International Journal of Epidemiology, 2021, 1250–1259
doi: 10.1093/ije/dyaa290
Advance Access Publication Date: 16 January 2021
Original article

Cardiovascular Disease

Duration of diabetes-related complications and mortality in type 1 diabetes: a national cohort study

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Received 13 February 2020; editorial decision 15 December 2020

Abstract

Background: People with type 1 diabetes often live for many years with different combinations of diabetes-related complications. We aimed to quantify how complication duration and total complication burden affect mortality, using data from national registers.

Methods: This study included 33 396 individuals with type 1 diabetes, registered in the Swedish National Diabetes Register at any time between 2001 and 2012. Each individual was followed and classified according to their time-updated diabetes-related complication status. The main outcomes were all-cause mortality, cardiovascular (CV) mortality and non-CV mortality. Poisson models were used to estimate the rate of these outcomes as a function of the time-updated complication duration.

Results: Overall, 1748 of the 33 396 individuals died during 198 872 person-years of follow-up. Overall, the time-updated all-cause mortality rate ratio (MRR) was 2.25 [95% confidence interval (CI): 1.99–2.54] for patients with diabetic kidney disease, 0.98 (0.82–1.18) for patients with retinopathy and 4.00 (3.56–4.50) for patients with cardiovascular disease relative to individuals without complications. The excess rate was highest in the first period after a diagnosis of CVD, with an 8-fold higher mortality rate, and stabilized after some 5 years. After diagnosis of diabetic kidney disease, we observed an increase in all-cause mortality with an MRR of around 2 compared with individuals without diabetic kidney disease, which stabilized after few years.

Conclusions: In this cohort we show that duration of diabetes-related complications is an important determinant of mortality in type 1 diabetes, for example the MRR associated with CVD is highest in the first period after diagnosis of CVD. A stronger focus on time-updated information and thorough consideration of complication duration may improve risk stratification in routine clinical practice.

Key words: Type 1 diabetes, epidemiology, diabetes-related complications, mortality

Key Messages

- Conducting a study of 33 396 individuals with type 1 diabetes, we show that diabetic kidney disease and cardiovascular disease are related to increased mortality, whereas diabetic retinopathy is not.
- The association between cardiovascular disease and mortality is not stable over time. The risk is highest in the first period after a diagnosis of a cardiovascular event, with an 8-fold higher mortality rate.
- Diabetic kidney disease is associated with an elevated mortality risk which stabilizes at a mortality rate ratio of around 2 relative to individuals with type 1 diabetes without complications, after few years with diabetic kidney disease.
- The absolute mortality rate increases with age at a higher rate in individuals with cardiovascular disease and/or diabetic kidney disease than in individuals without these complications.

Introduction

Type 1 diabetes is a complex and dynamic disease, which typically sees both microvascular and macrovascular complications develop over time.[1] Despite improvements in clinical management, the mortality rate in individuals with type 1 diabetes still exceeds that of the background population.[2–4] Cardiovascular disease (CVD) is the main driver of morbidity and mortality,[3,5–7] but microvascular complications are also important contributors to morbidity and mortality.[2,8,9]

It is well known that duration of diabetes, age and, as recently shown, age at diagnosis are important determinants of morbidity and mortality.[10] One study has shown that the effect of diabetic kidney disease on mortality depends marginally on duration,[9] and in the general population CVD raises mortality immediately after an event, followed by declining risk over time.[11,12] Increasingly, health care systems across the globe collect longitudinal electronic health care records, and we pursue the idea that important prognostic information can be found by applying a longitudinal approach to the data increasingly collected in routine electronic clinical records and registers.

We used nationwide data from Swedish registers, to investigate how macrovascular and microvascular complications are associated with all-cause mortality, cardiovascular (CV) mortality and non-CV mortality in type 1 diabetes as a function of the duration and combination of complications.

Methods

The Regional Ethical Review Board, University of Gothenburg, Sweden, approved the study (approval number 776–14). All individuals provided informed consent for inclusion in the NDR.

