

# Life expectancy associated with different ages at diagnosis of type 2 diabetes in high-income countries: 23 million person-years of observation



Emerging Risk Factors Collaboration\*



## Summary

**Background** The prevalence of type 2 diabetes is increasing rapidly, particularly among younger age groups. Estimates suggest that people with diabetes die, on average, 6 years earlier than people without diabetes. We aimed to provide reliable estimates of the associations between age at diagnosis of diabetes and all-cause mortality, cause-specific mortality, and reductions in life expectancy.

**Methods** For this observational study, we conducted a combined analysis of individual-participant data from 19 high-income countries using two large-scale data sources: the Emerging Risk Factors Collaboration (96 cohorts, median baseline years 1961–2007, median latest follow-up years 1980–2013) and the UK Biobank (median baseline year 2006, median latest follow-up year 2020). We calculated age-adjusted and sex-adjusted hazard ratios (HRs) for all-cause mortality according to age at diagnosis of diabetes using data from 1515718 participants, in whom deaths were recorded during 23·1 million person-years of follow-up. We estimated cumulative survival by applying age-specific HRs to age-specific death rates from 2015 for the USA and the EU.

**Findings** For participants with diabetes, we observed a linear dose–response association between earlier age at diagnosis and higher risk of all-cause mortality compared with participants without diabetes. HRs were 2·69 (95% CI 2·43–2·97) when diagnosed at 30–39 years, 2·26 (2·08–2·45) at 40–49 years, 1·84 (1·72–1·97) at 50–59 years, 1·57 (1·47–1·67) at 60–69 years, and 1·39 (1·29–1·51) at 70 years and older. HRs per decade of earlier diagnosis were similar for men and women. Using death rates from the USA, a 50-year-old individual with diabetes died on average 14 years earlier when diagnosed aged 30 years, 10 years earlier when diagnosed aged 40 years, or 6 years earlier when diagnosed aged 50 years than an individual without diabetes. Using EU death rates, the corresponding estimates were 13, 9, or 5 years earlier.

**Interpretation** Every decade of earlier diagnosis of diabetes was associated with about 3–4 years of lower life expectancy, highlighting the need to develop and implement interventions that prevent or delay the onset of diabetes and to intensify the treatment of risk factors among young adults diagnosed with diabetes.

**Funding** British Heart Foundation, Medical Research Council, National Institute for Health and Care Research, and Health Data Research UK.

**Crown Copyright** © 2023 Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

## Introduction

The prevalence of type 2 diabetes is increasing globally, driven mainly by behavioural and societal factors related to obesity, nutrition, and physical activity.<sup>1–3</sup> In 2021, 537 million adults were estimated to have diabetes worldwide, with increasing numbers diagnosed at younger ages.<sup>3,4</sup>

Previous estimates have suggested that adults with type 2 diabetes die, on average, 6 years earlier than their counterparts without diabetes.<sup>5–7</sup> However, how this average reduction in life expectancy varies according to age at diagnosis is uncertain.<sup>8–19</sup> Valid characterisation of this association requires prospective comparison of outcomes within the same cohorts of people with diabetes diagnosed at varying ages. However, few population cohorts have had sufficient statistical power, detail, and duration of follow-up to enable reliable estimation.<sup>20–25</sup> Moreover, previous modelling studies—which used

state-transition models and life tables that rely on inputs from aggregated data—have considered diabetes only as a binary condition (ie, absent or present) when estimating its effect on life expectancy.<sup>7,26–29</sup> Few published studies have therefore directly analysed the association of age at diagnosis of diabetes with mortality and life expectancy.<sup>17,18,25</sup>

We aimed to provide reliable estimates of the associations of age at diagnosis of diabetes with all-cause mortality, cause-specific mortality, and reductions in life expectancy in high-income countries. We analysed individual records from 97 long-term, prospective cohorts, involving 1515718 participants followed up for a total of 23·1 million person-years.

## Methods

### Study design, data sources, and participants

We conducted a combined analysis of individual-participant data from two large-scale data sources,

*Lancet Diabetes Endocrinol*

2023; 11: 731–42

Published Online

September 11, 2023

[https://doi.org/10.1016/S2213-8587\(23\)00223-1](https://doi.org/10.1016/S2213-8587(23)00223-1)

See [Comment](#) page 709

\*Members of the writing committee are listed at the end of the Article and a full list of investigators is provided in the appendix (p 34).

Correspondence to:

Prof Emanuele Di Angelantonio, Department of Public Health and Primary Care, University of Cambridge, Cambridge CB1 8RN, UK  
ed303@medschl.cam.ac.uk

See Online for appendix

### Research in context

#### Evidence before this study

We searched MEDLINE for records published in English from database inception to Nov 30, 2022, that reported on associations of age at diagnosis or duration of diabetes with all-cause mortality and years of life lost according to age at diagnosis. Search terms related to exposure (diabetes, diabetes mellitus, age at diagnosis, age of onset, duration), outcomes (mortality, death, life expectancy, survival), study design (cohort studies, cohort, prospective) and association measures (relative risk, hazard ratio, risk ratio, rate ratio). Only a few studies have analysed these associations directly or had sufficient statistical power, detail, and duration of follow-up to enable reliable estimation. Findings generally showed higher mortality risk with younger age at diagnosis of type 2 diabetes, but interpretation was limited by different categorisations used.

#### Added value of this study

We used information from large-scale data sources covering 19 high-income countries and containing individual records on 1 515 718 participants, in whom deaths were recorded during 23·1 million person-years of follow-up. We calculated age-adjusted and sex-adjusted hazard ratios for all-cause mortality according to age at diagnosis of type 2 diabetes and estimated

cumulative survival by applying the age-specific estimates to contemporary age-specific death rates. We found a steep linear dose-response association between earlier age at diagnosis of diabetes and higher risk of all-cause mortality. Our public health modelling suggested that, for individuals surviving to age 50 years, those with diabetes diagnosed aged 30 years died 14 years earlier, those diagnosed aged 40 years died 10 years earlier, and those diagnosed aged 50 years died 6 years earlier, on average, than individuals without diabetes—in other words, every decade of earlier diagnosis of type 2 diabetes was associated with about 3–4 years of reduced life expectancy. Our study provides reliable estimates of the associations of age at diagnosis of diabetes with all-cause mortality in high-income countries.

#### Implications of all the available evidence

Because earlier diagnosis of type 2 diabetes is associated with shorter life expectancy, high priority should be given to developing and implementing interventions that prevent or delay the onset of the condition, especially as its prevalence among younger age groups is increasing globally. The evidence also highlights the need for intensive treatment of risk factors for premature mortality among young adults diagnosed with diabetes.

each constituting prospective population cohort studies with information on age at diagnosis of diabetes (appendix pp 2–3, 24). The first data source, the Emerging Risk Factors Collaboration (ERFC), is a collaboration of prospective cohort studies with information about various risk factors, cardiovascular disease outcomes, and mortality.<sup>30</sup> Prospective cohort studies contributing to the ERFC were included in this analysis if they met all the following criteria: had recruited participants on the basis of informed consent; did not select participants on the basis of having previous chronic disease (including cardiovascular disease and diabetes); had recorded information on diabetes status and age at diagnosis of diabetes; had recorded cause-specific deaths; and had accrued more than 1 year of follow-up. The second data source was the UK Biobank, a single, large prospective study in which participants were recruited from 22 centres throughout the UK.<sup>31</sup> After giving consent, participants provided biological samples and completed a touch-screen questionnaire, a computer-assisted interview, and a physical examination (appendix p 26). Data from participants in the UK Biobank have been linked with death records of the UK Office for National Statistics through National Health Service identification numbers. For all studies, written informed consent was obtained from participants and approval was obtained from relevant ethics committees.

We ascertained baseline diabetes status on the basis of self-report information, medical records, medication usage, or a combination of these factors (appendix

p 4).<sup>5,32</sup> To calculate age at diagnosis of diabetes, we used information recorded at the baseline enrolment survey in prospective cohort studies, supplemented, when available, by information on new-onset incident type 2 diabetes recorded during follow-up (appendix p 27). For 37 513 (79·1%) of 47 404 new-onset incident cases, age at diagnosis of diabetes was calculated using the date of diagnosis provided by the contributing cohorts. For the remaining 9891 (20·9%) new-onset incident cases, for which information was provided as diabetes status (yes or no) at date-stamped resurveys, we estimated the age at diagnosis as the participant's age at the midpoint of the two consecutive surveys between which the participant developed diabetes (appendix pp 2–3). We also computed an accuracy indicator as the half-width of the time interval between the two surveys, and the average was 2·4 years (SD 0·9; appendix pp 2–3).

