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Association of Age at Type 1 Diabetes Onset With Survival, Cardiovascular, and Kidney Outcomes: A Nationwide Cohort Study

Araz Rawshani, Björn Eliasson, Darren K. McGuire, Naveed Sattar, Hertzel C. Gerstein, Jetish Isufi, Julia Zaccai, Aymeric Mahieu, and Aidin Rawshani

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Older Age at Type 1 Diabetes Diagnosis Is Associated With Lower Risk of Mortality and Cardiovascular and Kidney Complications

Context

This was a retrospective cohort study to investigate the association between:

- Age at type 1 diabetes diagnosis
- Mortality, cardiovascular, and kidney outcomes



Individuals with type 1 diabetes in the Swedish National Diabetes Register

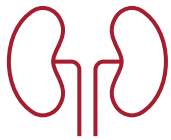
We analyzed the change in risk per 1-year older age at type 1 diabetes diagnosis.

Key Findings

Each 1-year older age at type 1 diabetes diagnosis was associated with a 1.7% lower risk of mortality.



- 3.0% lower risk of acute myocardial infarction
- 2.8% lower risk of heart failure



- 3.9% lower risk of diabetic nephropathy
- 3.6% lower risk of end-stage kidney disease

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  This study examined the association of age at type 1 diabetes diagnosis with mortality, cardiovascular events, and kidney disease using a longer follow-up period and finer increments of age at diagnosis than previously examined.
- **What is the specific question we wanted to answer?**
  How does risk change with age at type 1 diabetes diagnosis?
- **What did we find?**
  Excess risk of mortality, cardiovascular events, and end-stage kidney disease was inversely associated with age at type 1 diabetes diagnosis. Each additional year later in type 1 diabetes diagnosis was associated with 1.7% lower probability of death.
- **What are the implications of our findings?**
  Delaying the onset of type 1 diabetes might lower the risk of serious health complications.

Association of Age at Type 1 Diabetes Onset With Survival, Cardiovascular, and Kidney Outcomes: A Nationwide Cohort Study

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ORIGINAL ARTICLE

OBJECTIVE

To investigate the association of age at type 1 diabetes diagnosis with incident mortality, cardiovascular, and kidney outcomes.

RESEARCH DESIGN AND METHODS

In this retrospective cohort study, individuals ≥18 years of age with type 1 diabetes with one or more entries in the Swedish National Diabetes Register (from January 1998 to December 2019) were followed from the date of first registration up to December 2020. Cox proportional hazards models were used to examine risk per 1-year increase in age at type 1 diabetes diagnosis and excess risk relative to comparator individuals from the Swedish Total Population Register.

RESULTS

Cohorts consisted of 34,155 individuals with type 1 diabetes and 150,026 comparator individuals. The hazard ratio (HR) per 1-year increase in age at type 1 diabetes diagnosis was 0.98 (95% CI 0.98, 0.99) for all-cause mortality, indicating a 1.7% lower probability per 1-year increase in age at type 1 diabetes diagnosis (8.2% lower probability per 5-year increase). Corresponding HRs per 1-year increase in age at diagnosis were 0.97 (0.97, 0.98) for cardiovascular mortality and 0.99 (0.98, 0.99) for noncardiovascular mortality. Excess risk relative to comparator individuals was greatest when type 1 diabetes diagnosis occurred from 0 to 10 years of age, with HRs of 3.23 (2.92, 3.58) for all-cause mortality, 5.73 (4.32, 7.59) for cardiovascular mortality, and 3.01 (2.70, 3.36) for noncardiovascular mortality.

CONCLUSIONS

Younger age at type 1 diabetes diagnosis is associated with greater risk of mortality and complications, with each additional year delay in onset being significantly associated with lower risk.

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Type 1 diabetes is a chronic autoimmune disease that can develop at any age and is associated with elevated risk of serious health consequences and reduced life expectancy (1–4). Previous studies indicated that younger age at type 1 diabetes onset and longer duration of type 1 diabetes are associated with higher risk of these

consequences (3,5–7). In one study, early onset of type 1 diabetes (from 0 to 10 years of age) was associated with a 4.1-fold higher risk of death compared with control individuals, whereas later onset (26–30 years of age) was associated with a 2.8-fold higher risk of death compared with control individuals (3). Similarly, early onset of type 1 diabetes (0–10 years of age) was associated with an 11.4-fold higher risk of cardiovascular disease compared with control individuals, whereas later onset (26–30 years of age) was associated with a 3.9-fold higher risk of cardiovascular disease compared with control individuals (3). These findings suggest that delay of type 1 diabetes onset may be associated with reduced risk of complications and premature death. Indeed, delaying the onset of type 1 diabetes is possible with disease-modifying therapy (8–12).

The current study adds to a previous analysis of the relationship between age at type 1 diabetes diagnosis and incident outcomes by extending the follow-up period, including a larger sample size, and using a modeling strategy that captures associations with 1-year increments in age at diagnosis. This allows hypothetical quantification of the degree to which delaying the age at type 1 diabetes diagnosis might translate into improved outcomes.

RESEARCH DESIGN AND METHODS

Data Sources and Study Cohort

This retrospective cohort study used the Swedish National Diabetes Register (NDR), which is linked to other Swedish national registries. The NDR includes data on almost all individuals with diabetes ≥18 years of age in Sweden. Comparator individuals were identified using the Total Population Register, which includes data on the entire Swedish population. The study was approved by the Swedish Ethical Review Authority, Uppsala, Sweden (2020-04796). No informed consent was required.

