Danish Funen Diabetes Database (FDDB) and the UK Biobank (Figure S2),[20,21] which are both considered low-risk regions.[22] The FDDB is a population-based cohort including individuals with all types of diabetes from the geographical region of Funen, Denmark, from 2003 onwards. The cohort covers over 90% of the individuals with type 1 diabetes in Funen. It was launched as an online database, serving as a digital healthcare platform for clinical practice and communication among healthcare providers involved in diabetes care. The FDDB participants are considered representative of the entire population with type 1 diabetes in Denmark.[20] The UK Biobank is a population-based cohort of more than 500 000 participants, aged 40–70 years, who were recruited in the United Kingdom between 2006 and 2010. All participants underwent a baseline assessment, comprising a touchscreen questionnaire, physical examination and collection of blood samples. The definition of type 1 diabetes in each data source is provided in Table S1. The NDR was approved by the Swedish Ethical Review Authority. The FDDB and UK Biobank were approved by the Danish Data Protection Agency and the Northwest Multicenter Research Ethics Committee (ref 21/NW/0157), respectively. Informed consent was obtained from all participants from all three data sources.

2.2 | Predictors and outcome variables

The predictors were prespecified based on existing risk scores for CVD in individuals with type 1 diabetes[8–11,13,14] and ready availability in clinical practice. Predictors comprised age at diabetes onset (years), smoking status (current vs. former/never), body mass index (BMI; kg/m^2), systolic blood pressure (SBP; mmHg), glycated haemoglobin (HbA1c; mmol/mol), estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2), non-high-density lipoprotein (HDL) cholesterol (defined as total cholesterol minus HDL cholesterol; mmol/L), albuminuria (albumin excretion rate normal to mildly increased [<30 mg/24 h or <3 mg/mmol], moderately increased [30–300 mg/24 h or 3–30 mg/mmol] or severely increased [>300 mg/24 h or > 30 mg/mmol])[23] and retinopathy (yes/no). Age (years) was used as the time scale. The rationale behind the selection of predictors in the model is provided in the

Supplementary Methods section. The models were derived separately for males and females to account for differences in the relative effects of predictors and baseline risks.

The primary outcome was the occurrence of first incident CVD events, defined as a composite of nonfatal myocardial infarction, nonfatal stroke or cardiovascular mortality. This endpoint aligns with the primary endpoint of SCORE2 and SCORE2-Diabetes.[24,25] Cardiovascular mortality was defined as sudden death or death due to coronary heart disease, heart failure or stroke. Deaths from non-cardiovascular causes were treated as competing events. For the NDR and FDDB, endpoints were obtained by linkage to mortality registers and national patient registers, containing nationwide information on all hospitalizations and outpatient visits. For the UK Biobank, endpoints were obtained by linkage with Hospital Episode Statistics. Details on endpoint definitions and corresponding International Classification of Diseases 10th revision codes are provided in Table S2.

2.3 | Statistical analyses

Since complete-case analysis may lead to possible bias,[26] missing predictor values were multiply imputed based on predictive mean matching using 10 imputed datasets (aregImpute-function, Hmisc package, R statistical software). Details on the percentages and handling of missing data are provided in Table S3 and the Supplementary Methods section, respectively. Continuous predictors were truncated at the 1st and 99th percentile to limit the effect of outliers. Two complementary Cox proportional hazards models were fitted: one for the prediction of CVD events (Function A) and one for prediction of the competing endpoint non-CVD mortality (Function B) to adjust for competing risks. Age was used as the time axis (left truncation), which means that participants contribute from their age at study entry to their age at the end of follow-up. This method allows the estimation of age-specific baseline survival rates, enabling predictions beyond the follow-up duration of the derivation data.[27] The proportional hazards assumption was assessed visually by plotting Schoenfeld residuals against time and an interaction with age was added to the model if a violation was observed. Continuous predictors were log or square transformed if doing so improved model fit based on Akaike's information criterion. Baseline survival rates for both functions were derived using 1-year intervals and smoothed using a local polynomial regression (LOESS) function. By combining the coefficients from both functions with the smoothed baseline survival rates, lifetables with 1-year intervals were created for every remaining life year.[27] The lifetime and 10-year risks were estimated by summation of the annual predicted risks from current age until the maximum age of 90 years and for the first 10 years, respectively. The maximum age was defined as 90 years to ensure reliable predictions (based on availability of at least 100 observations per year of age). The CVD-free life expectancy was defined as the median survival without CVD (i.e., the age at which the estimated cumulative survival equals 50%). Model discrimination was quantified using c-statistics, corrected for competing risks.[28] As direct observation of lifetime risks is impossible in cohort data, model calibration was evaluated at the maximum duration of the cohorts by visual assessment of the expected versus observed risks, that is, at 7 years for the FDDB and at 13 years for the UK Biobank. The model was recalibrated for differences in baseline risk using expected versus observed (E/O) ratios. Model assumptions are provided in Table S4. All analyses were performed with R-statistic programming (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

2.4 | Prediction of individual treatment effects

By combining predictions from the model with estimated treatment effects from randomized clinical trials or meta-analyses, the model can be used to estimate individualized benefit from cardiovascular risk management.[27] Examples to illustrate the long-term effects of prevention include the effect of lifetime and 10-year SBP lowering (hazard ratio [HR] 0.80 per 10 mmHg SBP reduction[29]) and the effect of low-density lipoprotein (LDL) cholesterol lowering (HR 0.79 per 1 mmol/L LDL cholesterol reduction[30]).