We classified mortality according to the primary cause (or, in its absence, the underlying cause) on the basis of coding from the International Classification of Diseases (revisions 8–10) to at least three digits, or according to study-specific classification systems. Classification of deaths was based on death certificates, supplemented in 76 studies by medical records, findings on autopsy, and other sources in the ERFC. The date of the latest mortality follow-up was Dec 31, 2015, in the ERFC and Nov 30, 2020, in the UK Biobank.

#### Statistical analysis

To be eligible for the analysis, recorded information about participants' age, sex, and history of diabetes was required.

To focus the analysis on individuals with type 2 diabetes, we excluded 3695 participants who were diagnosed with diabetes at younger than 30 years and therefore would be more likely to have type 1 diabetes. To assess dose–response relationships, we categorised participants according to their history of diabetes (yes or no) and their age at diagnosis in 10-year groups: 30 years to less than 40 years, 40 years to less than 50 years, 50 years to less than 60 years, 60 years to less than 70 years, and 70 years or older. We also assessed the continuous shape of associations using fractional polynomials, then calculated adjusted associations, guided by the dose–response analyses results and previous evidence for other continuous covariates. The primary outcome was all-cause mortality, with additional outcomes of deaths from cardiovascular disease, cancer, and causes other than cardiovascular disease or cancer (defined as other causes; appendix pp 5–6). Hazard ratios (HRs) for age at diagnosis of diabetes were calculated separately within each study using time-dependent Cox proportional hazards regression models (ie, allowing diabetes status, age at diagnosis, and other covariates to change during follow-up, when reassessed). The timescale for the survival analysis was duration (in years) since entry to the study at baseline. Participants were included in analyses of mortality outcomes irrespective of previous non-fatal events. For each specific cause of death, participants' data were censored if a participant was lost to follow-up, died from another cause, or reached the end of the follow-up period. HRs calculated in this manner for each cause of death are aetiologically interpretable and provide reliable assessments of the marginal cause-specific associations—including in the case of competing risks with low to moderate correlations of failure times—that would be typical of most practical circumstances.<sup>33–35</sup> Sensitivity analyses were conducted for cause-specific mortality considering death from causes other than the specified cause as competing risks using the Fine-Gray regression model. Study-specific estimates (ie, log HRs) were then pooled across studies by multivariate random-effects meta-analysis, because heterogeneity was expected as a result of analysing diverse data sources.<sup>36</sup> To avoid model overfitting, studies with fewer than ten deaths for any outcome (ie, all-cause and cause-specific death) were excluded from the main analyses for relevant outcomes. Further sensitivity analyses excluded studies with fewer than 80 deaths (ie, applying a stricter ten events per variable rule at the study level). The proportional hazards assumption, assessed by meta-analysis of study-specific interaction of the coded exposure variable (indicators or continuous) and the survival analysis time in years, was met ( $p > 0.05$ ).

Because the principal objective of our study was to estimate reductions in life expectancy according to age at diagnosis of diabetes, for our main analysis we calculated HRs stratified by sex and adjusted for age only. A secondary objective was to explore the extent to which the age-specific

relevance of diabetes could be related to other known factors associated with mortality risk. HRs were therefore sequentially adjusted for several variables mostly recorded after the diagnosis of diabetes: smoking status, BMI, systolic blood pressure, total cholesterol, measures of glycaemia, measures of renal function, measures of inflammation, level of education, and self-reported use of medications. These variables were selected considering subject matter knowledge and data availability. The order of sequential adjustment reflected prioritisation of a variable as a confounder, mediator, or indicator of severity of diabetes, consistent with principles of the modified disjunctive cause criterion reasoning.<sup>37</sup> We investigated effect modification using tests for interaction for individual characteristics (age, sex, smoking, and history of cardiovascular disease) and by meta-regression of study-specific log HRs (ie, outcome) on study-level characteristics (diabetes diagnosis information available, median year of baseline, and median year of follow up) assuming normal error terms<sup>36</sup> and using a 0.001 significance threshold to make some allowance for multiple testing (ie, 0.01/7 for seven interactions assessed at 0.01 nominal significance each). Between-study heterogeneity of log HRs was assessed by the  $I^2$  statistic.<sup>38</sup>

Details of the methods used to estimate reductions in life expectancy by age at diagnosis of diabetes are provided in the appendix (p 28). In brief, estimates of cumulative survival from age 40 years onwards according to age at diagnosis of diabetes were calculated by applying the HRs for cause-specific mortality (specific to age at risk and sex) to respective mortality rates obtained from the detailed mortality component of the US Centers for Disease Control and Prevention's CDC WONDER database,<sup>39</sup> which recorded 2.7 million deaths among more than 320 million individuals during 2015.<sup>9,13</sup> This method does not rely on the survival estimates from the cohort data; instead, it makes inferences by estimating age-at-risk specific HRs from the cohort data, which are then combined with external population age-specific mortality rates.<sup>11</sup> Supplementary analyses used EU death rates for 2015. We calculated two-sided  $p$  values and used a significance level of  $p < 0.05$  unless stated otherwise. Analyses were done using Stata (version 15.1).

#### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

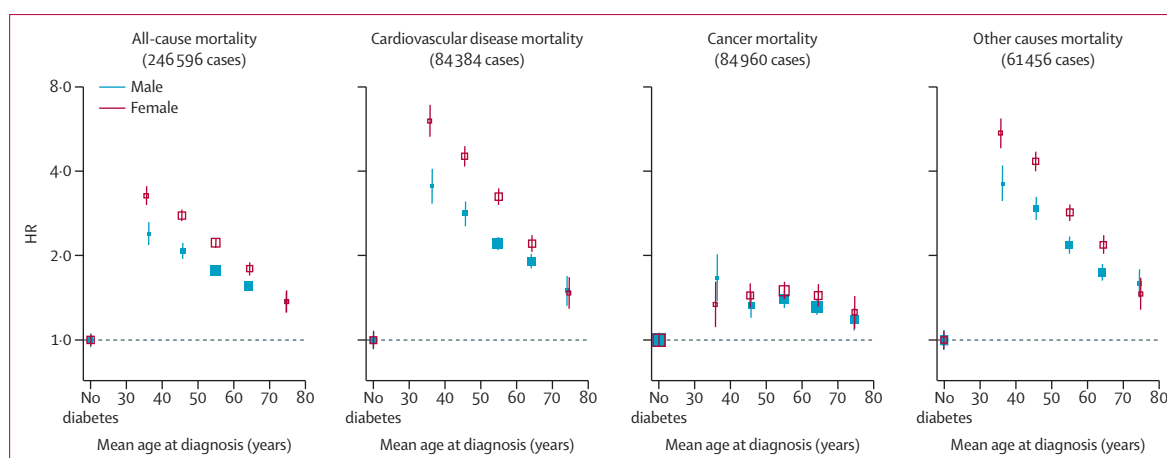
#### Results

Sufficient information for inclusion was available for 1515718 participants from 97 prospective cohorts, comprising 1017695 participants from 96 ERFC cohorts and 498023 participants from the UK Biobank (table 1, appendix pp 2–3). For participants from the ERFC, the median year of recruitment was 1990 (range 1961–2007) and the median year of latest follow-up was 2015