Data sources

Data were obtained from registers that have national coverage and were linked at the individual level using unique personal identification numbers. The Swedish National Diabetes Register (NDR) has previously been described and contains time-updated clinical records on adult individuals with type 1 diabetes in Sweden gradually included since 1998.[13] The NDR includes data on date of diagnosis of diabetes and diabetes-related complications, risk factors and self-reported lifestyle habits. We retrieved information on demographic and socioeconomic status from Statistics Sweden.[14] Coexisting conditions were added to the dataset from the Swedish Inpatient Register.[15] The Cause of Death Register, based on death certificates, provided the date and cause of

death. The data sources were linked for the period between 1 January 2001 through 31 December 2012.

Cohort

Sweden follows the current World Health Organization (WHO) diagnostic criteria for diabetes, i.e. fasting plasma glucose ≥7.0 mmol/L, 2-h plasma glucose ≥11.1 mmol/L or HbA1c (glycated haemoglobin) >48 mmol/mol. All patients included in the registry have provided informed consent. Both specialist clinics and primary health care clinics report to the NDR; however, the NDR does not contain clinical information on diabetes type. Therefore, type 1 diabetes was epidemiologically defined as those with diabetes onset at age 30 years or younger and who were treated with only insulin. This definition has been validated as accurate in 97% of cases.[16] The study included all individuals who had at least one registration of both kidney function and retinopathy status in the NDR. The individual entry date (index date) for this analysis was the earliest date an individual had a valid registration of both a retinal and renal function assessment, using the later of the two dates if they differed.

Determinants and covariates

To assess renal function, we used laboratory measurements of estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations and/or urinary albumin/creatinine ratio. Laboratory measurements also included HbA1c and lipid levels. Ophthalmologists reported retinal assessments directly to the NDR. Data on body mass index (BMI), blood pressure and heath behaviours, i.e. physical activity level, smoking and alcohol habits, were entered into the NDR, whereas data on medication were obtained from the Swedish Prescribed Drugs register. Data on marital status, socioeconomic status, individual income and educational level were obtained from Statistics Sweden.

Outcomes

The outcomes in this study were all-cause mortality, cardiovascular mortality and non-cardiovascular mortality. The identification of cardiovascular mortality was based on primary and contributory diagnoses (ICD-codes) in the Cause of Death registry (Supplementary Table S1, available as Supplementary data at *IJE* online).

The definition of diabetic kidney disease included both albuminuria and/or abnormal eGFR. Albuminuria was defined as a urinary albumin/creatinine ratio greater than 3 mg/mmol or a urinary albumin clearance of more than 20 μg/min (or 20 mg/L) on two out of three urine samples within 1 year. The date of the second abnormal sample defined the date of diabetic kidney disease. Abnormal eGFR was defined as eGFR under 60 mL min^{-1} [1.73 $m]^{-2}$. The definition of retinopathy included presence of either mild, moderate or severe non-proliferative retinopathy or proliferative retinopathy and was based on the International Classification of Diseases (ICD-codes) (Supplementary Table S1, available as Supplementary data at *IJE* online).

We accessed the Swedish Inpatient Registry to retrieve information on the first recorded date for hospital admission due to cardiovascular disease defined as coronary heart disease, acute myocardial infarction, stroke, peripheral arterial disease or heart failure (Supplementary Table S1, available as Supplementary data at *IJE* online).

Statistical analysis

Characteristics of included individuals are presented by sex as means [standard deviation (SD)] and proportions (%). As previously described, the index date in this study was the earliest date individuals had a valid assessment of both microvascular complications. To allow for time-updated analysis, follow-up time was split at each registration in the NDR and further into 1-year age intervals. Each interval was assigned the time-updated values for age, duration of diabetes, current date (effect by calendar year) and duration of each complication type at the start of the interval (time scales). We used Poisson models with log of the risk time (the length of each interval) as offset for mortality outcomes (all cause, CV and non-CV mortality), with natural splines to assess the effect of the time scales, while also including the indicators of each type of complication. In addition to the time scales, we included sex, region of birth and the time-updated values for marital status, smoking status, income, educational level, HbA1c, systolic blood pressure, BMI and low-density lipoprotein (LDL)-cholesterol. We present both overall and sex-specific mortality rate ratios (MRRs) between individuals with and without each complication.