2.5 | Sensitivity analysis

To ensure the applicability of the model to the contemporary type 1 diabetes population, the model was additionally validated in the subgroup of individuals in the derivation data who were included in the last 15 years (from January 2005 onwards).

2.6 | Data and resource availability

The data analysed in the present study are not compliant with publishing individual data in an open-access institutional repository but are available upon reasonable request.

3 | RESULTS

3.1 | Model derivation

The model was derived in 39 756 individuals with type 1 diabetes from the NDR without a history of CVD. The median (interquartile interval [IQI]) age at baseline was 28 (21–40) years and 45% were female. The median (IQI) age at diabetes diagnosis was 14 (9–21) years and the mean (standard deviation [SD]) HbA1c concentration was 66 (16) mmol/mol (8.2% [1.5%]). Baseline characteristics are presented in Tables 1 and S5 (non-imputed data). During a median (IQI) follow-up time of 11.8 (6.1–17.1) years, 4608 incident CVD events and 1316 nonvascular deaths were observed. The number of observations and the number of events per age year are shown in Figure S3. Coefficients for individual predictions and HRs are shown in Tables S6 and S7, respectively. The internal validation c-statistics were 0.85 (95% confidence interval [CI] 0.84–0.85) in males and 0.85 (95% CI 0.84–0.86) in females for CVD. For non-CVD mortality, the internal validation c-statistics were 0.72 (95% CI 0.70–0.74) in males and 0.75

TABLE 1 Baseline characteristics of the data sources used for model derivation and external validation.

	Swedish NDR ($n = 39\,756$)	Funen Diabetes Database ($n = 2709$)	UK Biobank ($n = 1022$)
Age, years	28 (21–40)	43 (30–56)	53 (47–60)
Female sex, *n* (%)	17 710 (45)	1150 (42)	454 (44)
Age at diabetes onset, years	14 (9–21)	24 (13–38)	20 (13–26)
Current smoking, *n* (%)	5856 (15)	727 (27)	110 (11)
Medication use, *n* (%)			
Insulin pump	6230 (16)	N.A.	N.A.
Lipid-modifying medication	5219 (13)	874 (32)	641 (63)
Blood pressure-lowering medication	5958 (15)	64 (2)	566 (55)
Antiplatelet medication	8191 (21)	228 (8)	468 (46)
Systolic blood pressure, mmHg	126 (16)	129 (17)	138 (17)
Diastolic blood pressure, mmHg	73 (9)	78 (10)	77 (9)
Body mass index, kg/m^2	24.9 (4.1)	25.6 (4.3)	27.7 (5.0)
Laboratory values			
HbA1c, mmol/mol	65 (16)	65 (16)	63 (13)
Non-HDL cholesterol, mmol/L	3.2 (1.0)	3.1 (0.9)	3.0 (0.8)
LDL cholesterol, mmol/L	2.7 (0.8)	3.1 (1.0)	2.6 (0.7)
HDL cholesterol, mmol/L	1.6 (0.5)	1.6 (0.5)	1.5 (0.4)
Triglycerides, mmol/L	0.9 (0.7–1.3)	1.0 (0.7–1.5)	1.0 (0.7–1.6)
eGFR, mL/min/1.73 m^2	94 (31)	98 (22)	93 (18)
Albumin excretion rate			
Moderately increased	2923 (7)	346 (13)	N.A.
Severely increased	2416 (6)	32 (1)	N.A.
Retinopathy	19 177 (48)	1234 (46)	N.A.[a]

Note: Data are presented as *n* (%), mean (SD) or median (interquartile interval).
Abbreviations: AER, albumin excretion rate; eGFR, estimated glomerular filtration rate (estimated using the Chronic Kidney Disease Epidemiology Collaboration formula); HDL, high-density lipoprotein; LDL, low-density lipoprotein; N.A., not applicable; NDR, Swedish National Diabetes Register.
[a]Retinopathy data were partially based on International Classification of Diseases, 10th revision codes (Supplementary Methods).

(95% CI 0.73–0.77) in females. Calibration plots of predicted versus observed 10-year risks of CVD and non-CVD mortality are shown in Figure S4. Predicted 10-year risks of CVD agreed with observed 10-year risks. Prior to recalibration, predicted risks of non-CVD mortality were lower than observed risks (E/O ratio 0.74 in males and 0.72 in females). Age-specific baseline survival rates and plots of the smoothed baseline survival rates are provided in Table S8 and Figure S5, respectively. For individuals aged <40 years, the median (IQI) lifetime risk of CVD was 69.4% (60.2%–76.5%), the median (IQI) 10-year risk of CVD was 1.0% (0.5%–2.3%) and the estimated CVD-free life expectancy was 72 (67–76) years. For individuals aged ≥40 years, the corresponding values were 76.0% (68.5%–81.9%), 16.2% (9.5%–28.5%) and 72 (68–76) years (Figures 1 and S6).