	N	All participants	Participants without diabetes	Participants with diabetes, age at diagnosis*				
				30 to <40 years	40 to <50 years	50 to <60 years	60 to <70 years	≥70 years
<b>ERFC</b>								
Total number of participants	1017 695	1017 695 (100.0%)	948 775 (93.2%)	3253 (0.3%)	8763 (0.9%)	18 605 (1.8%)	21 527 (2.1%)	16 772 (1.6%)
Prevalent diabetes	1017 695	23 335 (2.3%)	..	2835 (87.2%)	5602 (63.9%)	7047 (37.9%)	5632 (26.2%)	2219 (13.2%)
Incident diabetes	1017 695	45 585 (4.5%)	..	418 (12.8%)	3161 (36.1%)	11 558 (62.1%)	15 895 (73.8%)	14 553 (86.8%)
Age at baseline, years	1017 695	54.6 (9.7)	54.4 (9.8)	49.4 (8.0)	51.0 (7.4)	55.5 (6.8)	60.6 (6.0)	67.6 (4.9)
Male sex	1017 695	463 920 (45.6%)	436 576 (46.0%)	1187 (36.5%)	4150 (47.4%)	8246 (44.3%)	7796 (36.2%)	5965 (35.6%)
Female sex	1017 695	553 775 (54.4%)	512 199 (54.0%)	2066 (63.5%)	4613 (52.6%)	10 359 (55.7%)	13 731 (63.8%)	10 807 (64.4%)
Current smoker	945 856	267 678 (28.3%)	252 507 (28.7%)	914 (28.9%)	2583 (30.6%)	4763 (26.6%)	4422 (21.1%)	2489 (15.3%)
Systolic blood pressure, mm Hg	753 256	135 (19)	134 (19)	135 (19)	138 (19)	142 (19)	143 (19)	146 (20)
BMI, kg/m <sup>2</sup>	890 293	26.0 (4.3)	25.8 (4.1)	27.9 (6.0)	28.6 (5.7)	28.9 (5.5)	28.5 (5.2)	27.8 (4.7)
Total cholesterol concentration, mmol/l	594 679	5.80 (1.11)	5.79 (1.11)	5.55 (1.15)	5.69 (1.15)	5.86 (1.12)	5.87 (1.14)	5.93 (1.15)
Random glucose concentration, mmol/l	398 521	5.39 (1.23)	5.25 (0.87)	8.20 (4.04)	7.98 (3.58)	7.51 (2.96)	6.94 (2.57)	6.42 (2.31)
Fasting glucose concentration, mmol/l	196 159	5.30 (1.09)	5.15 (0.64)	7.88 (3.77)	7.27 (3.38)	6.94 (2.66)	6.48 (2.03)	5.93 (1.33)
HbA <sub>1c</sub> , %	96 802	5.42 (0.79)	5.25 (0.48)	7.37 (1.89)	7.14 (1.79)	6.71 (1.59)	6.30 (1.22)	6.07 (0.95)
History of cardiovascular disease	1 017 695	73 091 (7.2%)	63 734 (6.7%)	422 (13.0%)	1097 (12.5%)	2256 (12.1%)	2820 (13.1%)	2762 (16.5%)
Medication use†	614 036	84 056 (13.7%)	66 186 (11.6%)	1060 (52.8%)	2610 (47.3%)	4777 (41.5%)	5261 (37.8%)	4162 (32.9%)
Vocational or university education level	389 924	99 850 (25.6%)	94 710 (25.9%)	313 (23.4%)	775 (23.2%)	1578 (22.8%)	1583 (21.4%)	891 (15.8%)
Non-White ethnic group	534 131	71 348 (13.4%)	61 154 (12.4%)	617 (35.0%)	1781 (32.8%)	3378 (30.5%)	2817 (22.1%)	1601 (15.3%)
<b>UK Biobank</b>								
Number of participants	498 023	498 023 (100.0%)	471 223 (94.6%)	1550 (0.3%)	5859 (1.2%)	11 041 (2.2%)	7406 (1.5%)	944 (0.2%)
Prevalent diabetes	498 023	24 981 (5.0%)	..	1550 (100.0%)	5810 (99.2%)	10 798 (97.8%)	6818 (92.1%)	5 (0.5%)
Incident diabetes	498 023	1819 (0.4%)	..	0	49 (0.8%)	243 (2.2%)	588 (7.9%)	939 (99.5%)
Age at baseline, years	498 023	57.0 (8.1)	56.8 (8.1)	52.8 (8.5)	54.0 (7.1)	60.8 (4.9)	65.4 (4.3)	62.0 (5.3)
Male sex	498 023	226 676 (45.5%)	210 224 (44.6%)	882 (56.9%)	3560 (60.8%)	6889 (62.4%)	4508 (60.9%)	613 (64.9%)
Female sex	498 023	271 347 (54.5%)	260 999 (55.4%)	668 (43.1%)	2299 (39.2%)	4152 (37.6%)	2898 (39.1%)	331 (35.1%)
Current smoker	497 789	52 494 (10.5%)	49 497 (10.5%)	243 (15.7%)	815 (14.0%)	1193 (10.8%)	665 (9.0%)	81 (8.6%)
Systolic blood pressure, mm Hg	497 112	138 (19)	137 (19)	137 (17)	138 (17)	141 (17)	144 (17)	145 (18)
BMI, kg/m <sup>2</sup>	495 426	27.5 (4.8)	27.2 (4.6)	31.3 (7.0)	32.1 (6.5)	31.7 (5.7)	30.8 (5.2)	30.3 (4.8)
Total cholesterol concentration, mmol/l	465 833	5.70 (1.14)	5.76 (1.11)	4.53 (1.10)	4.53 (1.09)	4.52 (1.05)	4.63 (1.09)	5.60 (1.16)
Random glucose concentration, mmol/l	426 110	5.10 (1.19)	4.97 (0.78)	8.93 (4.54)	7.92 (3.85)	7.35 (3.07)	6.67 (2.53)	5.66 (1.75)
Fasting glucose concentration, mmol/l	17 712	5.15 (1.12)	5.04 (0.70)	7.42 (4.23)	7.38 (3.59)	7.00 (2.99)	6.23 (2.28)	5.29 (0.81)
HbA <sub>1c</sub> , %	462 791	4.88 (0.89)	4.76 (0.61)	8.20 (2.27)	7.37 (2.20)	6.98 (1.76)	6.53 (1.53)	5.66 (1.20)
History of cardiovascular disease	498 023	69 693 (14.0%)	62 346 (13.2%)	363 (23.4%)	1316 (22.5%)	3122 (28.3%)	2344 (31.7%)	202 (21.4%)
Medication use†	490 758	135 849 (27.7%)	113 681 (24.5%)	1364 (90.0%)	4707 (82.3%)	9453 (87.1%)	6173 (84.8%)	471 (51.1%)
Vocational or university education level	494 242	298 113 (60.3%)	284 262 (60.7%)	875 (58.3%)	3237 (56.7%)	5811 (53.7%)	3362 (46.0%)	566 (60.1%)
Non-White ethnic group	496 231	26 390 (5.3%)	23 052 (4.9%)	363 (23.6%)	1167 (20.1%)	1234 (11.3%)	522 (7.1%)	52 (5.5%)

Data are n (%) or mean (SD). Differences in characteristics across categories of age at diagnosis of diabetes were all statistically significant (p<0.001 adjusted for age and sex) based on Wald tests. ERFC=Emerging Risk Factors Collaboration. \*Includes people with a history of diabetes at the baseline survey (prevalent diabetes) and people with diabetes diagnosed during follow-up (incident diabetes). †Includes use of lipid-lowering, antihypertensive, or antidiabetic medication at baseline.

**Table 1: Baseline characteristics of participants**



**Figure 1: Sex-specific HRs for all-cause and cause-specific mortality according to age at diagnosis of type 2 diabetes**

The mean age at diagnosis for the categories 30 to <40 years, 40 to <50 years, 50 to <60 years, 60 to <70 years and  $\geq 70$  years is plotted on the x axis. HRs are adjusted for age, and the reference (1.0) is people without diabetes. Studies with fewer than ten events of any outcome were excluded from the analysis of that outcome.

The sizes of the boxes are proportional to the inverse of the variance of the log-transformed HRs. Vertical lines represent 95% CIs. HR=hazard ratio.

(range 1980–2013); the corresponding values for the UK Biobank were 2009 and 2020. In the ERFC, most participants were enrolled in Europe (52.0%) or the USA and Canada (39.8%). Overall, the mean age of participants at baseline was 55.0 years (SD 9.2); 690 596 participants (45.6%) were male and 825 122 (54.4%) were female. In the ERFC, the age at diagnosis was available for 23 335 (56.7%) of 41 160 participants who had prevalent diabetes at baseline, and a further 45 585 participants were diagnosed with diabetes during follow-up (ie, new-onset disease). In the UK Biobank, the age at diagnosis was available for 24 981 (98.3%) of 25 416 participants who had prevalent diabetes, and a further 1819 participants were diagnosed with diabetes during follow-up. The mean age at diagnosis was 54.1 years (SD 9.0) for participants with prevalent diabetes and 64.9 years (8.5) for those with incident diabetes. Over a median follow-up of 12.5 years (5–95th percentiles 5.0–32.1; 23.1 million person-years at risk), 246 670 deaths were recorded, of which 84 443 were due to cardiovascular causes, 150 972 due to non-cardiovascular causes, and 11 255 due to unknown or ill-defined causes. The non-cardiovascular causes could be further categorised into 85 014 due to cancer and 61 516 due to causes other than cardiovascular disease or cancer (hereafter termed other causes; mainly diseases of the respiratory system or nervous system, infections, and external causes); the remaining 4442 deaths in this category had been coded as non-cardiovascular causes without the possibility of further subdivision (appendix p 5).