The interactions between different types of complications were assessed in a model without complication duration (Supplementary Figure S1, available as Supplementary data at *IJE* online), and since no interactions were found, the duration effects were assessed in a model with only the main effects of presence and duration of each complication. For individuals with more than one complication, mortality rate ratios compared with individuals without complications can be estimated by multiplication of the effect from each complication separately.

Microvascular complication status is interval-censored and transition dates need to be established. If the first

registration in NDR was without signs of microvascular complications, we used the date where the criterion was first met as the transition date. Out of 12 729 individuals with diabetic kidney disease, 7645 (60%) had a transition date established in this way, and for retinopathy the number was 6692 (26%) out of 25 362. For individuals with complications recorded at study entry, we imputed the onset dates by randomly drawing from the distribution of the duration of diabetes at the diagnosis of each specific complication, as observed in individuals with known transition dates. For cardiovascular disease, the first admission date with CVD in the study period was used. In total, 1862 out of 5046 (37%) had a transition date for cardiovascular disease during follow-up. For CVD events before the beginning of the study period, we do not have information on the exact date of diagnosis. For these individuals, we imputed the transition date using the same algorithm as described for the microvascular complications. We performed all analyses in 10 imputed datasets and summarized the obtained estimates using Rubin's rules.

Figure 1 shows follow-up time and number of deceased individuals from each complication state. Although individuals can have clinical diabetic kidney disease remission windows during the follow-up, we considered the risk of ever having reached the diagnostic threshold, and consequently modelled all complications as irreversible after their first occurrence. As an example, an individual could enter the study with a CVD diagnosis. If that individual developed diabetic kidney disease, the individual's state would change to 'diabetic kidney disease and CVD' and they would thus contribute with risk time initially to the 'CVD' state and subsequently to the 'diabetic kidney disease and CVD' state.

We performed a sensitivity analysis only including those individuals without complications at entry ($n = 12\,738$), in order to assess to what extent the imputation of complication onset dates preceding study entry influenced our results and conclusions.

Statistical analyses were performed in R, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org) using the Epi package for handling the data and analyses.[17,18] The multivariate imputation by chained equations (MICE) algorithm was used for imputation of missing data on covariates.

Results

Study population

During the study period, 36 872 eligible individuals with type 1 diabetes were initially identified. Of these, 3496 individuals were excluded because of lack of information on microvascular complication status, leaving 33 396 to be included in the study (Supplementary Figure S2, available as Supplementary data at *IJE* online). Individuals were gradually included in the NDR throughout the observation window. Supplementary Table S2, available as Supplementary data at *IJE* online, presents numbers of included individuals per year. The mean follow-up time was 6 years, the mean age was 38 years and the mean diabetes duration was 22 years at inclusion. In total, 18 249 individuals (54.6%) were men (Table 1).

In total, 1748 individuals died during 198 872 person-years of follow-up. Of these, 64 had no record of diabetes-related complications. The number of deceased individuals

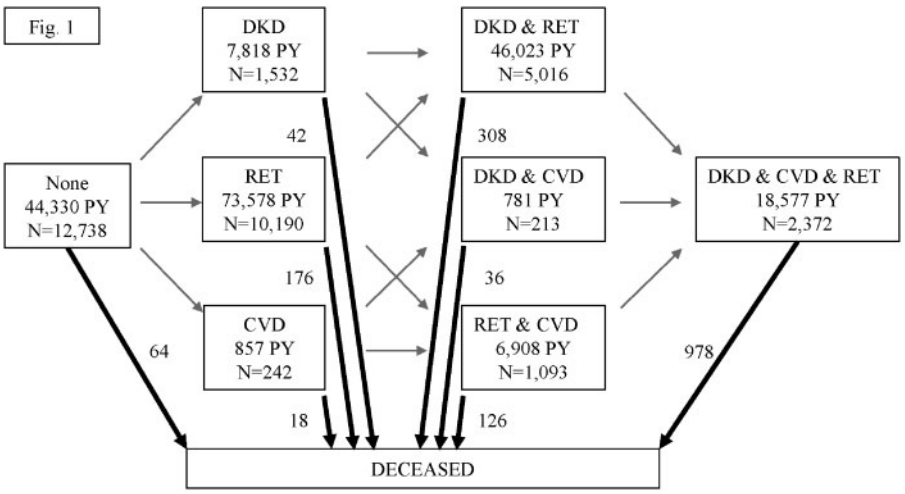

Figure 1 Patient flow in the study. Individuals can be in any of the complication states at study entry and may change states during follow-up. Individuals contribute follow-up time according to the time spent in each complication state. Grey arrows: transitions from one complication state to another. Black arrows: mortality from each state. The numbers on the arrows indicate the number of individuals who died from each state. The person-years (PY) of follow-up and number of individuals starting (*N*) in each state are indicated in each box. DKD, diabetic kidney disease; RET, retinopathy; CVD, cardiovascular disease