3.2 | Model validation

External model validation was performed in 2709 individuals with type 1 diabetes from the FDDB and 1022 individuals with type 1 diabetes from the UK Biobank. The median (IQI) ages were 43 (30–56) years for the FDDB and 53 (47–60) years for the UK Biobank, both higher as compared to the median age in the NDR. In the FDDB, 42% of the participants were female. The median (IQI) follow-up period was 8 (5–8) years, during which 168 CVD events were observed. In the UK Biobank, 44% of the participants were female. During a median (IQI) follow-up period of 12 (11–13) years, 155 CVD events were observed. Detailed baseline characteristics are presented in Table S9 and incidence rates for all data sources are provided in Table S10. Calibration plots are shown in Figure 2 (for males and females combined), Figures S7 and S8 (for males and females separately). c-statistics were 0.77 (95% CI 0.73–0.81) in the FDDB and 0.73 (95% CI 0.70–0.77) in the UK Biobank for CVD, in males and females combined. For non-CVD mortality, c-statistics were 0.74 (95% CI 0.70–0.79) in the FDDB and 0.60 (95% CI 0.54–0.66) in the UK Biobank. Prior to recalibration, predicted risks were higher than observed risks in the FDDB and the UK Biobank (E/O ratio 1.40 and 1.71 in males and 1.53 and 2.08 in females, respectively).

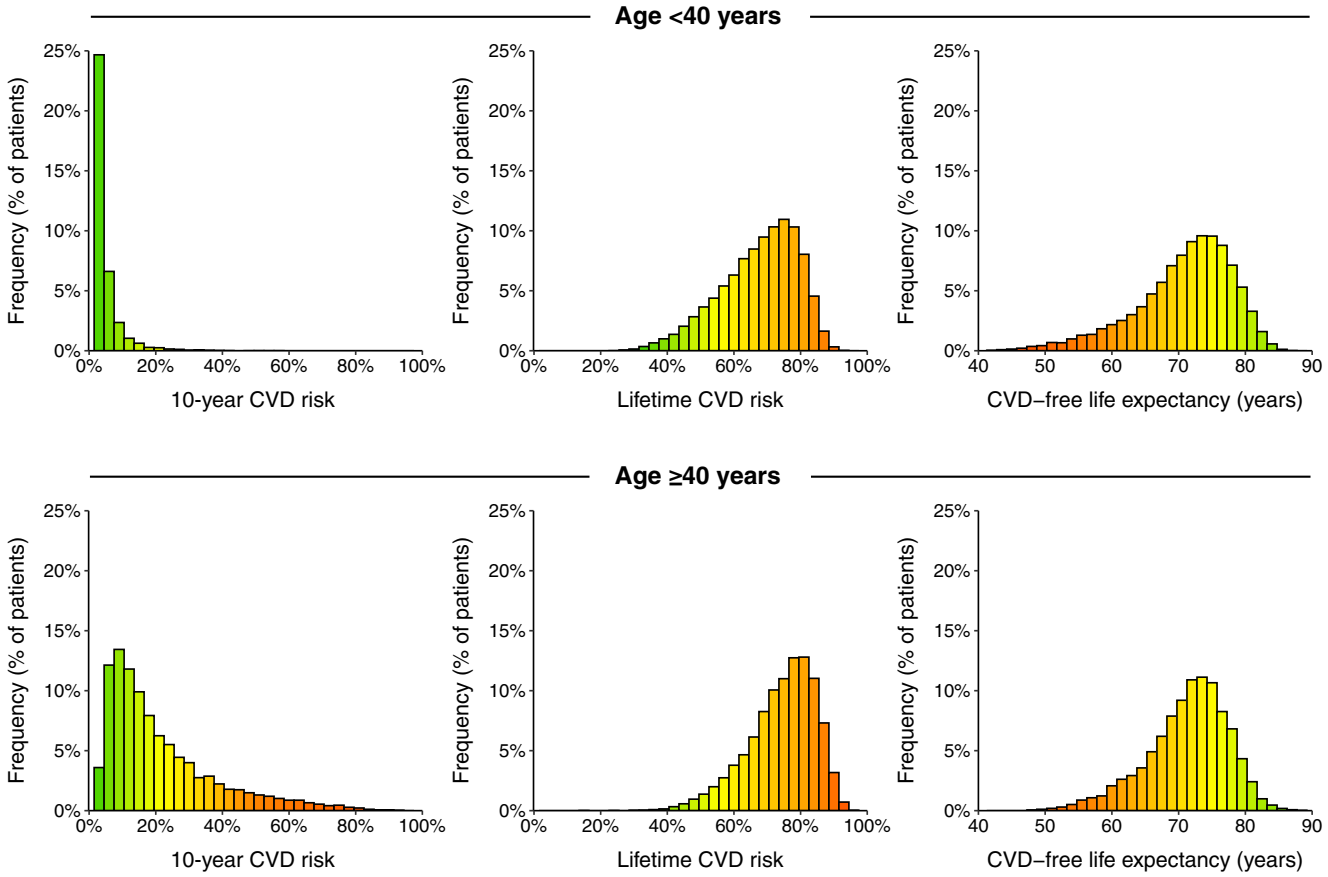
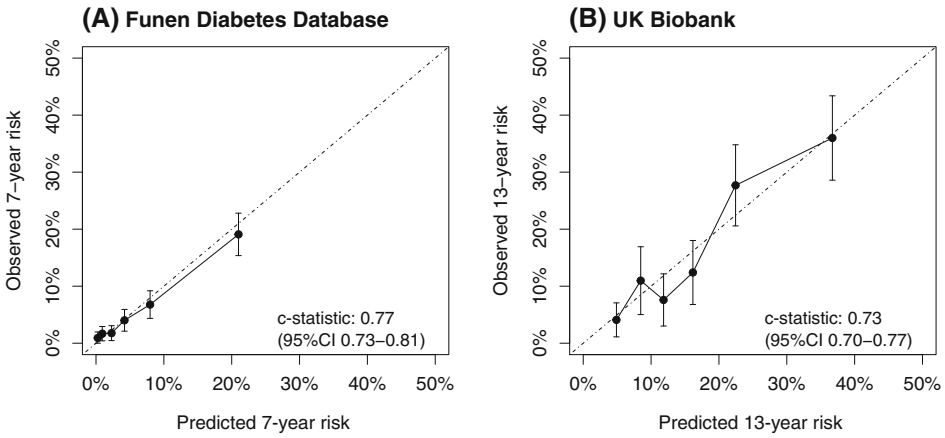