In analyses adjusted for age, we observed a linear dose-response association between earlier age at diagnosis of diabetes and higher risk of all-cause mortality, mortality due to cardiovascular disease, and mortality from other causes for each sex (figure 1). Findings were broadly similar in combined analyses adjusted for sex and continuous modelling with fractional polynomials

(appendix p 13). In further adjusted analyses, we used data from 92 cohorts and 1 132 277 participants with complete information on age at diagnosis of diabetes, age, sex, smoking status, BMI, systolic blood pressure, and total cholesterol. Compared with participants without a history of diabetes, HRs for all-cause mortality, adjusted for age and sex only, were 2.69 (95% CI 2.43–2.97) for those diagnosed at age 30–39 years, 2.26 (2.08–2.45) at age 40–49 years, 1.84 (1.72–1.97) at age 50–59 years, 1.57 (1.47–1.67) at age 60–69 years, and 1.39 (1.29–1.51) for those diagnosed aged 70 years and older (table 2). For participants diagnosed with diabetes aged 30–39 years, HRs were 4.20 (3.57–4.94) for vascular mortality, 1.55 (1.30–1.85) for cancer mortality, and 3.99 (3.50–4.55) for mortality from other causes. Across all ages, HRs per decade of earlier diagnosis of diabetes were 1.14 (1.08–1.19) for all-cause mortality, 1.19 (1.11–1.27) for vascular mortality, 0.95 (0.88–1.02) for cancer mortality, and 1.18 (1.10–1.27) for mortality from other causes (table 2).

HRs for all-cause mortality changed little after additional adjustment for other risk factors (BMI, systolic blood pressure, and total cholesterol; table 2). However, HRs were attenuated substantially after further adjustment for measures of glycaemia (ie, fasting glucose or HbA<sub>1c</sub>), a pattern also observed for cause-specific mortality (appendix p 7). HRs showed little change after adjustment for measures of renal function (ie, estimated glomerular filtration rate), inflammation (ie, C-reactive protein), or lipids (ie, non-HDL cholesterol, HDL cholesterol, and triglycerides; appendix p 7).

Broadly similar HRs to those reported in the previous paragraphs were observed in sensitivity analyses that compared results by study-level information available on diabetes (prevalent disease, incident disease, or both) and by participant characteristics (age, sex, smoking status, and history of cardiovascular disease; appendix p 14). HRs



	Number of events	Adjusted HR (95% CI)		
		Age and sex	Age, sex, and smoking	Age, sex, smoking, and other risk factors*
<b>All-cause mortality</b>				
Participants without diabetes	153 068	1 (ref)	1 (ref)	1 (ref)
Diagnosed aged 30 to <40 years	676	2.69 (2.43–2.97)	2.74 (2.49–3.02)	2.64 (2.41–2.90)
Diagnosed aged 40 to <50 years	2070	2.26 (2.08–2.45)	2.33 (2.14–2.53)	2.24 (2.06–2.43)
Diagnosed aged 50 to <60 years	4197	1.84 (1.72–1.97)	1.87 (1.75–1.99)	1.79 (1.69–1.90)
Diagnosed aged 60 to <70 years	4125	1.57 (1.47–1.67)	1.60 (1.51–1.70)	1.55 (1.46–1.64)
Diagnosed aged ≥70 years	3026	1.39 (1.29–1.51)	1.43 (1.33–1.55)	1.41 (1.31–1.53)
Per decade earlier	167 162	1.14 (1.08–1.19)	1.13 (1.08–1.19)	1.13 (1.07–1.19)
p value†	..	<0.0001	<0.0001	<0.0001
I <sup>2</sup> (95% CI)	..	67 (59–74)	68 (60–74)	67 (60–74)
<b>Cardiovascular disease mortality</b>				
Participants without diabetes	53 857	1 (ref)	1 (ref)	1 (ref)
Diagnosed aged 30 to <40 years	278	4.20 (3.57–4.94)	4.26 (3.65–4.99)	3.93 (3.41–4.53)
Diagnosed aged 40 to <50 years	821	3.19 (2.80–3.64)	3.31 (2.90–3.76)	2.93 (2.60–3.30)
Diagnosed aged 50 to <60 years	1564	2.31 (2.10–2.53)	2.36 (2.16–2.58)	2.10 (1.94–2.27)
Diagnosed aged 60 to <70 years	1580	1.95 (1.78–2.14)	1.98 (1.82–2.17)	1.81 (1.67–1.97)
Diagnosed aged ≥70 years	1251	1.50 (1.35–1.67)	1.54 (1.38–1.71)	1.48 (1.33–1.65)
Per decade earlier	59 351	1.19 (1.11–1.27)	1.19 (1.11–1.27)	1.19 (1.11–1.28)
p value†	..	<0.0001	<0.0001	<0.0001
I <sup>2</sup> (95% CI)	..	58 (47–67)	59 (48–67)	59 (48–67)
<b>Cancer mortality</b>				
Participants without diabetes	53 217	1 (ref)	1 (ref)	1 (ref)
Diagnosed aged 30 to <40 years	124	1.55 (1.30–1.85)	1.56 (1.31–1.86)	1.48 (1.24–1.76)
Diagnosed aged 40 to <50 years	433	1.28 (1.16–1.42)	1.32 (1.19–1.45)	1.25 (1.13–1.37)
Diagnosed aged 50 to <60 years	1211	1.33 (1.22–1.46)	1.37 (1.25–1.49)	1.35 (1.26–1.44)
Diagnosed aged 60 to <70 years	1178	1.27 (1.17–1.38)	1.29 (1.19–1.40)	1.28 (1.19–1.37)
Diagnosed aged ≥70 years	593	1.29 (1.18–1.42)	1.32 (1.20–1.44)	1.31 (1.20–1.42)
Per decade earlier	56 756	0.95 (0.88–1.02)	0.95 (0.88–1.02)	0.94 (0.88–1.02)
p value†	..	0.18	0.16	0.13
I <sup>2</sup> (95% CI)	..	26 (2–44)	24 (0–43)	24 (0–43)
<b>Other causes mortality</b>				
Participants without diabetes	35 986	1 (ref)	1 (ref)	1 (ref)
Diagnosed aged 30 to <40 years	250	3.99 (3.50–4.55)	4.04 (3.54–4.60)	3.90 (3.42–4.45)
Diagnosed aged 40 to <50 years	701	3.24 (2.88–3.64)	3.34 (2.96–3.76)	3.31 (2.95–3.71)
Diagnosed aged 50 to <60 years	1224	2.31 (2.09–2.54)	2.37 (2.15–2.60)	2.38 (2.16–2.64)
Diagnosed aged 60 to <70 years	1137	1.84 (1.67–2.02)	1.87 (1.70–2.05)	1.88 (1.71–2.06)
Diagnosed aged ≥70 years	861	1.66 (1.48–1.87)	1.71 (1.52–1.93)	1.76 (1.56–1.98)
Per decade earlier	40 159	1.18 (1.10–1.27)	1.18 (1.09–1.27)	1.16 (1.08–1.25)
p value†	..	<0.0001	<0.0001	<0.0001
I <sup>2</sup> (95% CI)	..	50 (35–61)	51 (36–62)	50 (36–62)

Analyses based on data from the Emerging Risk Factors Collaboration and the UK Biobank, including 92 cohorts and 1 132 277 participants with complete information on age at diagnosis of diabetes, age, sex, smoking, and other risk factors. HR=hazard ratio. \*Other risk factors were BMI, systolic blood pressure, and total cholesterol. †p value for linear analyses per decade earlier.

**Table 2: Adjusted HRs for all-cause and cause-specific mortality according to age at diagnosis of type 2 diabetes**

differed slightly according to the study-level median year of the study enrolment or follow-up period (appendix pp 14–15) and by data source (ie, ERFC or UK Biobank;

appendix p 16). Tests for interactions on an additive scale were generally supportive of positive interactions of female sex, current smoking, older age, and history of cardiovascular disease with diabetes status categorised according to age at diagnosis (appendix p 8). Associations were also broadly similar in analyses that estimated HRs for all-cause and cause-specific mortality according to duration of diabetes (ie, time since diagnosis) rather than age at diagnosis (appendix pp 9–10, 17). Supplementary analyses of mortality from causes other than cardiovascular disease suggested broadly similar associations for cancer mortality components but notable variations in the magnitude of associations for components of mortality from other causes (appendix p 11)—eg, HRs per decade earlier diagnosis of diabetes were 1.46 (95% CI 1.16–1.84) for renal disease mortality, 1.28 (1.07–1.53) for infection-related mortality, 1.21 (1.04–1.42) for external causes of mortality, 1.20 (1.03–1.40) for digestive system disease mortality, and 1.07 (0.96–1.19) for respiratory system disease mortality. Results of cause-specific mortality were broadly similar when using competing risks-adjusted analyses (appendix p 12). Loss to follow-up was less than 10% in most studies, but the proportion of right-censored participants and cause-specific deaths varied between cohorts (appendix pp 18–19). Sensitivity analyses that excluded studies with fewer than 80 cause-specific deaths showed similar findings to the main analyses that excluded studies with fewer than ten deaths for any outcome (appendix p 12).