The study included individuals with type 1 diabetes who had at least one entry in the NDR from 1 January 1998 to 31 December 2019. Cohort entry date was the date of the first recording in the NDR for individuals with type 1 diabetes during the same period. Baseline period was the period up to and excluding the cohort entry date. The follow-up period began at cohort entry and ended at the date of the outcome of interest, death, or 31 December 2020, whichever came first (Supplementary Fig. 1). As done previously, type 1 diabetes was defined based on the epidemiological definition of treatment with only insulin and a diagnosis at ≤30 years. This definition has been continuously internally validated to be accurate in almost all cases (∼97%) by comparing epidemiological classification and physician assessment. Each individual with type 1 diabetes was matched on age, sex, and county of residence at the time of cohort entry with five randomly selected comparator individuals not registered in the NDR at that time. Start date of the follow-up period for comparator individuals was the cohort entry date of the matched individuals with type 1 diabetes. After matching, individuals with type 1 diabetes with severe congenital disorders, metabolic disorders, and neurological disorders at cohort entry were excluded along with their matched comparator individuals (ICD-9 and ICD-10 codes provided in Supplementary Table 1). The remaining comparator individuals meeting exclusion criteria were also excluded, but matched individuals with type 1 diabetes were retained (Supplementary Fig. 2). Exclusion criteria were applied after matching because of data access limitations in the Total Population Register.

Age, sex, clinical and laboratory data, and type 1 diabetes–related lifestyle factors were obtained from the NDR at cohort entry for individuals with type 1 diabetes. Age and sex were obtained from the Total Population Register for comparator individuals. Preexisting events (from 1 January 1987 up to cohort entry) and intervening events were assessed using the Inpatient Registry and Outpatient Registry (collectively, the National Patient Register) and the NDR for retinopathy. The Outpatient Registry has been complete since 2002. Mortality was retrieved from the National Cause of Death Register. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies, Statistics Sweden, registry was used to obtain the most up-to-date socioeconomic data before the cohort entry date (i.e., education level, country of birth, income level, marital status, county of residence).

Outcomes and Exposures

Primary outcome measures were all-cause mortality, cardiovascular mortality, and noncardiovascular mortality. Secondary outcome measures were coronary heart disease, acute myocardial infarction, cerebrovascular disease (stroke), cardiovascular disease (defined as acute myocardial infarction or cerebrovascular disease), heart failure, major adverse cardiovascular events (defined as acute myocardial infarction, cerebrovascular disease, or heart failure), atrial fibrillation, end-stage kidney disease, and peripheral artery disease. Diabetic nephropathy and diabetic foot disease were assessed as exploratory outcome measures. Only first occurrences were analyzed as outcomes (ICD-9 and ICD-10 codes provided in Supplementary Table 1).

For individuals with type 1 diabetes, age at diagnosis was defined as age of first diagnosis of type 1 diabetes per the NDR. Age at type 1 diabetes diagnosis was analyzed as a continuous and a categorical (0–10, 11–15, 16–20, 21–25, and 26–30 years) variable. Age at diagnosis as a continuous variable is referred to here as age at type 1 diabetes diagnosis in years, whereas age at diagnosis as a categorical variable is referred to as categories of age at type 1 diabetes diagnosis. Duration of type 1 diabetes was defined as the period from diagnosis until cohort entry date and was treated as a continuous variable. For comparator individuals, duration of type 1 diabetes was set to 0.

As attained age, age at onset, and diabetes duration are mathematically linked, collinearity among these time-related variables was considered a priori. Alternative parameterizations were evaluated during model development, and the final approach was selected on the basis of simulation-informed methodological work to provide stable and clinically interpretable estimates while avoiding overparameterization of deterministically related variables.

Statistical Analyses

For each incident outcome, individuals with a preexisting condition were excluded from the analysis of that specific outcome. Crude incidence rates for each outcome were described as event rates per 100,000 person-years for individuals with type 1 diabetes and comparator individuals.

Risk in Individuals With Type 1 Diabetes

Cox regression models using cubic splines were applied to examine the association of age at type 1 diabetes diagnosis in years with risk of study outcomes. Attained age was used as the underlying timescale, with delayed entry (left truncation) at the age of registration in the NDR. The placement of knots was determined based on empirical quantiles of the data. The model was adjusted for sex, race and ethnicity, individual income, marital status, calendar year, and education to address potential confounding of these factors. In addition, the association between age at type 1 diabetes diagnosis in years and risk of study outcomes was examined using Cox regression assuming a linear association with age at type 1 diabetes diagnosis in years and using the same timescale and adjustment covariates. Hazard ratios (HRs) were interpreted per unit change in age (i.e., per year).

A similar analysis was conducted to examine the association of duration of type 1 diabetes with risk of study outcomes. As above, attained age served as the timescale, with delayed entry at the age of registration in the NDR, and the model was adjusted for sex, race and ethnicity, individual income, marital status, education, and age at diagnosis. An interaction term between age at diagnosis and duration of type 1 diabetes was added to the Cox regression models, assuming a linear association of age at diagnosis and duration of type 1 diabetes with the hazard function of outcomes.