Table 1 Characteristics of included individuals at entry in this study

	Male	Female
N	18249	15147
Follow-up (years)	5.9 (2.8)	6.0 (2.7)
Entry in this study (year)	2007 (2.7)	2007 (2.7)
Deceased	1028 (5.6%)	720 (4.8%)
Age (years)	37 (15)	38 (15)
Duration of diabetes (years)	22 (15)	23 (15)
HbA_{1c} (mmol/mol)	64 (14.8)	65 (15.7)
HbA_{1c} (%)	8.0 (1.4)	8.1 (1.5)
Systolic blood pressure (mmHg)	128 (15.6)	124 (16.7)
Diastolic blood pressure (mmHg)	74 (9.3)	72. (8.8)
Age at diabetes diagnosis (years)	16 (7.7)	15 (7.7)
Antihypertensive medication	5438 (29.8%)	4211 (27.8%)
Body mass index (kg/m^2)	25.3 (3.8)	25.3 (4.6)
LDL cholesterol (mmol/L)	2.65 (0.81)	2.63 (0.80)
Lipid-lowering medication	3961 (21.7%)	3060 (20.2%)
Estimated GFR($ml/min/1.73\ m^2$)	96 (29.8)	89 (29.5)
Current smoker, *n* (%)	2141 (11.7%)	2285 (15.1%)
Physically active, *n* (%)	12748 (69.9%)	10729 (70.8%)
Income[a]	1521 (1358.46)	1322 (1013)
Education		
9 years or less	4688 (25.7%)	3778 (24.9%)
10–12 years	9568 (52.4%)	7661 (50.6%)
College/university	3993 (21.9%)	3708 (24.5%)
Unmarried	12473 (68.3%)	9651 (63.7%)
Coexisting conditions		
Retinopathy	10181 (55.8%)	8490 (56.1%)
Diabetic kidney disease	4723 (25.9%)	4410 (29.1%)
Cardiovascular disease	2202 (12.1%)	1718 (11.3%)

Data are means (SD) or *n* (%).The sum of individuals with different complications does not add up to 100%, as patients may have more than one complication at entry.

GFR, glomerular filtration rate; HbA_{1c}, glycated haemoglobin.

[a]Income in 100 Swedish kroners per year.

with diabetic kidney disease, retinopathy or CVD at date of study exit was 1364, 1588 and 1158, respectively. Supplementary Table S3, available as Supplementary data at *IJE* online, presents crude all-cause mortality rates, CV mortality rates and non-CV mortality rates, both overall (both sexes) and by sex. The mortality rates were higher in individuals with complications than in individuals without. Overall, men had higher mortality rates than women.

Mortality risk

In a model that does not consider duration of complications, both diabetic kidney disease and CVD were associated with higher all-cause mortality, CV mortality and non-CV mortality whereas retinopathy was not. For all outcomes associated with cardiovascular disease, we observed higher MRRs in women (Supplementary Figure S3, available as Supplementary data at *IJE* online).