FIGURE 1 Distribution of 10-year risk of cardiovascular disease (CVD), lifetime risk of CVD and CVD-free life expectancy, for individuals aged <40 years and ≥40 years, in males and females combined.

FIGURE 2 External validation of the model (A) predicting 7-year risk of cardiovascular disease (CVD) in the Funen Diabetes Database ($n = 2709$) and (B) predicting 13-year risk of CVD in the UK Biobank ($n = 1022$), in males and females combined, after recalibration.



3.3 | Prediction of individual treatment effects

Two examples demonstrating the effect of 10 mmHg SBP reduction and 1.5 mmol/L LDL cholesterol reduction on the risk of CVD and the likely gain in CVD-free life expectancy are shown in Figure 3. Patient A, a 50-year-old male smoker, would be estimated to experience approximately 6.9% reduction in lifetime risk (number needed to treat [NNT] 14), 0.9% reduction in 10-year risk of CVD (NNT 111), and a median gain in CVD-free life expectancy of 1.9 years (i.e., 50% of the individuals with the same characteristics would have a CVD-free life expectancy of 1.9 years or less and 50% of the individuals would have a CVD-free life expectancy of 1.9 years or more), in case of a reduction in SBP from 140 mmHg to 130 mmHg. Patient B, a 40-year-old female non-smoker, would be estimated to experience approximately 6.8% reduction in lifetime risk of CVD (NNT 15), 1.1% reduction in 10-year risk of CVD (NNT 91) and 2.0 years gain in CVD-free life expectancy, if her LDL cholesterol level was lowered from 4 mmol/L to 2.5 mmol/L.