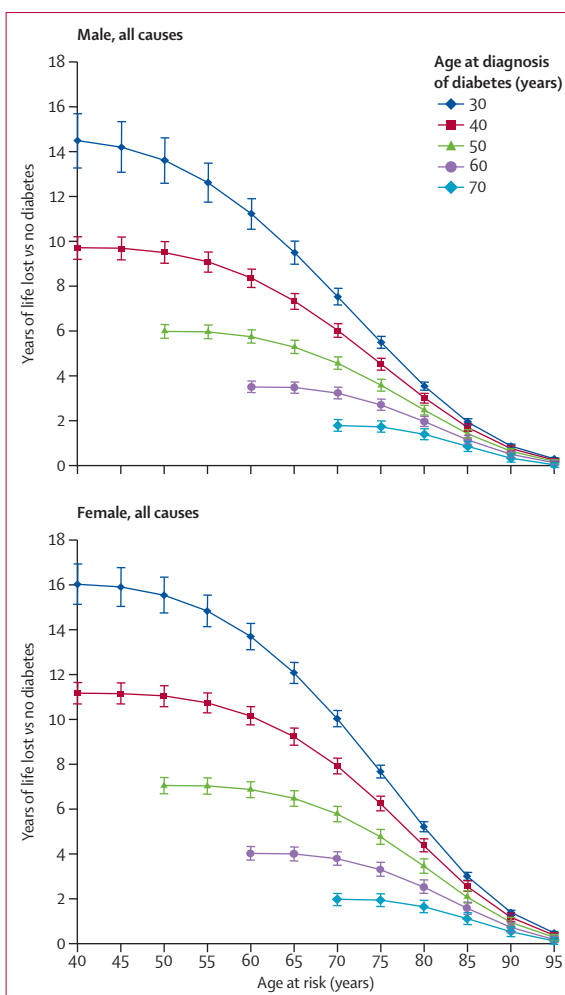
Compared with the absence of diabetes at different attained ages, earlier age at diagnosis of diabetes was associated with greater reductions in life expectancy, using 2015 death rates from the USA (figure 2). For example, at age 50 years, individuals who were diagnosed with diabetes aged 30 years died, on average, about 14 years earlier than individuals without diabetes; those diagnosed aged 40 years died around 10 years earlier, and those diagnosed aged 50 years died around 6 years earlier (figure 2). These estimates were slightly higher in women (16, 11, and 7 years) than in men (14, 9, and 5 years; figure 2). Depending on age and sex, deaths due to cardiovascular disease accounted for about 30–45% of the reduction in life expectancy associated with diabetes, with the remaining proportion being largely due to deaths from causes other than cardiovascular disease or cancer (appendix p 20). Findings were broadly similar in analyses using EU death rates from 2015, with corresponding estimates of death at around 13, 9, or 5 years earlier on average (appendix p 21). In supplementary analyses that included people diagnosed with diabetes before the age of 30 years, we found similar patterns in estimated reductions in life expectancy; the highest estimated reductions were in people diagnosed in the youngest age groups and were notably higher in women than in men (appendix pp 22–23). At age 50 years, the estimates corresponded to about 2–3 years reduction per decade of earlier diagnosis.

## Discussion

By analysing more than 23 million person-years of longitudinal data from population cohorts in 19 high-income countries, we found a steep linear dose–response association between earlier age at diagnosis of diabetes and higher risk of all-cause mortality. Overall, every decade of earlier diagnosis of diabetes was associated with about 3–4 years of reduced life expectancy. Our modelling has suggested that, for individuals surviving to age 50 years, those diagnosed with diabetes aged 30 years died 14 years earlier than individuals without diabetes, those diagnosed aged 40 years died 10 years earlier, and those diagnosed aged 50 years died 6 years earlier. The strongest associations with earlier age at diagnosis of diabetes were for vascular (eg, myocardial infarction and stroke) and other non-neoplastic causes of death—mainly respiratory, neurological, and infectious diseases and external causes. Our estimates show that the reduction in life expectancy associated with diabetes is slightly greater for women than for men. These findings suggest that high priority should be given to developing and implementing interventions that prevent or delay onset of diabetes, especially as the prevalence of diabetes among younger adults is increasing globally.<sup>3</sup>

Our observation of higher HRs for mortality with earlier age at diagnosis of diabetes suggests that the relative effect of diabetes is greatest at ages at which the underlying risk of mortality in the general population is lowest. Such effects have previously been observed for other cardiovascular risk factors, including blood pressure<sup>40</sup> and LDL-cholesterol.<sup>41</sup> Conversely, in older adults, in whom the underlying mortality risk is high, the proportional relevance of diabetes is smaller. Previous studies have suggested that individuals who develop type 2 diabetes at younger ages might have more aggressive phenotypes<sup>42</sup> (characterised by higher BMI, higher blood pressure, higher concentrations of proatherogenic lipids,<sup>43</sup> and faster deterioration in glycaemic control<sup>24,44</sup>) than individuals who develop diabetes at older ages, potentially leading to premature mortality.<sup>45</sup> Our findings are consistent with this hypothesis, suggesting that the large excess mortality associated with diabetes at younger ages could, in part, reflect cumulative exposure to worsened metabolic profiles. Furthermore, we observed substantial attenuation of excess mortality associated with diabetes after adjustment for glycaemic markers, suggesting that early detection of diabetes by screening and intensive glucose management are relevant to the prevention of long-term complications in adults with type 2 diabetes.<sup>46–48</sup>

Our study had several strengths and is distinctive and complementary to previous studies.<sup>7–19,26–29</sup> Our focus on age at diagnosis of diabetes avoided the inherent difficulties in defining age at onset of diabetes (which could require near continuous assessment of glycaemic status)<sup>49</sup> and in defining the duration of diabetes (which could be confounded by the timing of entry into, and



**Figure 2: Estimated years of life lost by age at diagnosis of type 2 diabetes compared with people without diabetes**

Estimates of cumulative survival from age 40 years onwards according to age at diagnosis of diabetes, calculated by applying hazard ratios (specific to age at risk) for all-cause mortality associated with age at diagnosis to 2015 US death rates at age 40 years or older.

the duration of participation in, prospective cohort studies). Furthermore, our study estimated age at diagnosis of diabetes using information from people diagnosed with prevalent diabetes and those diagnosed with incident diabetes. Our access to individual-participant data avoided the limitations of previous literature-based reviews, allowing extensive sensitivity analyses to assess potential sources of heterogeneity and interactions according to study-level and individual-level characteristics. Our estimation of reductions in life expectancy relied on age-specific HRs directly estimated from individual-level data and applied to contemporary population-specific mortality rates. This approach was desirable because HRs are often less variable across similar populations and time and can be more precisely estimated in combined data synthesis as in our study. The generalisability of the findings was

enhanced by inclusion of data from 97 prospective studies from 19 high-income countries recruited between 1961 and 2009, with latest follow-up between 1980 and 2020.

Our study also had potential limitations. The contributing prospective studies defined diabetes in varying ways; however, we found no major differences in results across studies due to such variation. Between-study heterogeneity of associations was moderate to high, and was not explained by the characteristics assessed in subgroup analyses. We did not have information on the pathophysiological subtype of diabetes; however, given that we excluded participants who were diagnosed with diabetes at younger than 30 years, inferring that the large majority of participants had type 2 diabetes could be reasonable.<sup>50</sup> We did not have information on whether individuals with diabetes were treated or followed-up differently depending on their age at diagnosis or duration of diabetes (eg, in terms of type of medication, dose or intensity of treatment)—such factors would be likely to affect long-term disease outcomes. Residual confounding due to measurement error in variables considered for adjustment (eg, smoking) has not been addressed. We also did not have information on other comorbidities (eg, mental health conditions) and socioeconomic variables that would have been useful to adjust for. Our analysis involved participants who were mostly of European continental ancestry; future studies should seek to evaluate these results in other ethnic and racial groups. Finally, although we found broadly similar results for cause-specific mortality using competing and non-competing adjusted models, the aetiological interpretation is limited for models adjusted for competing risk.<sup>51</sup> However, non-competing risk-adjusted models might be subject to selection bias, because HRs are calculated conditional on those who have survived.<sup>52</sup>

In conclusion, this study suggests that every decade of earlier diagnosis of diabetes is associated with about 3–4 years of lower life expectancy, highlighting the need to develop and implement interventions that prevent or delay the onset of diabetes and to intensify the treatment of risk factors among young adults diagnosed with diabetes.

