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Cardiorenal Outcomes in Middle-Aged and Older Adults With Type 1 and Type 2 Diabetes

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Keywords

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Type 1 diabetes (T1D) is an increasingly common autoimmune disorder characterized by absolute insulin deficiency, premature morbidity and mortality, and excess health care spending.[1] Although traditionally considered a disease of early life, most incident and prevalent cases of T1D now occur in adults.[2] Cardiovascular and kidney disease are leading causes of death and disability among individuals with T1D,[1,2] but knowledge concerning the incidence of these important complications during later life stages, and how it compares with type 2 diabetes (T2D), is limited. In this population-based prospective cohort study

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that enrolled middle-aged and older adults at baseline, we evaluated risk factor control and cardiorenal outcomes among individuals with T1D vs T2D.

METHODS

The UK Biobank study design and population have been described.[3] Briefly, the UK Biobank is a prospective cohort study that enrolled >500,000 participants aged 37 to 73 years, recruited between 2006 and 2010. All participants provided written informed consent, approved by the North West Multi-Centre Research Ethics Committee. Secondary use of data under UK Biobank application 7089 was approved by the Mass General Brigham Institutional Review Board.

In this analysis, we considered UK Biobank participants without a prior diagnosis of atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), or heart failure (HF) and with available glycated hemoglobin (HbA_{1c}) and other risk factor measurements. We then identified individuals with normoglycemia, prediabetes, T1D, and T2D using a combination of International Classification of Diseases (ICD)-10th Revision codes, self-reported physician diagnoses, laboratory data, and medication records. Participants with a form of diabetes other than T1D or T2D (eg, gestational diabetes only) were excluded from the analysis.

Among participants with T1D and T2D, we evaluated the prevalence of baseline risk factor control: 1) body mass index <30 kg/m^2; 2) HbA_{1c} <7.0%;3) low-density lipoprotein cholesterol <100 mg/dL;4) systolic blood pressure <130 mm Hg; 5) never smoking; and 6) urine albumin-to-creatinine ratio <30 mg/g, respectively.

Cardiorenal outcomes were ascertained from diagnoses linked to inpatient care episodes. The primary study outcome was a composite of ASCVD (coronary artery disease [myocardial infarction, coronary revascularization, chronic ischemic heart disease, or ischemic cardiomyopathy], ischemic stroke, and peripheral artery disease [atherosclerosis of the aorta or peripheral arteries, peripheral artery revascularization, or lower extremity amputation]), HF, CKD (including end-stage kidney disease [ESKD]), and all-cause death. CKD was defined as CKD (stages 3–4) or ESKD (CKD stage 5, ESKD, kidney replacement therapy, or kidney allotransplantation). Secondary outcomes were the individual components of the composite cardiorenal outcome. Events were defined as newly diagnosed fatal/nonfatal conditions after UK Biobank enrollment. If a participant experienced ≥2 different events, the first event of each type was considered an outcome.

Age-adjusted incidence rates (per 1,000 person-years) were estimated for each outcome applying the direct standardization method based on the 2010 UK population projections. Associations between glycemic status and cardiorenal outcomes were assessed using multivariable-adjusted Cox proportional hazards models. The proportional hazards assumption was evaluated using Schoenfeld residuals, without evidence of violation. Adjusted HRs (aHRs) with 95% CI for each outcome were calculated using the T2D group as the reference. Models were adjusted a priori for key sociodemographic and clinical characteristics. Procedures used for assessment of sociodemographic and clinical

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covariates have been described.[3,4] The end of the observation period was defined as the date of event, last follow-up, or death, whichever came first. We additionally evaluated the association of baseline HbA_{1c} with cardiorenal outcomes and death in T1D and T2D, using normoglycemia as reference. All analyses were performed using R version 4.3.3 (R Foundation), and 2-sided *P* values <0.05 were considered statistically significant.

RESULTS

Among 437,087 UK Biobank participants without prevalent ASCVD, CKD, or HF (mean age, 56.8 years; 55.4% female), 361,400 (82.7%) had normoglycemia, 57,087 (13.1%) had prediabetes, 17,655 (4.0%) had T2D, and 945 (0.2%) had T1D. UK Biobank participants with T1D were younger (age 55.5 ± 8.2 years vs 59.7 ± 7.2 years) and more often female (44.7% vs 40.0%) and White (96.1% vs 86.8%) compared with those with T2D.