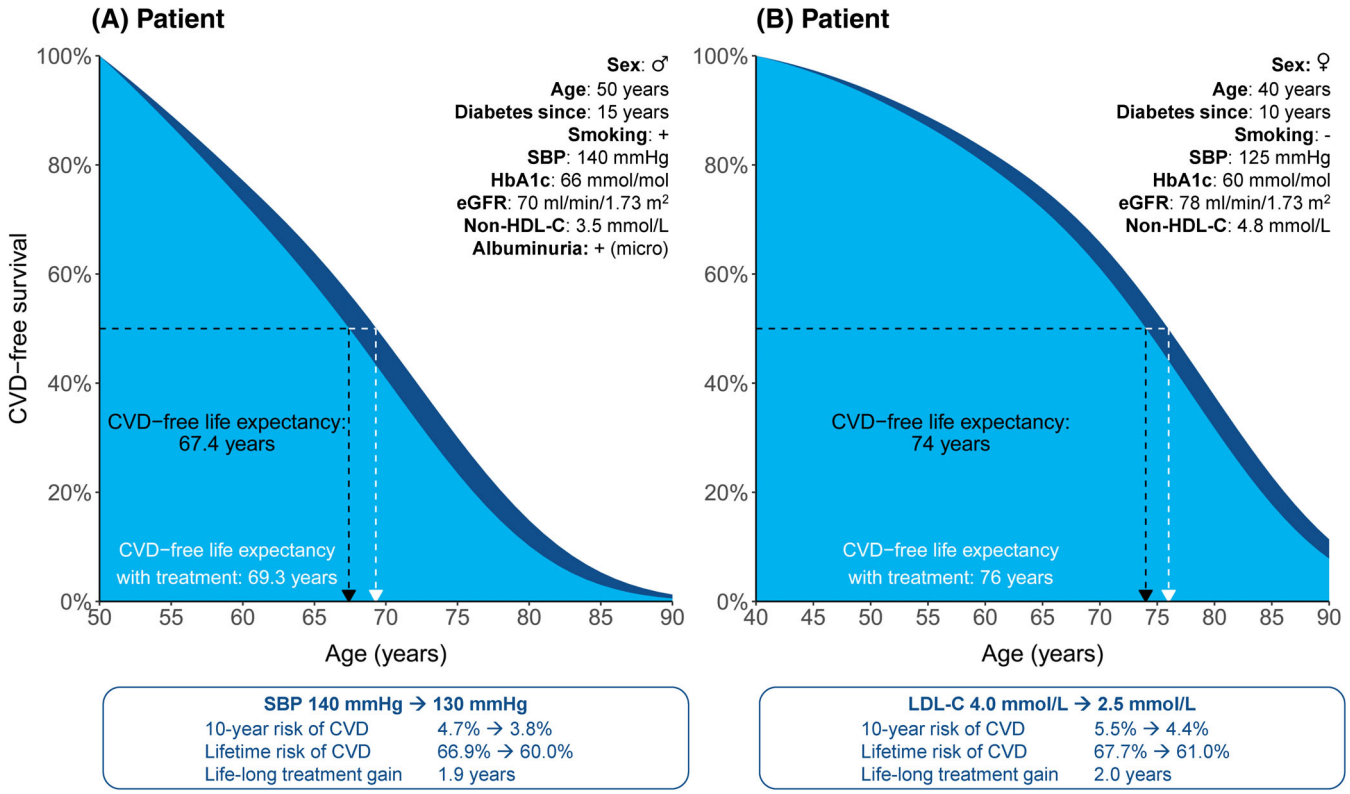


FIGURE 3 Examples of individualized benefit from 10 mmHg reduction in systolic blood pressure (SBP) (Patient A) and 1.5 mmol/L low-density lipoprotein cholesterol (LDL-C) reduction (Patient B) on 10-year risk of cardiovascular disease (CVD), lifetime risk of CVD and CVD-free life expectancy. In addition to the characteristics listed in the figure, Patient A has a body mass index (BMI) of 25 kg/m^2, uses multiple daily insulin injections and atorvastatin 20 mg, has an LDL-C level of 2.7 mmol/L and has no retinopathy. Patient B has a BMI of 26 kg/m^2, uses insulin multiple daily injections, has an LDL-C level of 4 mmol/L and has no albuminuria and retinopathy. A median gain in CVD-free life expectancy of 1.9 years indicates that 50% of the individuals with the same characteristics would have a CVD-free life expectancy of 1.9 years or less and 50% of the individuals would have a CVD-free life expectancy of 1.9 years or more. eGFR, estimated glomerular filtration rate (estimated using the Chronic Kidney Disease Epidemiology Collaboration formula; HbA1c, glycated haemoglobin.

3.4 | Sensitivity analysis

Predicted 10-year risks of CVD in individuals included in the last 15 years ($n = 22\,166$) agreed with observed risks, with a c-statistic of 0.89 (95% CI 0.88–0.91) in males and females combined. The corresponding calibration plot is shown in Figure S9.

4 | DISCUSSION

This study describes the development and external validation of the LIFE-T1D model for the estimation of lifetime and 10-year risk of CVD in individuals with type 1 diabetes without established CVD. The model is based on readily available predictors and enables identification of individuals at high risk of CVD who may be targeted for benefit from preventive treatment.

Existing CVD prediction models developed in individuals with type 1 diabetes rely on relatively short-term prediction horizons of typically 10 years or less.[8–13] For example, a previous risk model was externally validated for 10-year CVD risk in 33 183 individuals from the Swedish NDR, resulting in a well-calibrated model with a c-statistic of 0.82.[8] Comparing the present model to this previous model is challenging due to the difference in endpoints, predictors and prediction horizon. Our endpoint comprises nonfatal myocardial infarction, nonfatal stroke and cardiovascular mortality, thus aligning with the current guideline-supported SCORE2 and SCORE2-Diabetes risk calculators,[24,25] while the endpoint of the previous model also included unstable angina, transient ischaemic attack, peripheral artery disease, revascularizations and amputations.[8] For LIFE-T1D, we selected predictors that are readily available in the outpatient clinic and electronic patient records, thus facilitating the integration of this model into daily practice. In addition, we made separate models for males and females to account for differences in the relative effects of predictors and baseline risks, since previous studies in the general population showed that the effects of well-recognized cardiovascular risk factors, including smoking and total cholesterol, differ between males and females. Our finding of a comparable absolute risk in males and females is in line with a previous study.[31] Notably, that study also found females to have a higher excess CVD risk compared to males, which is supported by a large meta-analysis.[2] This can partly be explained by the fact that females in the general population have a lower risk of CVD events compared to males.

The main difference between earlier risk models in type 1 diabetes and LIFE-T1D is the lifetime prediction horizon. As type 1 diabetes is a near-lifelong disease, with the majority of patients being diagnosed before the age of 30 years, very long-term estimates may be more informative when discussing and individualizing risk and benefit in individuals with type 1 diabetes. Since the CVD risk increases with age and diabetes duration, the 10-year CVD risk in young patients is usually very low. However, as also demonstrated by the present study, the lifetime risk in these individuals may still be substantial. Lifetime risk estimates may underscore the necessity of early and sustained management of modifiable cardiovascular risk factors, even when short-term risk appears negligible. Older persons, in contrast, often have a high 10-year risk, but because of their shorter remaining life expectancy, the potential absolute benefits derived from preventive therapies may be relatively small. Therefore, especially in younger and older individuals, lifetime risk and CVD-free life expectancy are more informative measures and may help guide personalized therapeutic decisions and lifestyle modifications. Estimation of lifetime risk and benefit is also recommended by the 2021 ESC prevention guideline as those measures are easy to interpret for patients and healthcare providers and may improve communication of potential treatment benefits to patients.[22] Another important aspect of the LIFE-T1D model is that it accounts for the impact of the competing risk of non-CVD mortality. This statistical adjustment is crucial in preventing overestimation of risks and the potential benefits of CVD risk-modifying treatments, especially in older individuals, in whom the risk of non-CVD death is high.[32] It should be noted that the existing CVD prediction models in individuals with type 1 diabetes were not adjusted for competing risks.[8–11,13]