Figure 2 presents both the overall MRRs and the sex-specific MRRs among individuals with diabetic kidney disease, CVD or retinopathy, compared with individuals without that complication as a function of duration of the complication. Retinopathy had limited effect on mortality. After diagnosis of diabetic kidney disease, we observed a substantial increase in all-cause mortality for both men and women (blue curve in panel a in figure 2), which was sustained over time. Women had a lag period of some 3 years before the MRR reached the level seen in men (blue curve in panels b and c in figure 2). The pattern of associations was similar for CV mortality (blue curves in panels d, e and f) and for non-CV mortality (blue curves in panels g, h and i in figure 2). For individuals with CVD, we saw a high mortality rate immediately after diagnosis (the black curves in Figure 2). CVD was associated with an 8-fold higher all-cause mortality in the period after diagnosis for both sexes and slightly higher for women than men (black curves in panels a, b and c in figure 2). The mortality excess associated

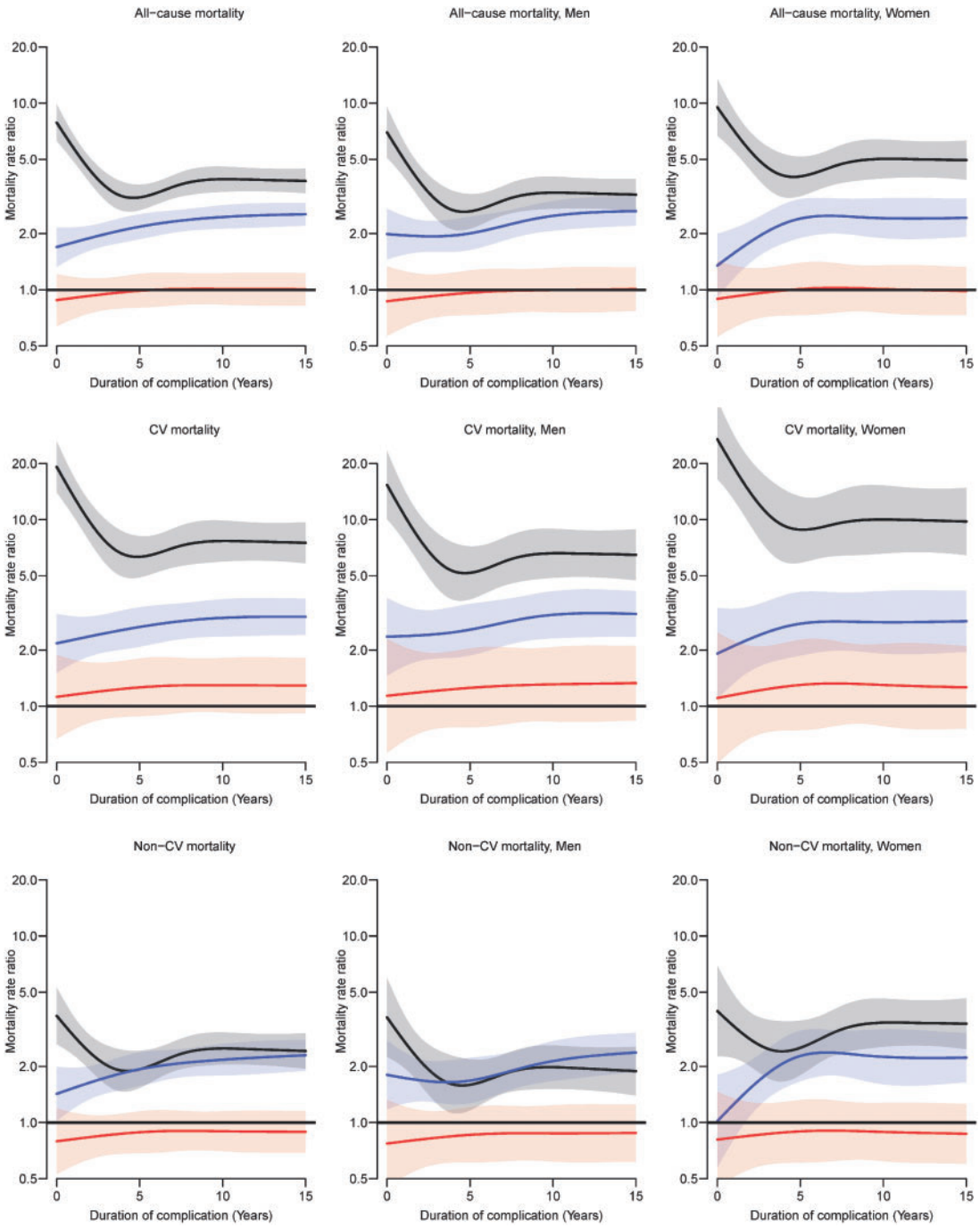

Figure 2 Effect of duration of complications. Adjusted all-cause mortality rate ratios (first row), cardiovascular mortality rate ratios (second row) and non-cardiovascular mortality rate ratios (third row) in individuals with complications compared with individuals without, as a function of duration of complications. Models are adjusted for current age (spline model with four parameters), duration of diabetes (spline model with three parameters), calendar year (linear effect), HbA1c, income, educational level, smoking status, LDL-cholesterol, systolic blood pressure, lipid-lowering medication, antihypertensive medication, sex (panels in first column) and region of birth. Pooled estimates by Rubin's rules from 10 datasets. First column is men and women collectively. Second column is men separately and third column is women separately