Participants with T1D vs T2D had greater risk factor control (mean risk factors controlled: 3.2 vs 2.9; $P < 0.001$) at baseline. Individuals with T1D more often had body mass index <30 kg/m^2 (74.1% vs 44.3%), never smoked (54.2% vs 47.7%), systolic blood pressure <130 mm Hg (31.8% vs 22.7%), low-density lipoprotein cholesterol <100 mg/dL (50.2% vs 41.2%), and urine albumin-to-creatinine ratio <30 mg/g (87.8% vs 85.6%) compared with T2D. However, only 24.8% of individuals with T1D (52.1% with T2D) had HbA_{1c} <7%. All 6 risk factors were controlled in only 2.9% with T1D and 1.8% with T2D.

Over a median follow-up of 13.7 years (Q1–Q3: 12.8–14.5 years), individuals with T1D had greater risk of the composite cardiorenal outcome (aHR: 1.28; 95% CI: 1.14–1.43; $P < 0.001$) compared with T2D (Figure 1A). This finding appeared to be driven by ASCVD (aHR: 1.34; 95% CI: 1.16–1.55; $P < 0.001$) and all-cause death (aHR: 1.22; 95% CI: 1.02–1.45; $P = 0.026$). Covariate-adjusted risks of HF and CKD were similar between T1D and T2D.

For both T1D and T2D, higher HbA_{1c} at baseline was associated with a higher rate of cardiorenal outcomes and all-cause death. However, higher HbA_{1c} levels were more steeply associated with the rate of the composite cardiorenal outcome, ASCVD, and CKD, but not HF, in participants with T1D compared with T2D (Figure 1B).

DISCUSSION

In this population-based prospective cohort study, we found that middle-aged and older adults with T1D experienced higher risk of cardiorenal events or death compared with T2D, despite younger age and greater baseline risk factor control. However, risk factor control was limited in both T1D and T2D, and worse glycemic control was more steeply associated with cardiorenal events in T1D compared with T2D. Taken together, these findings highlight the importance of efforts targeting comprehensive risk factor control across the lifespan, especially in T1D populations. Novel pharmacotherapeutic and other disease management approaches may also be needed.

These findings support and extend those from a prior population-based analysis from Norway and Sweden, which identified higher rates of ASCVD, HF, and CKD in T1D

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compared with T2D.[5] We did not observe evidence of between-group differences in incident HF and kidney events, which may relate to differences in population characteristics, study design, and/or statistical power. Notably, participants with T1D in this analysis were >10 years older, on average, than those from Norway and Sweden. Further, data regarding important clinical, socioeconomic, and lifestyle risk factors—all explicitly considered herein—were unavailable in the aforementioned analysis.[5] Whereas these differences enabled a more rigorous assessment of this target population for which data are especially lacking, some between-group differences may have been attenuated.

Key limitations of this analysis should be highlighted. First, healthy volunteer bias in the UK Biobank may have produced underestimation of the prevalence and impact of T1D and T2D. Second, there is potential for misclassification of exposures and outcomes. Third, HbA_{1c} was not systematically collected during follow-up. Fourth, whether these findings are generalizable to more diverse populations, lower-income countries, and other global regions is uncertain.

CONCLUSIONS

Despite younger age and greater risk factor control, middle-aged and older adults with T1D in the UK Biobank experienced higher rates of cardiorenal events and death compared with T2D. These findings emphasize the need for novel strategies targeting cardiorenal health in this high-risk and growing population with unique clinical challenges.

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UK Biobank data are available by application (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

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What is the clinical question being addressed?

How do cardiorenal outcomes compare between middle-aged and older adults with T1D and T2D?

What is the main finding?

Despite greater risk factor control, middle-aged and older adults with T1D vs T2D had higher risk of cardiorenal outcomes or death.