#### Emerging Risk Factors Collaboration

Writing committee: Stephen Kaptoge, Luanluan Sun, Matthew Walker, Sarah Spackman, Lisa Pennells (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK and Victor Phillip Dahdaleh Heart and Lung Research Institute, University of Cambridge, Cambridge, UK), Sreenivasa Rao Kondapally Seshasai (Cardiovascular Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK), Thomas Bolton (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK and BHF Data Science Centre, Health Data Research UK, London, UK), Feven Ataklte (Department of Internal Medicine, Boston Medical Center and Boston University School of Medicine, Boston, MA, USA), Peter Willeit (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK and Clinical Epidemiology Team, Medical University of Innsbruck,

Innsbruck, Austria), Steven Bell (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK and Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK), Steven Burgess (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK, BHF Centre of Research Excellence, School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK, and Medical Research Council Biostatistics Unit, University of Cambridge, Cambridge, UK), Servet Altay (Department of Cardiology, Trakya University School of Medicine, Edirne, Turkey), Gerd Assmann (Assmann Foundation for Prevention, Münster, Germany), Yoav Ben-Shlomo (Population Health Sciences, University of Bristol, Bristol, UK), Lyle G Best (Missouri Breaks Industries Research, Eagle Butte, SD, USA), Cecilia Björkelund (Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden), Dan G Blazer (School of Medicine, Duke University, Durham, NC, USA), Hermann Brenner (Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany and Network Aging Research, Heidelberg University, Heidelberg, Germany), Eric J Brunner (Department of Epidemiology and Public Health, University College London, London, UK), Gilles R Dagenais (Quebec Heart and Lung Institute, Quebec, QC, Canada), Jackie A Cooper (William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University of London, London, UK), Cyrus Cooper (MRC Lifecourse Epidemiology Centre University of Southampton, Southampton, UK), Carlos J Crespo (Oregon Health and Science University and Portland State University Joint School of Public Health, Portland, OR, USA), Mary Cushman (Larner College of Medicine, The University of Vermont, Burlington, VT, USA), Ralph B D'Agostino Sr (Mathematics and Statistics Department, Boston University, Boston, MA, USA), Makoto Daimon (Global Center of Excellence Program Study Group, Yamagata University Faculty of Medicine, Yamagata, Japan and Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Aomori, Japan), Lori B Daniels (UCSD Division of Cardiovascular Medicine, Sulpizio Cardiovascular Center, La Jolla, CA, USA), Rachel Dankner (The Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer, Israel; School of Public Health, Department of Epidemiology and Preventive Medicine, Tel Aviv University, Tel Aviv, Israel; and The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY, USA), Karina W Davidson (The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY, USA), Renate T de Jong (Amsterdam University Medical Centers, VUMC, Amsterdam, Netherlands), Chiara Donfrancesco (Department of Cardiovascular, Endocrine-metabolic Diseases and Aging, Istituto Superiore di Sanità, Rome, Italy), Pierre Ducimetiere (Inserm - Université Paris Sud - CESP Villejuif, Paris, France), Petra J M Elders (Department of General Practice, Amsterdam UMC, Vrije Universiteit, Amsterdam Public Health Research Institute, Amsterdam, Netherlands), Gunnar Engström (Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden), Ian Ford (Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK), John Gallacher (Department of Psychiatry, University of Oxford, Oxford, UK), Stephan J L Bakker (Department of Internal Medicine, University Medical Centre Groningen, University of Groningen, Groningen, Netherlands), Uri Goldbourt (Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel), Agustín Gómez de la Cámara (12 Octubre Hospital Research Institute, Madrid, Spain), Sameline Grimsgaard (Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway), Vilmondur Gudnason (Faculty of Medicine, University of Iceland, Reykjavik, Iceland and Icelandic Heart Association, Kopavogur, Iceland), Per-Olof Hansson (Region Västra Götaland, Sahlgrenska University Hospital, Department of Medicine Geriatrics and Emergency Medicine/Östra, Gothenburg, Sweden and Institute of Medicine, Department of Molecular and Clinical Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden), Hironori Imano (Public Health, Osaka University Graduate School of Medicine, Suita, Japan), J Wouter Jukema (Department of Cardiology, Leiden University Medical



Center, Netherlands; Einthoven Laboratory for Experimental Vascular Medicine, LUMC, Leiden, Netherlands; and Netherlands Heart Institute, Utrecht, Netherlands), Christopher Kabrhel (Center for Vascular Emergencies, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA), Jussi Kauhanen (University of Eastern Finland, Kuopio, Finland), Maryam Kavousi (Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands), Stefan Kiechl (Department of Neurology, Medical University Innsbruck, Innsbruck, Austria), Matthew W Knuiman (School of Population and Global Health, The University of Western Australia, Crawley, WA, Australia), Daan Kromhout (Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands), Harlan M Krumholz (Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT, USA; Department of Health Policy and Management, Yale School of Public Health, New Haven, CT, USA; and Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA), Lewis H Kuller\* (Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA, USA), Tiina Laatikainen (National Institute for Health and Welfare, Helsinki, Finland), Debbie A Lawlor (MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK and Population Health Science, Bristol Medical School, University of Bristol, UK), Haakon E Meyer (Norwegian Institute of Public Health, Oslo, Norway), Kenneth Mukamal (Beth Israel Deaconess Medical Centre, Harvard Medical School, Harvard University, Boston, MA, USA), Paul J Nietert (Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA), Toshiharu Ninomiya (Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan), Dorothea Nitsch (Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK), Børge G Nordestgaard (Department of Clinical Biochemistry and the Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Denmark; The Copenhagen City Heart Study, Frederiksberg Hospital, Copenhagen University Hospital, Denmark; and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark), Luigi Palmieri (Department of Cardiovascular, Dysmetabolic and Ageing-Associated Diseases, Istituto Superiore di Sanità, Rome, Italy), Jackie F Price (Usher Institute, University of Edinburgh, Edinburgh, UK), Paul M Ridker, Qi Sun (Center Cardiovascular Disease Prevention, Division of Preventive Medicine and Division of Cardiovascular Diseases, Brigham and Women's Hospital, Harvard Medical School, Harvard University, Boston, MA, USA), Annika Rosengren (Sahlgrenska University Hospital, Gothenburg, Sweden and Östra Hospital, Gothenburg, Sweden), Ronan Roussel\* (Chef de Service Endocrinologie Diabétologie Nutrition, Département Hospitalo-Universitaire FIRE Groupe Hospitalier Bichat - Claude Bernard, Paris, France), Masaru Sakurai (Department of Social and Environmental Medicine, Kanazawa Medical University, Uchinada, Japan), Veikko Salomaa (National Institute for Health and Welfare, Helsinki, Finland), Ben Schöttker (Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany and Network Aging Research, University of Heidelberg, Heidelberg, Germany), Jonathan E Shaw (Clinical Diabetes and Epidemiology, Baker Heart and Diabetes Institute, Melbourne, VIC, Australia), Timo E Strandberg (University of Helsinki and Helsinki University Hospital, Helsinki, Finland and University of Oulu, Center for Life Course Health Research, Oulu, Finland), Johan Sundström (Department of Medical Sciences, Uppsala University, Uppsala, Sweden), Hanna Tolonen (Department of Public Health Solutions, National Institute for Health and Welfare (THL), Helsinki, Finland), Aage Tverdal (Norwegian Institute of Public Health, Centre for Fertility and Health, Oslo, Norway), WM Monique Verschuren (National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands), Henry Völzke (Universitätsmedizin Greifswald, Institut für Community Medicine, Abteilung SHIP/ Klinisch-Epidemiologische Forschung, Greifswald, Germany), Lynne Wagenknecht (Wake Forest School of Medicine, Wake Forest University, Winston-Salem, NC, USA), Robert B Wallace (College of Public Health, University of Iowa, Iowa, IA, USA), S Goya Wannamethee (Department of Primary Care and Population Health, University College London, London, UK), Nicholas J Wareham (MRC Epidemiology Unit, School of Clinical Medicine, University of Cambridge, Cambridge, UK), Sylvia Wassertheil-Smolter (Department of Epidemiology and Population Health, Albert Einstein College of Medicine, New York, NY, USA), Kazumasa Yamagishi (Department of Public Health Medicine, Faculty of Medicine and Health Services Research and Development Center, University of Tsukuba, Tsukuba, Japan), Bu B Yeap (Medical School, The University of Western Australia, Perth, WA, Australia and Department of Endocrinology and Diabetes, Fiona Stanley Hospital, Perth, WA, Australia), Seamus Harrison, Simon G Thompson (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK), Michael Inouye (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Victor Phillip Dahdaleh Heart and Lung Research Institute, University of Cambridge, Cambridge, UK; BHF Centre of Research Excellence, School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; Baker Heart and Diabetes Institute, Melbourne, VIC, Australia; Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Hinxton, UK; Cambridge Baker Systems Genomics Initiative, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; and Department of Clinical Pathology, University of Melbourne, Parkville, VIC, Australia), Simon Griffin (MRC Epidemiology Unit, School of Clinical Medicine, University of Cambridge, Cambridge, UK and Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK), Adam S Butterworth (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Victor Phillip Dahdaleh Heart and Lung Research Institute, University of Cambridge, Cambridge, UK; BHF Centre of Research Excellence, School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Hinxton, UK; and NIHR Blood and Transplant Research Unit in Donor Health and Behaviour, University of Cambridge, Cambridge, UK), Angela M Wood (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Victor Phillip Dahdaleh Heart and Lung Research Institute, University of Cambridge, Cambridge, UK; BHF Centre of Research Excellence, School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Hinxton, UK; NIHR Blood and Transplant Research Unit in Donor Health and Behaviour, University of Cambridge, Cambridge, UK; and Cambridge Centre for AI in Medicine, Cambridge, UK), Naveed Sattar† (Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK), John Danesh† (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Victor Phillip Dahdaleh Heart and Lung Research Institute, University of Cambridge, Cambridge, UK; BHF Centre of Research Excellence, School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; NIHR Blood and Transplant Research Unit in Donor Health and Behaviour, University of Cambridge, Cambridge, UK; Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Hinxton, UK; and Department of Human Genetics, Wellcome Sanger Institute, Hinxton, UK), Emanuele Di Angelantonio† (BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Victor Phillip Dahdaleh Heart and Lung Research Institute, University of Cambridge, Cambridge, UK; BHF Centre of Research Excellence, School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Hinxton, UK; NIHR Blood and Transplant Research Unit in Donor Health and Behaviour, University of Cambridge,