The overestimation of the CVD risk in the FDDB and UK Biobank likely reflects the transfer of the prediction model from a moderate-risk region to two low-risk regions.[22] Another potential reason is that CVD events are detected and reported with a higher degree of accuracy in Sweden than in the UK and Denmark, although all three countries are known for having robust healthcare systems with established infrastructures for monitoring and reporting health outcomes.[33] Furthermore, an important factor to consider is the 'healthy cohort effect' associated with the UK Biobank. Its recruitment strategy possibly attracted more healthy individuals, resulting in a sample that does not fully represent the UK population with type 1 diabetes.[34] The age inclusion criterion of 40–70 years led to a higher median age in the UK Biobank study population as compared to the NDR. The method used to obtain outcome data in the UK Biobank may have resulted in an underestimation of the absolute CVD risk. However, strokes and myocardial infarctions are typically well recorded in hospital settings[35] and mortality data is acquired from the death registry. Therefore, the extent of this underestimation is likely minimal. Considering the UK Biobank reflects a healthy cohort and lacks reliable data on albuminuria and retinopathy, whereas the FDDB accurately represents the type 1 diabetes population in Denmark and is in this case a larger data source, we recommend applying the recalibration factor from the FDDB for clinical use of the model in low-risk regions.

In addition to the lifetime prediction horizon and the statistical adjustment for competing risks, a strength of the LIFE-T1D model is its basis on contemporary and representative data. Although the model was derived in individuals included from 1998 onwards, it performed well in individuals included between 2005 and 2020. The NDR and FDDB participants are considered representative for the diabetes populations from Sweden and Denmark and the NDR population covers nearly the entire Swedish population with diabetes.[18,20] In addition, the model was derived in a large study population, allowing for accurate predictions and generalizability to other individuals with type 1 diabetes.

Limitations of this study must also be considered. First, the model was developed in a moderate-risk region and externally validated in two low-risk regions, as defined by the 2021 ESC prevention guidelines.[22] Ideally, validation should be performed in more data sources and also extend to high-risk and very high-risk regions to ensure the model's broader applicability across all risk regions. Previous research, however, has demonstrated the stability of the relative effects of cardiovascular risk factors across geographical areas.[36] Second, information on socioeconomic status (SES) was not included in the model, although a lower SES is known to be related to a higher risk of CVD and mortality.[37] Although some aspects of SES are indirectly represented by other predictors in the model, these predictors probably do not fully capture the impact of SES on the CVD risk.[38] Should these predictors become more easily usable in the future, they could be relatively easily added to the prediction model, as described in a recently published study.[39] Third, there was a high percentage of missing data for eGFR, non-HDL cholesterol and retinopathy in the NDR. However, the current approach maximized the use of existing data, including subsequent available measurements, while preserving the statistical power. Fourth, there was an absence of reliable data on albuminuria and retinopathy in the UK Biobank. This may have affected the model's discriminative ability, although the impact is probably reduced due to the inclusion of other related (proxy) variables in the model.[40–44] While it may also have affected the calibration of the model, the overestimation of the CVD risk in the UK Biobank is more likely attributable to the variance in baseline risks between a moderate-risk region to a low-risk region. It should also be noted that the data sources used for model derivation and validation primarily consisted of individuals of White ethnicity. Ethnicity was not used as a predictor due to insufficient representation from diverse ethnic groups.

Although the model predicts lifetime risk, it could be validated for only a 13-year period, owing to the follow-up time of the validation cohorts. A previous study has demonstrated that lifetime estimates based on the methodology used in the present study are reliable for at least 17 years.[27] Nevertheless, it should be kept in mind that lifetime estimates rely on several assumptions. For example, the model assumes that the baseline survival for each interval is equal for all patients, during that interval. As the field of diabetes management continues to evolve, an increasing number of individuals with type 1 diabetes will adopt advanced medical devices for glucose control, including hybrid closed-loop systems. These advancements could lead

to a reduced baseline risk in the future. Hence, the model would benefit from updating in the future to ensure its continued accuracy in risk assessment. Moreover, the model assumes predictors follow a natural course over time, although predictors might change with age. However, if the change in predictor levels reflects the change over time in the derivation data, no adjustment is needed. It is also assumed that relative treatment effects are constant over time and equal for all patients for whom a treatment is recommended, as there is no evidence from large trials or meta-analyses that the relative effect of cardiovascular risk reduction differs between subgroups of individuals with type 1 diabetes.[30] Of note, the current model does not allow for the prediction of other adverse outcomes in individuals with type 1 diabetes, including microvascular complications, nonfatal heart failure and peripheral artery disease including amputations. Microvascular complications not only significantly reduce the quality of life, but also lead to a higher risk of macrovascular complications and mortality.[45] For individuals with type 2 diabetes, a recently developed model can be used to estimate the lifetime risk of end-stage kidney disease,[46] but this model has not been validated in individuals with type 1 diabetes. For individuals with type 1 diabetes, existing models can only predict shorter-term risk of microvascular outcomes.[47,48] Developing a lifetime prediction model for microvascular complications in type 1 diabetes on the basis of larger datasets with longer follow-up duration, offers a promising direction for future research.