with CVD declined during the first 3 years after CVD and thereafter stabilized at an MRR of around 4. The association between CVD and CV mortality was much stronger in women than in men. Women with a CVD event experienced a 30-fold CV mortality rate increase in the period following the CVD event, and this mortality rate increase stabilized at an MRR of around 10 a few years after the event (black curves in panel f in figure 2). In men, the respective MRRs were 15 and 6 (black curves in panel e in figure 2). For non-CV mortality, the occurrence of a cardiovascular event was

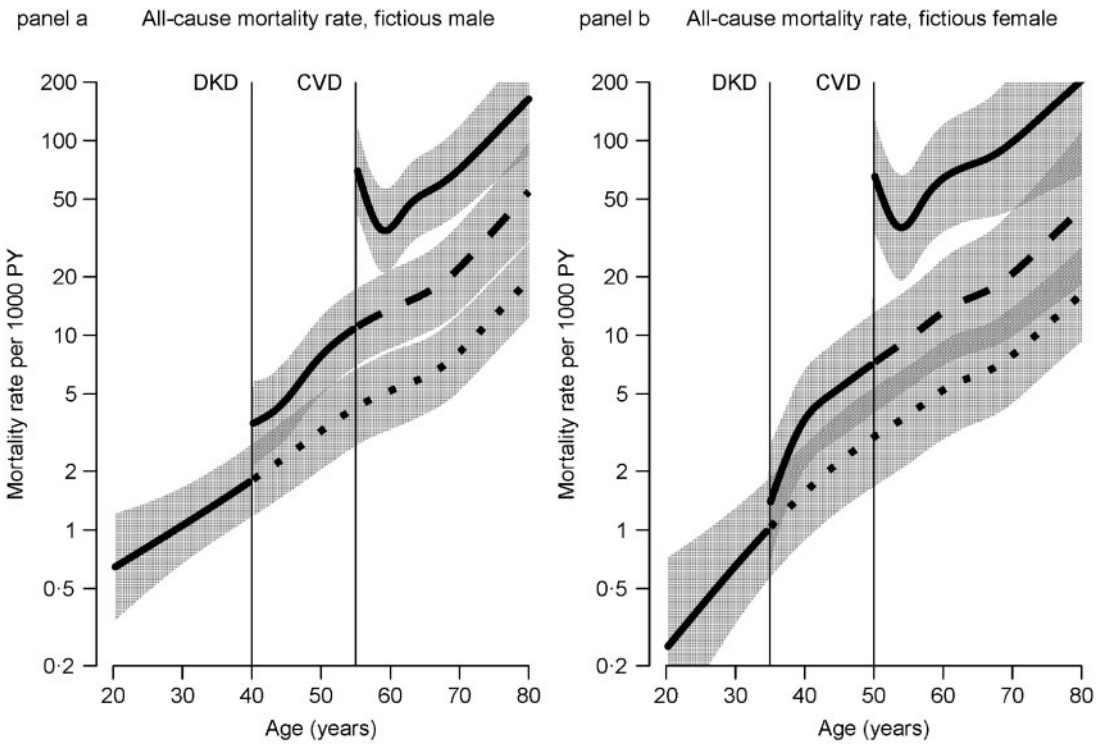

Figure 3 Examples of the evolution of all-cause mortality rates with age and a progressive complication burden by sex, panel A: the solid line: hypothetical male patient profile, HbA1c of 57 mmol/mol throughout follow-up, type 1 diabetes diagnosed at age 20, 9 years of education, median income, not married, born in Sweden with diabetic kidney disease (DKD) diagnosed at age 40 and cardiovascular disease (CVD) at age 55. Panel B: the solid line: hypothetical female patient, HbA1c of 57 mmol/mol throughout follow-up, type 1 diabetes diagnosed at age 20, 9 years of education, median income, not married, born in Sweden with diabetic kidney disease diagnosed at age 35 and cardiovascular disease at age 50. Short dashed line: profile with same specifications, but no complications during follow-up. Long dashed line: profile with same specifications, but no CVD during follow-up. Pooled estimates by Rubin's rules from 10 datasets