Excess Risk Between Individuals With Type 1 Diabetes and Comparator Individuals

Risk of study outcomes was analyzed using Cox proportional hazards models with attained age as the timescale. The comparator cohort served as the reference for the baseline hazard such that the baseline hazard corresponded to the hazard function of the comparator cohort across attained age. Each model included category of age at diagnosis, duration of type 1 diabetes, sex, race and ethnicity, individual income, marital status, year of inclusion in the registry, and education. Duration of type 1 diabetes among diagnosed individuals was mean centered by subtracting the mean duration of type 1 diabetes from each individual's duration. HRs were examined for males and females combined and separately. Differences between males and females were summarized descriptively, with no hypothesis testing.

Life-years lost were estimated by calculating the difference in predicted conditional median survival from ≥18 years of age between individuals with type 1 diabetes and comparator individuals. This analysis used Cox models incorporating age at diagnosis and sex. Methods for exploratory analyses that examined excess risk relative to the youngest category of age at type 1 diabetes diagnosis (0–10 years) are provided in the Supplementary Material.

Gradient Boosting Machine Learning Models

Gradient boosting machine learning (gbm package in R) was used to quantify the relative importance to the model of factors associated with risk of study outcomes. Analyses of right-censored survival data were implemented using random forest and gradient boosting algorithms. These analyses were conducted in the cohort with type 1 diabetes only. Individuals with type 1 diabetes with BMI <18.5 kg/m^2 were excluded from these analyses as this is often a marker of frailty and underlying comorbidities that may independently influence outcomes. This subgroup could introduce clinical heterogeneity and inflate risk estimates for individuals with type 1 diabetes beyond what is relevant to the broader patient population. Missing data were imputed using multiple imputation by chained equations with random forests using the mice package in R.

Data and Resource Availability

Access to the data sets is available from the sources stated in the article upon request to the data providers, upon fulfilling the legal and regulatory requirements, and with approval from the Swedish Ethical Review Authority.

RESULTS

Baseline Characteristics and Crude Incidence Rates

The final cohort consisted of 34,155 individuals with type 1 diabetes and 150,026 comparator individuals. Mean age at baseline for individuals with type 1 diabetes was 30.7 years, and 44.5% were women. Mean age at baseline for comparator individuals was 28.3 years, and 44.3% were women. The median follow-up period for individuals with type 1 diabetes was 12.9 years. Baseline characteristics are presented in Supplementary Table 2, with missing data shown in Supplementary Table 3. Descriptive data for all imputed characteristics used in the gradient boosting machine learning models are shown in Supplementary Table 4. The overall crude mortality rate was 205.0 deaths per 100,000 person-years in the comparator cohort and 836.3 deaths per 100,000 person-years in the type 1 diabetes cohort. Sex-specific mortality rates were 815.4 deaths and 861.8 deaths per 100,000 person-years for men and women with type 1 diabetes, respectively. Crude incidence rates and number of events are presented in Supplementary Tables 5–10.

Life Expectancy

Individuals with type 1 diabetes had significantly lower life expectancy than comparator individuals (Fig. 1). The number of life-years lost was more pronounced when the category of age at type 1 diabetes diagnosis was 0–10 or 11–15 years compared with older ages. Individuals in the category of 0–10 years had an estimated life expectancy of 70.2 years, resulting in a loss of 16.3 years relative to comparator individuals. By comparison, individuals in the category of 16–20 years had a loss of 10.7 years (Fig. 1*A*). When analyzed separately, women and men in the category of 0–10 years had a loss of 20.5 years and 13.4 years, respectively (Fig. 1*B* and *C*).

Excess Risk in Type 1 Diabetes

Relative to comparator individuals, individuals with type 1 diabetes displayed a significant excess risk for all fatal outcomes (i.e., primary outcomes) (Fig. 2). Individuals in the category of 0–10 years displayed the greatest excess risks, with an HR of 3.23 (95% CI 2.92, 3.58) for all-cause mortality, 5.73 (4.32, 7.59) for cardiovascular mortality, and 3.01 (2.70, 3.36) for noncardiovascular mortality (Fig. 2*A*). Excess risks were less pronounced and similar across older age categories. In women, excess risk was greatest when the category of age at type 1 diabetes diagnosis was 0–10 years, whereas men showed similar excess risk across categories of age at type 1 diabetes diagnosis (Fig. 2*B*).

Excess risk for individuals with type 1 diabetes relative to comparator individuals