In conclusion, lifetime risk of CVD as well as CVD-free life expectancy and the effect of preventive treatment thereon can be estimated for individuals with type 1 diabetes using the new LIFE-T1D model. This may aid in early identification of individuals who would benefit most from preventive treatment options and may improve shared decision making in clinical practice. Validation in additional cohorts will improve future clinical implementation.

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CONFLICT OF INTEREST STATEMENT

M.W. has received consultancy fees from Amgen and Freeline. B.E. reports personal fees (expert panels, lectures) from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Navamedic, Novo Nordisk, RLS Global, and Sanofi, all outside the submitted work. N.S. reports honoraria for consultancy from Amgen, AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi. All fees are unrelated to the submitted work. No other potential conflicts of interest relevant to this article were reported.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15531.

DATA AVAILABILITY STATEMENT

The data analyzed in the current study are not compliant with publishing individual data in an open-access institutional repository but are available upon reasonable request.

ORCID

Marga A. G. Helmink https://orcid.org/0000-0002-5748-2026
Steven H. J. Hageman https://orcid.org/0000-0003-2299-6745
Björn Eliasson https://orcid.org/0000-0003-2569-4160
Naveed Sattar https://orcid.org/0000-0002-1604-2593
Frank L. J. Visseren https://orcid.org/0000-0003-3951-5223
Jannick A. N. Dorresteijn https://orcid.org/0000-0002-0190-8526
Sanne A. E. Peters https://orcid.org/0000-0003-0346-5412
Mark Woodward https://orcid.org/0000-0001-9800-5296
Kurt Højlund https://orcid.org/0000-0002-0891-4224
Jan Erik Henriksen https://orcid.org/0000-0002-1908-7017
Henrik Toft Sørensen https://orcid.org/0000-0003-4299-7040
Erik H. Serné https://orcid.org/0000-0003-0657-7225
Thomas T. van Sloten https://orcid.org/0000-0003-2870-482X
Reimar W. Thomsen https://orcid.org/0000-0001-9135-3474
Jan Westerink https://orcid.org/0000-0001-5021-5227

REFERENCES

1. Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of cardiovascular disease and Total mortality in adults with type 1 diabetes: Scottish registry linkage study. *PLoS Med*. 2012;9(10):e1001321.
2. Huxley RR, Peters SAE, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(3):198-206.
3. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376(15):1407-1418.
4. Gubitosi-Klug RA, Lachin JM, Backlund JYC, Lorenzi GM, Brillon DJ, Orchard TJ. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. *Diabetes Care*. 2016;39(5):686-693.
5. Marx N, Federici M, Schütt K, et al. ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023;44(39):4043-4140.
6. ElSayed NA, Aleppo G, Aroda VR, et al. 10. Cardiovascular disease and risk management: standards of Care in Diabetes—2023. *Diabetes Care*. 2023;46(Suppl_1):S158-S190.
7. De Ferranti SD, De Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Circulation*. 2014;130(13):1110-1130.