associated with an around 4-fold mortality rate increase following the event (panels g, h and i in figure 2) both overall (both sexes collectively) and for men and women separately.

Figure 3 translates the results into a clinical context, illustrating how the absolute mortality rate would develop as a function of age, diabetes duration and duration of CVD and/or diabetic kidney disease, in two hypothetical long-term disease and complications trajectories, one for each sex. Mortality increases approximately exponentially (linearly on the log scale) with duration of diabetes, calendar year and age (dashed lines represent a person without complications). When diabetic kidney disease or CVD is diagnosed, the mortality rate moves to the higher level associated with the new complication state and follows its slope as longer duration in that state accrues. Figure 3 illustrates that the absolute mortality rate in individuals with diabetic kidney disease and/or CVD increases faster than in individuals without complications.

Restricting the analyses to individuals without complications at entry ($n = 12\ 738$) resulted in a much smaller number of individuals who died from each complication state and shorter follow-up time. The magnitude of the effect on mortality was similar, with the results from the full cohort for all three complications (Supplementary Figure S4, available as Supplementary data at *IJE* online).

Discussion

This study shows that time-updated diabetes-related complication duration carries important prognostic information. The excess mortality rate related to CVD was apparent in the period directly after diagnosis of CVD, reaching an MRR of 8 for all-cause mortality in individuals with CVD compared with individuals without, before stabilizing around an MRR of 4 after few years. After diagnosis of diabetic kidney disease, we observed a sustained increase in all-cause mortality with an MRR of around 2 compared with individuals without diabetic kidney disease. Complication duration after 5 years affected the mortality rate ratio between individuals with and without complications minimally, whereas the absolute risk difference increased with increasing duration of complications.

MRRs of the time-fixed estimates in our study were comparable to those from other studies.[6,8,9] For diabetic kidney disease, the 2-fold higher mortality risk was

apparent directly after diagnosis and the shape of the MRR curves was fairly stable during the follow-up period. Diabetic kidney disease is a complication that develops slowly over time and the mortality risk builds up during this period. The processes increasing the likelihood of diabetic kidney disease presumably overlap with those increasing mortality. The diagnosis of diabetic kidney disease brings this risk into the statistical model on a specific date, which in turn leads to the observed jump in the MRRs. However, our results do not suggest that a clinical diagnosis of diabetic kidney disease per se causes the mortality increase, but rather that it may partly reflect the way the progressive nature of the disease process is captured in a state transition model.

In addition to the described statistical phenomenon, CVD does have an immediate event-related fatal component reflected in the higher MRR observed in the period shortly after the event. The large increase in mortality briefly after a CVD event may be related to a non-fatal and a fatal event happening in quick succession, for example due to an unstable coronary plaque, or to physiological changes after the CVD event such as a large drop in ejection fraction. In addition, there is a possibility for reverse causality, e.g. a CVD event triggered or exacerbated by late-stage cancer that leads to mortality soon after the CVD event occurred.

We also observed a higher non-CVD mortality in individuals with CVD. Individuals with CVD may be released from hospital and pass away at home or a patient with CVD may die from concurrent disease (e.g. cancer and its complications). In both cases it is likely that the diagnosis of CVD may erroneously be omitted from the registered Cause of Death.