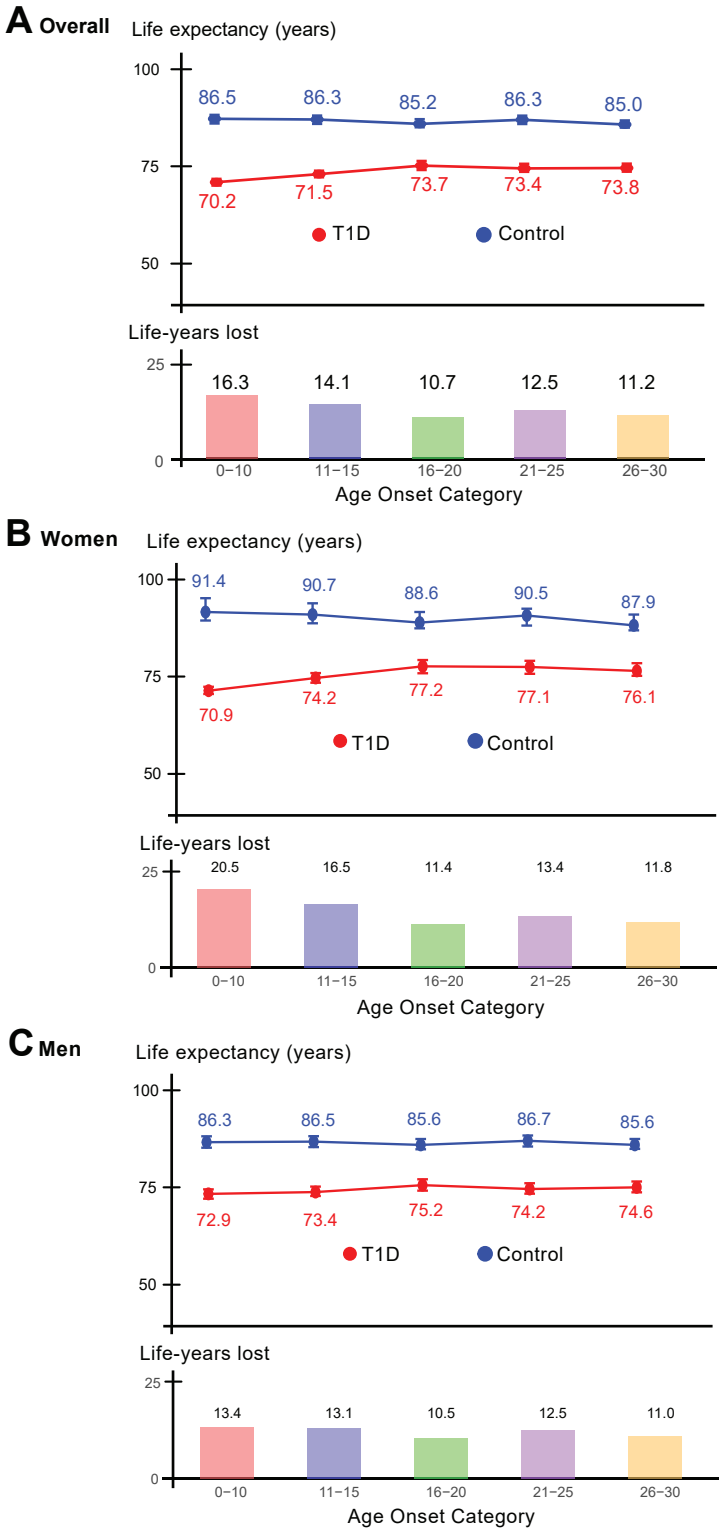


Figure 1—Adjusted life expectancy for individuals with type 1 diabetes (T1D) and comparator individuals and life-years lost for those with T1D. Life expectancy was the predicted conditional median survival from ≥18 years of age. *A*: Both sexes combined. *B*: Women only. *C*: Men only. Error bars indicate the 95% CI.

declined with higher categories of age at type 1 diabetes diagnosis for all nonfatal outcomes (i.e., secondary and exploratory outcomes) except diabetic nephropathy and atrial fibrillation (Fig. 3). The lower excess risk with older categories of age at type 1 diabetes diagnosis was more apparent in women than men for major adverse cardiovascular events, acute myocardial infarction, coronary heart disease, heart failure, and cardiovascular disease (Supplementary Fig. 3).

Cox models comparing categories of age at type 1 diabetes diagnosis, using the category of 0–10 years as the reference, generally showed a lower risk for individuals with older ages at type 1 diabetes diagnosis (Supplementary Figs. 4 and 5). Probability of all-cause mortality was 13% lower when the category of age at type 1 diabetes diagnosis was 11–15 years (HR 0.87 [95% CI 0.79, 0.96]) and 30% lower when the category was 16–20 years (0.70 [0.63, 0.78]). Probability of cardiovascular mortality was not significantly different when the category of age at type 1 diabetes diagnosis was 11–15 years but was 41% lower when the category was 16–20 years (0.59 [0.47, 0.74]).

Association of Age at Type 1 Diabetes Diagnosis and Duration of Type 1 Diabetes With Fatal and Nonfatal Outcomes

There was an inverse association between age at type 1 diabetes diagnosis in years and risk for all study outcomes except atrial fibrillation (Fig. 4). The HR per 1-year increase was 0.98 (95% CI 0.98, 0.99) for all-cause mortality, indicating a 1.7% lower likelihood of mortality per 1-year increase in age at type 1 diabetes diagnosis in years (8.2% lower likelihood per 5-year increase) (Supplementary Table 11). The HR per 1-year increase in age at type 1 diabetes diagnosis in years was 0.97 (0.97, 0.98) for cardiovascular mortality and 0.99 (0.98, 0.99) for noncardiovascular mortality. For both all-cause mortality and noncardiovascular mortality, the slope was steeper between 0 and 15 years of age and plateaued after ∼15 years of age (Fig. 4). In spline analyses, the association between younger age at diagnosis and higher all-cause mortality was strongest up to late adolescence, after which the curve largely plateaued, whereas several other complications continued to show a more graded association into early adulthood. In contrast, risk of cardiovascular mortality showed an approximately linear association with age at type 1 diabetes diagnosis in years (Fig. 4). The most pronounced HRs per 1-year increase in age at type 1 diabetes diagnosis in years were noted for peripheral artery disease (0.97 [0.96, 0.98]), end-stage kidney disease (0.96 [0.96, 0.97]), and diabetic nephropathy (0.96 [0.96, 0.97]).