Cambridge, UK; and Health Data Science Centre, Human Technopole, Milan, Italy). \*Deceased †Joint senior authors

#### Contributors

SK, NS, JD, and EDA conceived and designed the study; all authors acquired and interpreted the data; SK and EDA performed the analyses and have access to all data in the study; SK, EDA, LS, NS, and JD drafted the manuscript, which was critically revised by all authors. SK and EDA verified the underlying data. All authors are responsible for the decision to submit the manuscript for publication.

#### Declaration of interests

ASB reports grants outside of this work from AstraZeneca, Bayer, Biogen, BioMarin, Merck, Novartis, and Sanofi. BGN reports consulting fees from AstraZeneca, Sanofi, Regeneron Pharmaceuticals, Ionis Pharmaceuticals, Amgen, Kowa Pharmaceuticals, Denka, Amarin, Novartis, Novo Nordisk, Esperion Therapeutics, Silence Therapeutics, and Ultragenyx; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Sanofi, Amgen, Kowa Pharmaceuticals, Denka, Amarin, Novartis, Novo Nordisk, Abbott Laboratories, Mankind Pharma; and participation on a data safety monitoring board or advisory board for AstraZeneca, Ionis Pharmaceuticals, Kowa Pharmaceuticals, Novartis, and Esperion. BBY reports grants from the National Health and Medical Research Council paid to his institutions (Medical School, The University of Western Australia, Perth, WA, Australia; and Department of Endocrinology and Diabetes, Fiona Stanley Hospital, Perth, WA, Australia). CK reports grants from the US National Institutes of Health (NIH); grants or contracts from Grifols and Diagnostica Stago; consulting fees from BMS Pfizer; participation on a data safety monitoring board or advisory board for BMS Pfizer; a leadership or fiduciary role on the RECOVER-CDC Steering Committee; and stock or stock options for Insera. CC reports consulting fees from the Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda, and UCB. DAL reports grants from the UK Medical Research Council (MRC), National Institute for Health and Care Research (NIHR), BHF, European Research Council, NIH, and Diabetes UK paid to her institutions (MRC Integrative Epidemiology Unit and Population Health Science, Bristol Medical School, University of Bristol, Bristol, UK); and participation on a data safety monitoring board or advisory board for the UK Biobank, Bradford Institute Health Research, and NIHR-BHF. DN reports grants outside of this work from GSK and participation on a data safety monitoring board or advisory board for GSK. EDA reports grants from the BHF, NIHR, and an NIHR Senior Investigator Award; and participation on a data safety monitoring board or advisory board from Our Future Health and EURAC Research. HMK reports grants outside of this work from the NIH Agency for Healthcare Research and Quality, Foundation for a Smoke-Free World, State of CT Department of Public Health, US Food and Drug Administration, Johnson & Johnson, American Heart Association, Centers for Medicare & Medicaid Services, Google, and Pfizer; consultant fees from Massachusetts Medical Society, Eyedentifeye, and F-Prime; participation on a data safety monitoring board or advisory board for Aetna, Reality Labs, Element Science, and United Health; stock or stock options for Element Science and Eyedentifeye; and is a co-founder of Hugo Health and Refactor Health. JSu reports stock or stock options from Anagram Kommunikation, and Symptoms Europe. JD reports support from a BHF Professorship and NIHR Senior Investigator Award; and grants or contracts from Merck Sharp & Dohme, Novartis, Pfizer, and AstraZeneca, outside the submitted work. JG reports grants or contracts from the MRC; payment or honoraria for lectures and support for attending meetings and/or travel from Yonsei University; and leadership or a fiduciary role for Dementias Platform UK and the BrainWaves study. JSh reports grants or contracts from AstraZeneca; consulting fees from AstraZeneca, Sanofi, Novo Nordisk, MSD, Eli Lilly, and Pfizer; and payment or honoraria for lectures and support for attending meetings and/or travel from AstraZeneca, Mylan, Sanofi, Boehringer Ingelheim, Zuellig Pharma, and Abbott. KJM reports grants from the NIH. LS is now a full-time employee at Regeneron Genetics Center. LEW reports grants from the National Heart, Lung, and Blood Institute (NHLBI), NIH. NS reports grants

paid to their institution (University of Glasgow, Glasgow, UK) from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics; consulting fees from Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Merck, Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen Pharmaceuticals, and Novo Nordisk. PJN reports grants from NIH. PMR has received institutional research grant support from Kowa Pharmaceuticals, Novartis, Amarin, Pfizer, Esperion, Novo Nordisk, and the NHLBI; has served as a consultant to Novartis, AstraZeneca, Kowa Pharmaceuticals, and Novo Nordisk; and receives compensation for service on the Peter Munk Advisory Board (University of Toronto, Toronto, ON, Canada), the Leducq Foundation, and the Baim Institute (Boston, MA, USA). RTD reports grants from Takeda Pharmaceuticals and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen. SGT has received institutional research grant support from the BHF. SJG is a trustee of the Novo Nordisk UK Research Foundation medical research charity. SKi reports grants or contracts from VAScage (Research Centre on Vascular Ageing and Stroke, project number 868624) of the Austrian Research Promotion Agency FFG (COMET program—Competence Centers for Excellent Technologies) funded by the Federal Ministry for Climate Protection, Environment, Energy, Transport, Innovation and Technology; the Federal Ministry for Labour and Economy; and the federal states Tyrol (via Standortagentur), Salzburg, and Vienna (via Vienna Business Agency). SK has received institutional research grant support from the BHF, the UK MRC, the UK NIHR, and Health Data Research UK. SB has received institutional research grant support from the Wellcome Trust and the MRC. SWS reports receiving institutional grants from the NIH, royalties from Springer Publishing, and consulting fees from Fred Hutchinson Cancer Institute and State University of NY at Buffalo. TS reports consulting fees from Amarin, Amgen, Novartis, Orion Pharma, Raisio Group, and Sankyo; and a leadership or fiduciary role for the Finnish guidelines for dyslipidaemia. VS reports receiving institutional grants from Juho Vainio Foundation and Bayer. All other authors declare no competing interests.

#### Data sharing

Data from the UK Biobank are available to any legitimate scientific research on application. Data from the Emerging Risk Factors Collaboration are available at the discretion of the principal investigators of the individual studies.

#### Acknowledgements

This research was conducted using the UK Biobank Resource under application number 13784. No specific funding was obtained for this manuscript. The coordinating centre was supported by core funding from the British Heart Foundation (RG/18/13/33946), Cambridge BHF Centre of Research Excellence (RE/18/1/34212) and BHF Chair Award (CH/12/2/29428), and NIHR Cambridge Biomedical Research Centre (BRC-1215-20014; NIHR203312). JD holds a BHF Professorship and an NIHR Senior Investigator Award. AMW is part of the BigData@Heart Consortium, funded by the Innovative Medicines Initiative-2 Joint Undertaking under grant agreement 116074 and is supported by the BHF-Turing Cardiovascular Data Science Award (BCDSA\100005). MI is supported by the Munz Chair of Cardiovascular Prediction and Prevention and by the UK Economic and Social Research 878 Council (ES/T013192/1). EDA holds a NIHR Senior Investigator Award. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

#### References

- 1 Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011; **378**: 31–40.
- 2 Zhou B, Lu Y, Hajifathalian K, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; **387**: 1513–30.