8. McGurnaghan SJ, McKeigue PM, Read SH, et al. Development and validation of a cardiovascular risk prediction model in type 1 diabetes. *Diabetologia*. 2021;64(9):2001-2011.
9. Soedamah-Muthu SS, Vergouwe Y, Costacou T, et al. Predicting major outcomes in type 1 diabetes: a model development and validation study. *Diabetologia*. 2014;57(11):2304-2314.
10. Vistisen D, Andersen GS, Hansen CS, et al. Prediction of first cardiovascular disease event in type 1 diabetes mellitus - the steno type 1 risk engine. *Circulation*. 2016;133(11):1058-1066.
11. Zgibor JC, Ruppert K, Orchard TJ, et al. Development of a coronary heart disease risk prediction model for type 1 diabetes: the Pittsburgh CHD in type 1 diabetes risk model. *Diabetes Res Clin Pract*. 2010;88(3):314-321.
12. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017;357:1-21.
13. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Gudbjörnsdottir S. A new model for 5-year risk of cardiovascular disease in type 1 diabetes; from the Swedish National Diabetes Register (NDR). *Diabetic Med*. 2011;28(10):1213-1220.
14. Tran-Duy A, Knight J, Palmer AJ, et al. A patient-level model to estimate lifetime health outcomes of patients with type 1 diabetes. *Diabetes Care*. 2020;43(8):1741-1749.
15. Woodward M. Cardiovascular disease and the female disadvantage. *Int J Environ Res Public Health*. 2019;16(7):1165.
16. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B, Steering Committee of the Swedish National Diabetes Register. The National Diabetes Register in Sweden: an implementation of the St. Vincent declaration for quality improvement in diabetes care. *Diabetes Care*. 2003;26(4):1270-1276.
17. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227-3337.
18. Hero C, Karlsson SA, Franzén S, et al. Adherence to lipid-lowering therapy and risk for cardiovascular disease and death in type 1 diabetes mellitus: a population-based study from the Swedish National Diabetes Register. *BMJ Open Diabetes Res Care*. 2020;8(1):e000719.
19. Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). *Diabetes Care*. 2010;33(7):1640-1646.
20. Adelborg K, Szentkúti P, Henriksen JE, et al. Cohort profile: the Funen diabetes database - a population-based cohort of patients with diabetes in Denmark. *BMJ Open*. 2020;10(4):1-11.
21. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):1-10.
22. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol*. 2022;29(1):5-115.
23. Kidney Disease Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;3(1):S1-S150.
24. SCORE2 Working Group and ESC Cardiovascular Risk Collaboration, Hageman S, Pennells L, et al. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*. 2021;42(25):2439-2454.
25. SCORE2-Diabetes Working Group and the ESC Cardiovascular Risk Collaboration, Pennells L, Kaptoge S, et al. SCORE2-diabetes: 10-year cardiovascular risk estimation in type 2 diabetes in Europe. *Eur Heart J*. 2023;44(28):2544-2556.
26. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol*. 2006;59(10):1087-1091.
27. Dorresteijn JA, Kaasenbrood L, Cook NR, et al. How to translate clinical trial results into gain in healthy life expectancy for individual patients. *BMJ*. 2016;352:i1548.
28. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology*. 2009;20(4):555-561.
29. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-967.
30. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371(9607):117-125.
31. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet*. 2018;392(10146):477-486.
32. Hageman SHJ, Dorresteijn JAN, Pennells L, et al. The relevance of competing risk adjustment in cardiovascular risk prediction models for clinical practice. Eur. *J Prev Cardiol*. 2023;30:1741-1747.
33. European Commission. Country Health Profiles [Internet]. 2022 [cited 2023 Sep 22]. Available from: https://health.ec.europa.eu/state-health-eu/country-health-profiles_en.
34. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *Am J Epidemiol*. 2017;186(9):1026-1034.
35. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ*. 2013;346:f2350.
36. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health*. 2019;7(10):e1332-e1345.
37. Rawshani A, Svensson AM, Rosengren A, Eliasson B, Gudbjörnsdottir S. Impact of socioeconomic status on cardiovascular disease and mortality in 24,947 individuals with type 1 diabetes. *Diabetes Care*. 2015;38(8):1518-1527.
38. Kimenai DM, Pirondini L, Gregson J, et al. Socioeconomic deprivation: an important, largely unrecognized risk factor in primary prevention of cardiovascular disease. *Circulation*. 2022;146(3):240-248.
39. Hageman SH, Petitjean C, Pennells L, et al. Improving 10-year cardiovascular risk prediction in apparently healthy people: flexible addition of risk modifiers on top of SCORE2. Eur. *J Prev Cardiol*. 2023;30:1705-1714.
40. Lind M, Pivodic A, Svensson AM, Ólafsdóttir AF, Wedel H, Ludvigsson J. HbA1c level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. *BMJ*. 2019;28(366):l4894.
41. Hietala K, Harjutsalo V, Forsblom C, Summanen P, Groop PH. Age at onset and the risk of proliferative retinopathy in type 1 diabetes. *Diabetes Care*. 2010;33(6):1315-1319.
42. Alleyn CR, Volkening LK, Wolfson J, Rodriguez-Ventura A, Wood JR, Laffel LMB. Occurrence of microalbuminuria in young people with type 1 diabetes: importance of age and diabetes duration. *Diabetic Med*. 2010;27(5):532-537.
43. Van Buren PN, Toto R. Hypertension in diabetic nephropathy: epidemiology, mechanisms, and management. *Adv Chronic Kidney Dis*. 2011;18(1):28-41.
44. Piscitelli P, Viazzi F, Fioretto P, et al. Predictors of chronic kidney disease in type 1 diabetes: a longitudinal study from the AMD annals initiative. *Sci Rep*. 2017;7(1):3313.
45. Garofolo M, Gualdani E, Giannarelli R, et al. Microvascular complications burden (nephropathy, retinopathy and peripheral polyneuropathy)

affects risk of major vascular events and all-cause mortality in type 1 diabetes: a 10-year follow-up study. *Cardiovasc Diabetol*. 2019;18(1):159.
46. Østergaard HB, Read SH, Sattar N, et al. Development and validation of a lifetime risk model for kidney failure and treatment benefit in type 2 diabetes: 10-year and lifetime risk prediction models. *Clin J Am Soc Nephrol*. 2022;17(12):1783-1791.
47. Schreur V, Ng H, Nijpels G, et al. Validation of a model for the prediction of retinopathy in persons with type 1 diabetes. *Br J Ophthalmol*. 2021;105(9):1286-1288.
48. Vistisen D, Andersen GS, Hulman A, et al. A validated prediction model for end-stage kidney disease in type 1 diabetes. *Diabetes Care*. 2021;44(4):901-907.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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