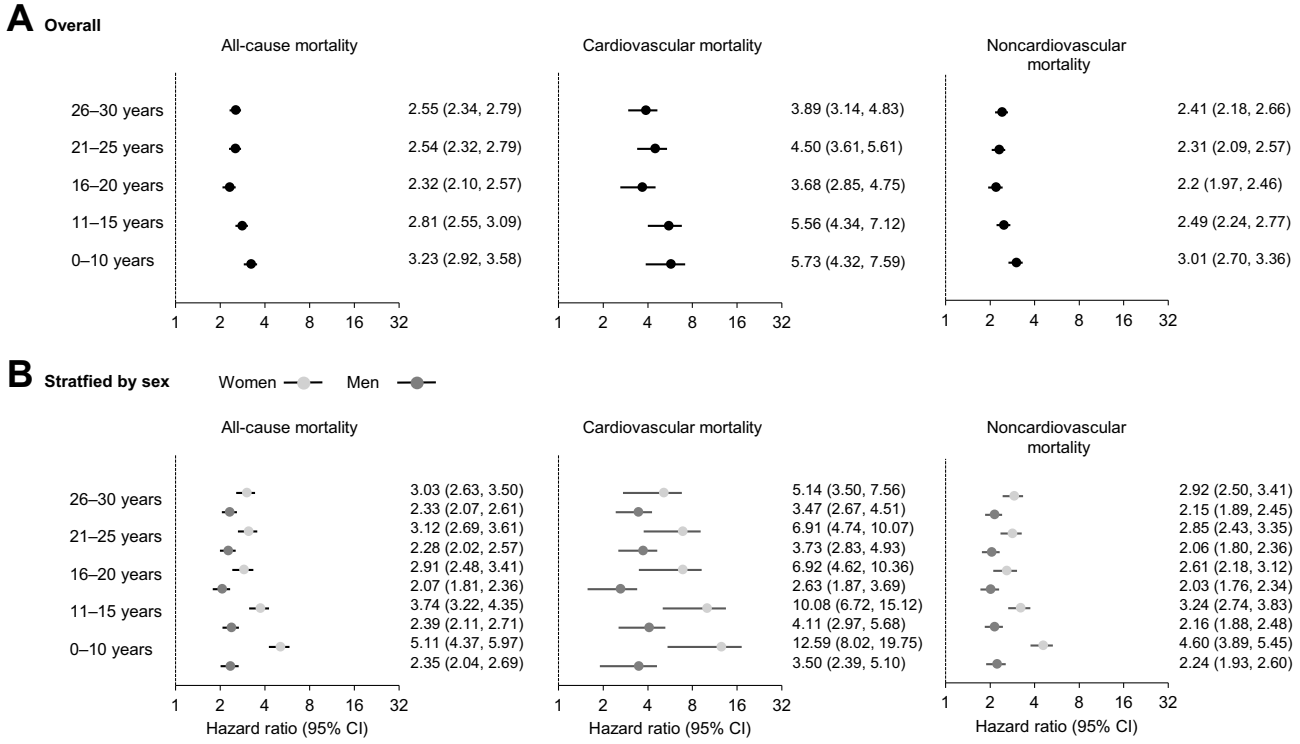


Figure 2—Excess risk of fatal outcomes in individuals with type 1 diabetes vs. comparator individuals. Excess risk is shown by categories of age at type 1 diabetes diagnosis for those with type 1 diabetes. *A*: Both sexes combined. *B*: Stratified by sex. Cox regression models were adjusted for category of age at type 1 diabetes diagnosis, sex, year of inclusion in the NDR, duration of type 1 diabetes, and socioeconomic variables.

Supplementary Fig. 6 shows the corresponding data for duration of type 1 diabetes. Supplementary Table 12 shows the HRs for the interaction terms between age at type 1 diabetes diagnosis and duration of type 1 diabetes.

Relative Importance of Risk Factors

The relative importance of different factors in predicting study outcomes is shown in Supplementary Figs. 7 and 8 based on gradient boosting machine learning models. Estimated glomerular filtration rate was the most important factor for predicting both all-cause mortality and cardiovascular mortality, while duration of type 1 diabetes and age at type 1 diabetes onset were second and fourth most important, respectively.

CONCLUSIONS

This study applied several methodological and analytical refinements to build upon earlier cohort studies from the Swedish NDR (3,7,13,14). Risk of mortality, cardiovascular, and kidney outcomes among individuals with type 1 diabetes according to age at type 1 diabetes diagnosis was investigated, with additional emphasis on incremental risk conferred by each year living with type 1 diabetes. Results demonstrated that excess risk of mortality, cardiovascular events, and end-stage kidney disease was inversely associated with age at diagnosis. The number of life-years lost was greater for individuals with type 1 diabetes diagnosed in younger age categories (i.e., 0–10 or 11–15 years) than in older age categories, especially for women, who lost 20.5 life-years due to an early onset of type 1 diabetes. Greater loss of life expectancy and excess risk of cardiovascular outcomes in women compared with men with type 1 diabetes is well established (2,3). Each additional year later of type 1 diabetes onset was associated with 1.7% lower probability of death (8.2% lower probability per 5-year delay) and 2.6% lower probability of cardiovascular death (12.3% lower probability per 5-year delay). Figures for acute myocardial infarction, coronary heart disease, heart failure, peripheral artery disease, end-stage kidney disease, and nephropathy were more pronounced, with a 5-year delay associated with 15–18% lower probability of the latter three. These findings suggest that a delay in type 1 diabetes onset might be associated with lower excess risk of mortality and serious health consequences compared with the general population. Cox regression with splines showed that risk of all-cause and noncardiovascular mortality was lower with older age at type 1 diabetes diagnosis until ∼15 years of age. Differing spline shapes across outcomes may indicate distinct underlying pathways, with the plateau in all-cause mortality after late adolescence possibly reflecting early-life vulnerability or imprinting associated with very early–onset disease, whereas continued gradients for other complications into early adulthood may more strongly reflect cumulative exposure and progression of organ-specific risk. While there is a need to interpret these data cautiously, the substantial hazards observed with type 1 diabetes diagnosis in childhood (<15 years of age) suggest that postponing the onset of type 1 diabetes even by a few years in childhood could be associated with a substantial reduction in the risk of future complications and mortality. The risk of cardiovascular mortality continued to be lower with older age at type 1 diabetes diagnosis, even beyond the late teenage years, suggesting that delaying type 1 diabetes