The crude all-cause mortality, CV mortality and non-CV mortality rates were higher in individuals with retinopathy than in individuals without. However, with a confidence interval of 0.8 to 1.2 for all-cause mortality after adjustment, we found reasonable evidence that retinopathy does not convey any clinically relevant excess risk of death. Other studies do report an increased mortality in individuals with retinopathy, but those studies do not take into consideration the time-updated complication burden (the effect from other complications) that may explain the reported associations.[19,20]

A previous meta-analysis reports women with type 1 diabetes to have a 37% higher risk of all-cause mortality and a 2-fold excess risk of fatal cardiovascular events than men with type 1 diabetes.[21] In line with these observations, we found a higher relative mortality in women. The excess relative risk in women may partly be explained by a generally higher absolute background mortality rate in men compared with women. Also, the excess mortality in women is largely driven by CVD, and there is some evidence that women with type 1 diabetes have a greater risk for CVD than men, due to poorer glycaemic and cardiovascular risk factor control in women [22] and greater impact of cardiovascular risk factors.[23,24]

The data we used consist of detailed time-updated information with repeated measures of clinical, socioeconomic and outcome data from a large type 1 diabetes cohort. Our results are relevant to other countries with similar health care systems that collect longitudinal electronic health care records. The Poisson model is able to deal with multiple related time scales and can isolate the effect of duration of complication(s) and time-updated complication load while accounting for the effects carried by age, calendar year, duration of diabetes and other covariates.

One of the strengths of this study is that the NDR has high coverage, with >95% of adults with type 1 diabetes in Sweden and 100% of outpatient diabetes clinics represented in the register.[25] The proportion of excluded individuals is small (<10%), and the selection process was not dependent on risk or outcome level, limiting the potential for this selection to introduce bias. Stratification of the screening interval for microvascular complications based on the current risk profile has been suggested.[26] In line with this idea, clinicians may be inclined to shorten the screening interval for microvascular complications in high-risk individuals and/or individuals with an unhealthy lifestyle (e.g. smokers, patients with hypertension or individuals with other complications). This could lead to a degree of information bias: if those more likely to develop complications have shorter screening intervals, their date of complication diagnosis would be brought forward, leaving them more risk time after the complication, which would ultimately lead to an underestimation of the mortality rates in this group. However, the screening interval for diabetic kidney disease is 3–4 months, meaning that the bias would have a limited impact.

Mortality may be dependent on severity of complications.[19,27] We did a sensitivity analysis including only individuals without complications at inclusion. The pattern of associations was similar, but the point estimates for diabetic kidney disease and retinopathy were smaller, which likely indicates that severity of complications does matter. Unfortunately, the small number of events and the limited follow-up time in this sensitivity analysis limited our possibility to investigate the role of complication severity further.

Conclusion

In type 1 diabetes, the MRR between individuals with and without cardiovascular disease is unstable over time. The

MRR is highest in the first period after a diagnosis of CVD, reaching an 8-fold higher all-cause mortality rate before stabilizing at an MRR of 4 compared with individuals without CVD. Our results argue in favour of considering the evolving complication burden and duration as an important additional source of prognostically relevant information that may improve personalized risk estimates in individuals with type 1 diabetes.

Supplementary data

Supplementary data are available at *IJE* online.

Funding

L.B. is funded by an unrestricted grant from the Innovation Fund Denmark. L.B. and D.R.W. are funded by an unrestricted grant from the Danish Diabetes Academy, which is supported by the Novo Nordisk Foundation. Study sponsors were not involved in study design, collection, analysis and interpretation of data, writing of the manuscript or the decision to submit the paper for publication.

Data availability

There are no additional data available. The data underlying this article cannot be shared publicly for ethical reasons. Data are available from the senior author A.M.S. on reasonable request.

Acknowledgements

Luke Johnston (Section of Epidemiology, Aarhus University, Denmark) is thanked for proofreading this manuscript.

Author contributions

L.B. is the guarantor of this work, analysed data and drafted the manuscript. He confirms full access to all the data, and final responsibility for accuracy of data analysis and the decision to submit for publication. L.B., S.G., A.M.S., M.E.J., B.C., S.F. and D.R.W. conceived of the idea, designed the study and reviewed and edited the manuscript. B.C. and S.F. provided statistical guidance. All authors accepted the final version of the manuscript for publication.

Conflict of interest

D.R.W., B.C. and M.E.J. own shares in Novo Nordisk A/S. M.E.J. has received research funding from Astra Zeneca and Amgen AB outside the submitted work. S.G. has received research funding and lectures fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi outside the submitted work.

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