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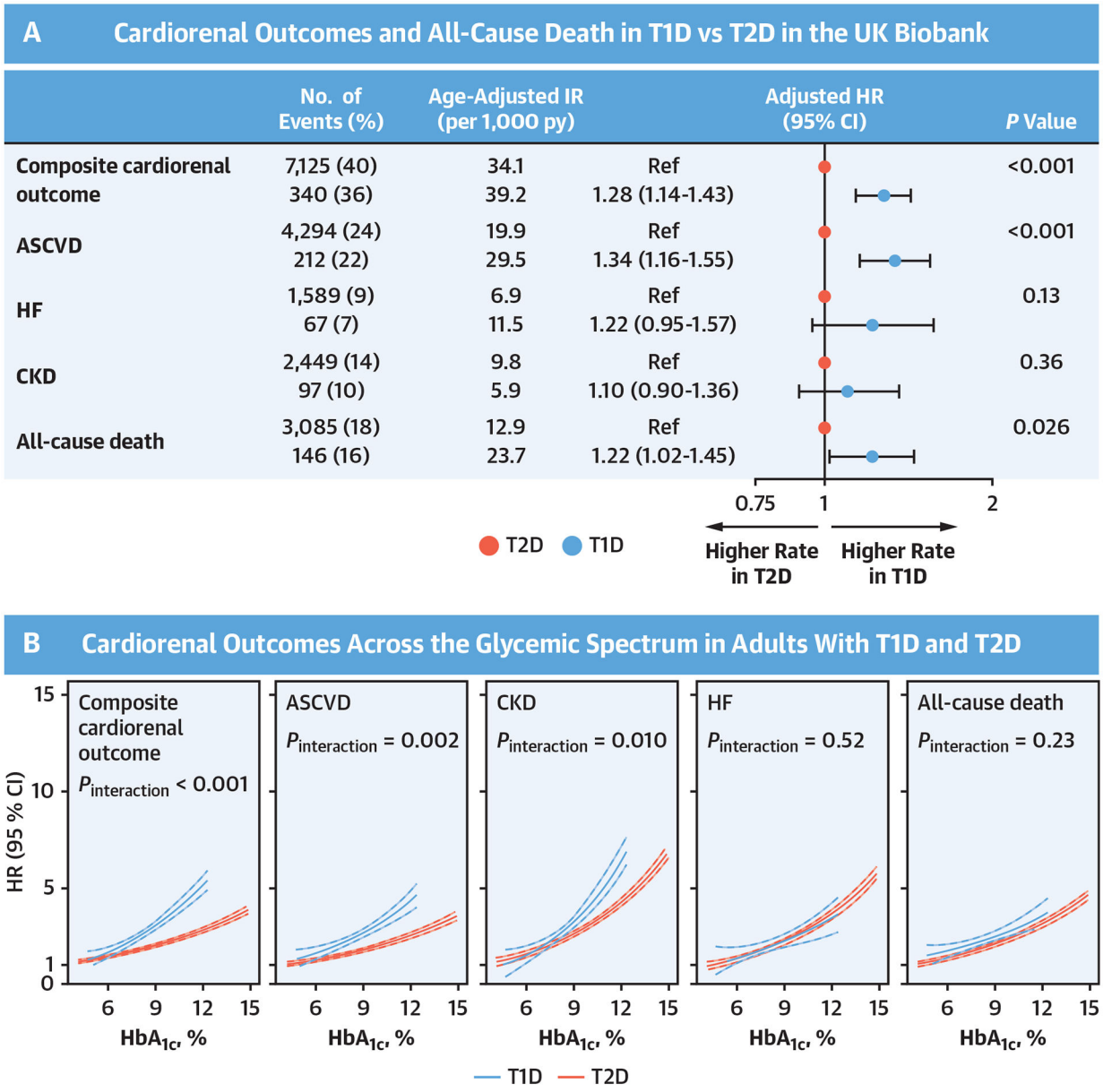

FIGURE 1.

Cardiorenal Outcomes Among Middle-Aged and Older Adults With T1D vs T2D in the UK Biobank

(A) Forest plot comparing covariate-adjusted HR and 95% CI of the composite cardiorenal outcomes and its individual components between type 1 diabetes (T1D) and type 2 diabetes (T2D). (B) Splines showing the covariate-adjusted HR and 95% CI of the composite cardiorenal outcomes and its individual components among participants with T1D and T2D by baseline glycated hemoglobin (HbA_{1c}), with normoglycemia as the reference group. *P* values in B refer to comparison of the HbA_{1c}-outcome relationship by diabetes type. Incidence rates were based on Kaplan-Meier estimation. Models were adjusted for sex, age, self-reported race and ethnicity, Townsend Deprivation Index, smoking status, alcohol consumption, diet composition, history of cancer, systolic blood

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pressure, antihypertensive prescription, non–high-density lipoprotein cholesterol, lipid-lowering medication prescription, high-sensitivity C-reactive protein, and urinary albumin-to-creatinine ratio. T1D was defined as International Classification of Diseases code for T1D or self-reported diagnosis of diabetes with T1D at first diagnosis date and insulin initiation without 1 year of diagnosis and insulin use at enrollment. T2D was defined as International Classification of Diseases code for T2D or self-reported diagnosis of diabetes with T2D at first diagnosis date or HbA_{1c} ≥6.5% or insulin use at enrollment or use of oral glucose-lowering therapy, excluding metformin, at enrollment. Normoglycemia defined as HbA_{1c} <5.7% among those without T1D or T2D. ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HF = heart failure; IR = incidence rate; py = patient-years; Ref = reference.