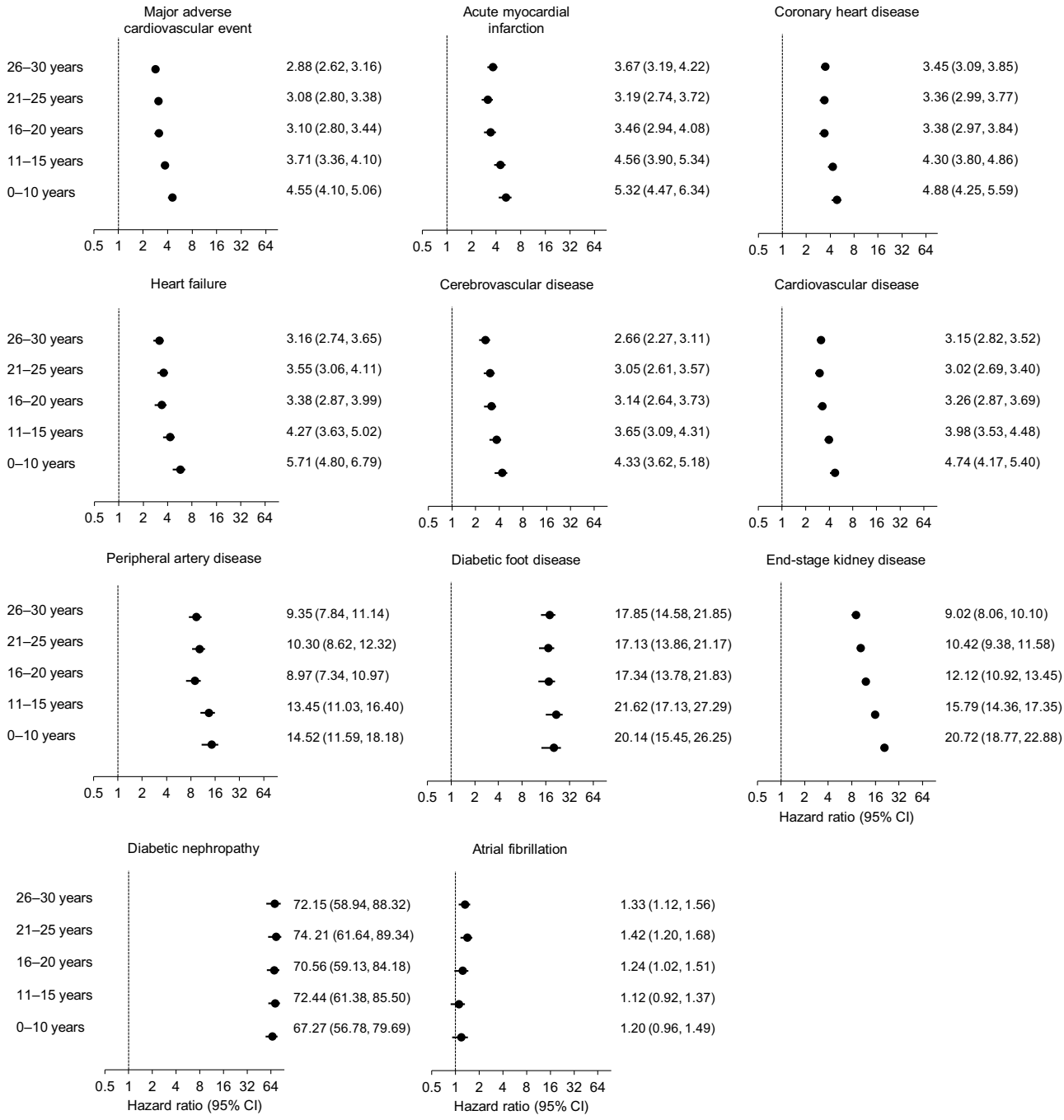


Figure 3—Excess risk of nonfatal outcomes in individuals with type 1 diabetes vs. comparator individuals. Excess risk is shown by categories of age at type 1 diabetes diagnosis for those with type 1 diabetes. Cox regression models were adjusted for category of age at type 1 diabetes diagnosis, sex, year of inclusion in the NDR, duration of type 1 diabetes, and socioeconomic variables.

beyond this period may be associated with lower risk of cardiovascular mortality in the population of individuals with type 1 diabetes.