- 3 Geiss LS, Wang J, Cheng YJ, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980–2012. *JAMA* 2014; **312**: 1218–26.
- 4 International Diabetes Federation. IDF Diabetes Atlas. <https://diabetesatlas.org> (accessed July 3, 2023).
- 5 Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; **364**: 829–41.
- 6 Gregg EW, Zhuo X, Cheng YJ, Albright AL, Narayan KMV, Thompson TJ. Trends in lifetime risk and years of life lost due to diabetes in the USA, 1985–2011: a modelling study. *Lancet Diabetes Endocrinol* 2014; **2**: 867–74.
- 7 Tomic D, Morton JI, Chen L, et al. Lifetime risk, life expectancy, and years of life lost to type 2 diabetes in 23 high-income jurisdictions: a multinational, population-based study. *Lancet Diabetes Endocrinol* 2022; **10**: 795–803.
- 8 Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA* 2006; **296**: 421–26.
- 9 Barnett KN, Ogston SA, McMurdo ME, Morris AD, Evans JM. A 12-year follow-up study of all-cause and cardiovascular mortality among 10,532 people newly diagnosed with Type 2 diabetes in Tayside, Scotland. *Diabet Med* 2010; **27**: 1124–29.
- 10 Gulliford MC, Charlton J. Is relative mortality of type 2 diabetes mellitus decreasing? *Am J Epidemiol* 2009; **169**: 455–61.
- 11 Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA* 2015; **314**: 52–60.
- 12 Al-Saeed AH, Constantino MI, Molyneaux L, et al. An inverse relationship between age of type 2 diabetes onset and complication risk and mortality: the impact of youth-onset type 2 diabetes. *Diabetes Care* 2016; **39**: 823–29.
- 13 Brun E, Nelson RG, Bennett PH, et al. Diabetes duration and cause-specific mortality in the Verona Diabetes Study. *Diabetes Care* 2000; **23**: 1119–23.
- 14 Silbernagel G, Rosinger S, Grammer TB, et al. Duration of type 2 diabetes strongly predicts all-cause and cardiovascular mortality in people referred for coronary angiography. *Atherosclerosis* 2012; **221**: 551–57.
- 15 Herrington WG, Alegre-Díaz J, Wade R, et al. Effect of diabetes duration and glycaemic control on 14-year cause-specific mortality in Mexican adults: a blood-based prospective cohort study. *Lancet Diabetes Endocrinol* 2018; **6**: 455–63.
- 16 Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. *Arch Intern Med* 2011; **171**: 404–10.
- 17 Huo L, Magliano DJ, Rancière F, et al. Impact of age at diagnosis and duration of type 2 diabetes on mortality in Australia 1997–2011. *Diabetologia* 2018; **61**: 1055–63.
- 18 Færch K, Carstensen B, Almdal TP, Jørgensen ME. Improved survival among patients with complicated type 2 diabetes in Denmark: a prospective study (2002–2010). *J Clin Endocrinol Metab* 2014; **99**: E642–46.
- 19 Knuiman MW, Welborn TA, Whittall DE. An analysis of excess mortality rates for persons with non-insulin-dependent diabetes mellitus in Western Australia using the Cox proportional hazards regression model. *Am J Epidemiol* 1992; **135**: 638–48.
- 20 Li HY, Jiang YD, Chang CH, Chung CH, Lin BJ, Chuang LM. Mortality trends in patients with diabetes in Taiwan: a nationwide survey in 2000–2009. *J Formos Med Assoc* 2012; **111**: 645–50.
- 21 Holden SH, Barnett AH, Peters JR, et al. The incidence of type 2 diabetes in the United Kingdom from 1991 to 2010. *Diabetes Obes Metab* 2013; **15**: 844–52.
- 22 Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. *JAMA* 2003; **290**: 1884–90.
- 23 Nwaneri C, Bowen-Jones D, Cooper H, Chikkaveerappa K, Afolabi BA. Falling mortality rates in type 2 diabetes mellitus in the Wirral Peninsula: a longitudinal and retrospective cohort population-based study. *Postgrad Med J* 2012; **88**: 679–83.
- 24 Huo X, Gao L, Guo L, et al. Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study. *Lancet Diabetes Endocrinol* 2016; **4**: 115–24.
- 25 Sattar N, Rawshani A, Franzén S, et al. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation* 2019; **139**: 2228–37.
- 26 Alva ML, Hoerger TJ, Zhang P, Cheng YJ. State-level diabetes-attributable mortality and years of life lost in the United States. *Ann Epidemiol* 2018; **28**: 790–95.
- 27 Tönnies T, Baumert J, Heidemann C, von der Lippe E, Brinks R, Hoyer A. Diabetes free life expectancy and years of life lost associated with type 2 diabetes: projected trends in Germany between 2015 and 2040. *Popul Health Metr* 2021; **19**: 38.
- 28 Koyama AK, Cheng YJ, Brinks R, et al. Trends in lifetime risk and years of potential life lost from diabetes in the United States, 1997–2018. *PLoS One* 2022; **17**: e0268805.
- 29 Leung M-YM, Pollack LM, Colditz GA, Chang S-H. Life years lost and lifetime health care expenditures associated with diabetes in the U.S., National Health Interview Survey, 1997–2000. *Diabetes Care* 2015; **38**: 460–68.
- 30 The Emerging Risk Factors Collaboration. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. *Eur J Epidemiol* 2007; **22**: 839–69.
- 31 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**: e1001779.
- 32 Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**: 2215–22.
- 33 Pintilie M. Analysing and interpreting competing risk data. *Stat Med* 2007; **26**: 1360–67.
- 34 Freidlin B, Korn EL. Testing treatment effects in the presence of competing risks. *Stat Med* 2005; **24**: 1703–12.
- 35 Tai BC, De Stavola BL, de Grotto V, GebSKI V, Machin D. First-event or marginal estimation of cause-specific hazards for analysing correlated multivariate failure-time data? *Stat Med* 2008; **27**: 922–36.
- 36 Thompson S, Kaptoge S, White I, Wood A, Perry P, Danesh J. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. *Int J Epidemiol* 2010; **39**: 1345–59.
- 37 VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol* 2019; **34**: 211–19.
- 38 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–58.
- 39 US Centers for Disease Control and Prevention. Underlying cause of death, 1999–2015. <https://wonder.cdc.gov/ucd-icd10.html> (accessed April 3, 2023).
- 40 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–13.
- 41 Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009; **302**: 1993–2000.
- 42 Hillier TA, Pedula KL. Characteristics of an adult population with newly diagnosed type 2 diabetes: the relation of obesity and age of onset. *Diabetes Care* 2001; **24**: 1522–27.
- 43 Wright AK, Welsh P, Gill JMR, et al. Age-, sex- and ethnicity-related differences in body weight, blood pressure, HbA<sub>1c</sub> and lipid levels at the diagnosis of type 2 diabetes relative to people without diabetes. *Diabetologia* 2020; **63**: 1542–53.
- 44 Steinarsson AO, Rawshani A, Gudbjörnsdóttir S, Franzén S, Svensson A-M, Sattar N. Short-term progression of cardiometabolic risk factors in relation to age at type 2 diabetes diagnosis: a longitudinal observational study of 100,606 individuals from the Swedish National Diabetes Register. *Diabetologia* 2018; **61**: 599–606.
- 45 Zoungas S, Woodward M, Li Q, et al. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia* 2014; **57**: 2465–74.

- 46 Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol* 2017; 5: 431–37.
- 47 Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; 52: 2288–98.
- 48 Simmons RK, Griffin SJ, Lauritzen T, Sandbæk A. Effect of screening for type 2 diabetes on risk of cardiovascular disease and mortality: a controlled trial among 139,075 individuals diagnosed with diabetes in Denmark between 2001 and 2009. *Diabetologia* 2017; 60: 2192–99.
- 49 Porta M, Curletto G, Cipullo D, et al. Estimating the delay between onset and diagnosis of type 2 diabetes from the time course of retinopathy prevalence. *Diabetes Care* 2014; 37: 1668–74.
- 50 Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. *Lancet Diabetes Endocrinol* 2018; 6: 122–29.
- 51 Mansournia MA, Nazemipour M, Etminan M. A practical guide to handling competing events in etiologic time-to-event studies. *Glob Epidemiol* 2022; 4: 100080.
- 52 Hernán MA. The hazards of hazard ratios. *Epidemiology* 2010; 21: 13–15.