The mortality findings are consistent with earlier studies in Finland and Sweden, which reported higher excess mortality in individuals with early-onset type 1 diabetes compared with those with later onset (3,5,6,15,16). The findings on excess risk of nonfatal outcomes were similar to those from a previous study (3). However, the magnitude of excess risk was higher in the previous study, especially in the youngest category of age at type 1 diabetes diagnosis, with an HR of coronary heart disease of 30.50 (95% CI, 19.98, 46.57) when age at type 1 diabetes diagnosis was 0–10 years compared with 4.88 (4.25, 5.59) in this study and an HR of acute myocardial infarction of 30.95 (17.59, 54.45) when age at type 1 diabetes diagnosis was 0–10 years compared with 5.32 (4.47, 6.34) in this study. Sex differences for excess risk of mortality were apparent in this study as in the previous study, although the effect of sex on excess risk was not statistically evaluated (3). Supporting these findings, a meta-analysis of 26 studies including 214,114 individuals reported that women with type 1 diabetes had a 37% greater

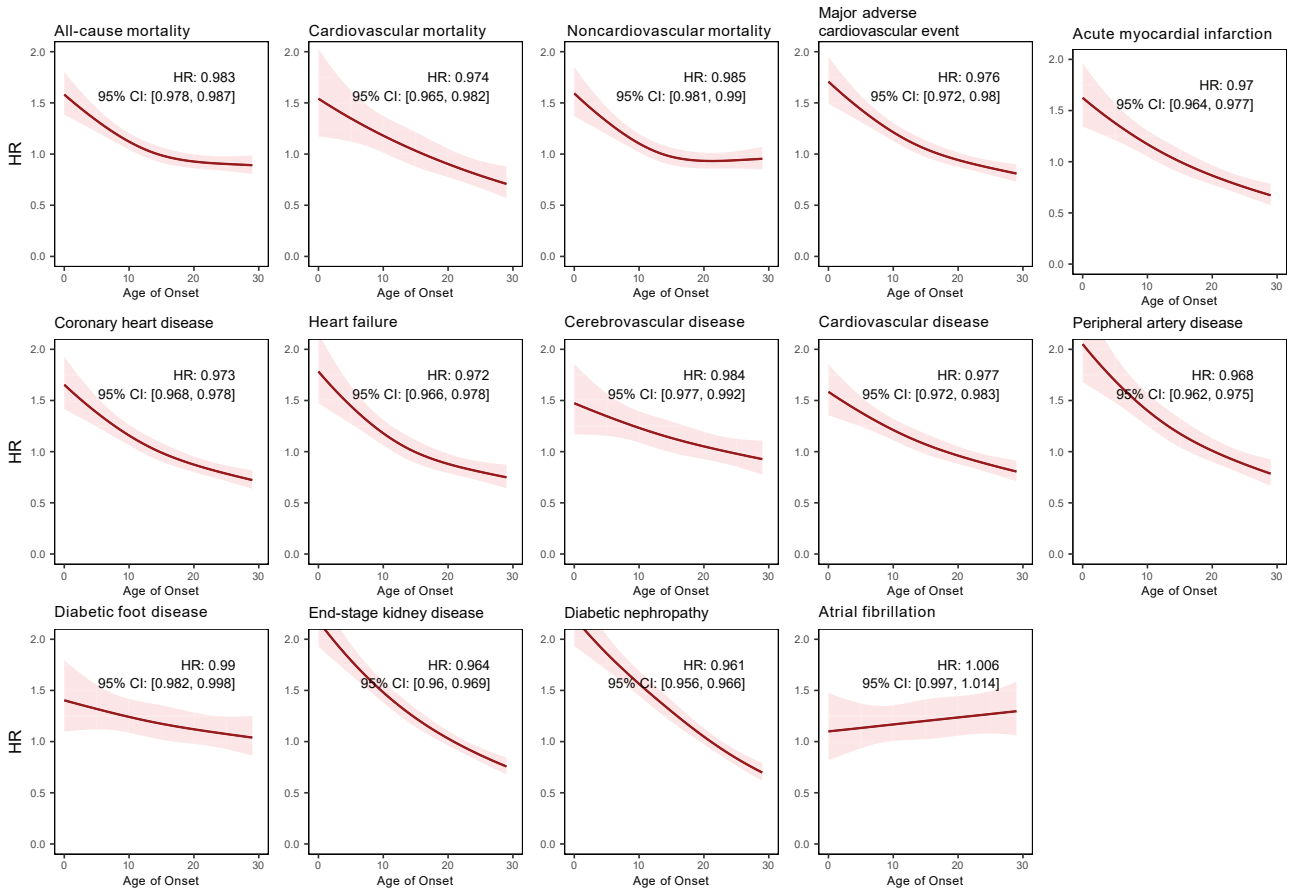


Figure 4—The relationship between risk of outcomes and age at type 1 diabetes diagnosis in years, using Cox regression and splines. The lines depict the association captured by the restricted cubic spline, and the shaded areas show the 95% CI. The HR in the upper right corner is per 1-year increase in age at type 1 diabetes diagnosis, assuming a linear association. Covariate adjustment was made for age, sex, and socioeconomic variables.

excess risk of all-cause mortality compared with men (17).

Importantly, this study should be interpreted as evaluating prognosis and excess risk among adults with established type 1 diabetes in a prevalent survivor cohort rather than as lifetime excess risk from the time of diagnosis. As participants entered follow-up after surviving to adulthood and registering in the NDR, early events and deaths before cohort entry were not captured. Accordingly, the observed associations may underestimate the full lifetime burden of early-onset type 1 diabetes.

These findings support the rationale for health care systems and physicians to place greater focus on delaying onset of clinical (stage 3) type 1 diabetes from an early age, especially in females. This is possible with recent progress in disease-modifying therapy for type 1 diabetes, which offers a potential paradigm shift from solely treating clinical disease to delaying the progression from preclinical to clinical type 1 diabetes (8–12). Use of disease-modifying therapy in preclinical type 1 diabetes requires screening to identify individuals with early-stage (stage 1 or 2) type 1 diabetes (18). Programs that facilitate early detection could potentially improve outcomes for those in the early stages of type 1 diabetes (19,20).

The results of this study should be generalizable to the Swedish population, given that the NDR provided coverage of 87% of all individuals with diabetes in Sweden in 2019 (21). However, applicability of the results to populations outside Sweden may be limited because of variability in genetics, health care, and environment across different regions.

There are several other limitations of this study. First, childhood- and adult-onset type 1 diabetes are not necessarily identical phenotypes and may differ in underlying biology, autoimmune tempo, β-cell reserve, clinical presentation, and subsequent disease trajectory. The observed risk gradient across diagnosis age-groups may reflect differences in disease phenotype, duration of exposure to hyperglycemia, treatment history, survivorship, and other clinical characteristics associated with age at onset. Therefore, later onset should not be interpreted as simply the same disease occurring later in time or that our findings imply that delaying onset would necessarily reproduce the risk differences observed here. Second, cohort entry date could occur only once an individual with type 1 diabetes had reached 18 years of age. Thus, events between the date of type 1 diabetes diagnosis and the cohort entry date were not captured for those diagnosed with type 1 diabetes before 18 years of age. As cohort entry was restricted to individuals who survived to adulthood, observed associations for childhood-onset type 1 diabetes may be attenuated, and excess risk associated with the earliest ages at diagnosis may therefore be underestimated. Third, we were unable to assess prior severe hypoglycemia or hospitalizations for severe

hypoglycemia and death due to a hypoglycemic episode; therefore, hypoglycemia-related events, including recurrent severe hypoglycemia and hypoglycemia unawareness, may represent an important unmeasured pathway linking earlier age at type 1 diabetes diagnosis to excess mortality. A further limitation concerns the interpretation of time-related variables. Attained age, age at type 1 diabetes diagnosis, and diabetes duration are deterministically linked since at any given age an individual's duration of diabetes is determined once their age at diagnosis is known. Our models account for this by using attained age as the underlying timescale while including age at diagnosis and duration as covariates, which provides stable and valid estimates. Nevertheless, this approach cannot fully separate the independent contributions of age at diagnosis and disease duration. Therefore, the resulting estimates are best understood to reflect their combined influence. Future studies comparing an incident cohort of individuals with newly diagnosed diabetes and individuals without diabetes would be valuable to further disentangle these effects. Additionally, because of access limitations inherent in the Swedish population registry data, selection criteria could not be applied prior to matching, which may have introduced the demographic differences observed between the type 1 diabetes and comparator cohorts. Finally, this study included individuals who entered the register before 2020. More recent technological advances may have an impact on future data.

In conclusion, individuals with a type 1 diabetes diagnosis in childhood and adolescence have higher risk of mortality and cardiovascular and kidney complications than individuals diagnosed later in life. The findings support providing greater monitoring for cardiovascular and kidney complications in individuals diagnosed with type 1 diabetes at young ages and are consistent with the notion that delaying onset of type 1 diabetes with disease-modifying therapy may lower the risk of complications and mortality.

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Duality of Interest. Ar.R. reported receiving personal fees from Sanofi, Amgen, AstraZeneca, Novo Nordisk, and Medtronic. B.E. reported receiving personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi. D.K.M. reported receiving research support for clinical trials leadership from Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Lilly USA, Lexicon Pharmaceuticals, NewAmsterdam Pharma, and Amgen and honoraria for consultancy from Lilly USA, Boehringer Ingelheim, Novo Nordisk, Bayer, Amgen, Kailera Therapeutics, Metsera, Alveus Therapeutics, Neurotronic, and Zealand Pharma. N.S. reported receiving consulting/speaker honoraria from Abbott Laboratories, AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceutical, Janssen, Menarini Ricerche, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi and grants from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics outside the submitted work. H.C.G. holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care and reported receiving research grants from Eli Lilly, Novo Nordisk, and Hanmi; continuing education grants from Eli Lilly, Abbott, Sanofi, Novo Nordisk, and Boehringer Ingelheim; honoraria for speaking from AstraZeneca, Eli Lilly, Novo Nordisk, Zuellig Pharma, Sanofi, Carbon Health, and Hansoh Pharmaceutical Group; consulting fees from Abbott, Bayer, Eli Lilly, Novo Nordisk, Pfizer, Sanofi, and Hanmi; and a patent for the use of GDF15 as a biomarker for metformin use. J.Z. and A.M. are employees of Sanofi. Ai.R. reported receiving personal fees from Sanofi, Novo Nordisk, and Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. Ar.R., B.E., and Ai.R were involved in the conception, design, and conduct of the study and the analysis and interpretation of the results. D.K.M., N.S., H.C.G., J.I., J.Z., and A.M. were involved in the interpretation of the results. All authors revised the manuscript critically and approved the final version. Ai.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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