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 1 515 718 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.

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*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).

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See Online for appendix

Introduction

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

Previous estimates have suggested that adults with type 2 diabetes die, on average, 6 years earlier than their counterparts without diabetes.[5–7] However, how this average reduction in life expectancy varies according to age at diagnosis is uncertain.[8–19] 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.[20–25] 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.[7,26–29] Few published studies have therefore directly analysed the association of age at diagnosis of diabetes with mortality and life expectancy.[17,18,25]

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 1 515 718 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,

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.[30] 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.[31] 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).[5,32] 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.[33–35] 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.[36] 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.[37] 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[36] 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.[38]

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,[39] which recorded 2·7 million deaths among more than 320 million individuals during 2015.[9,13] 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.[11] 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
ERFC								
Total number of participants	1017695	1017695 (100·0%)	948775 (93·2%)	3253 (0·3%)	8763 (0·9%)	18605 (1·8%)	21527 (2·1%)	16772 (1·6%)
Prevalent diabetes	1017695	23335 (2·3%)	..	2835 (87·2%)	5602 (63·9%)	7047 (37·9%)	5632 (26·2%)	2219 (13·2%)
Incident diabetes	1017695	45585 (4·5%)	..	418 (12·8%)	3161 (36·1%)	11558 (62·1%)	15895 (73·8%)	14553 (86·8%)
Age at baseline, years	1017695	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	1017695	463920 (45·6%)	436576 (46·0%)	1187 (36·5%)	4150 (47·4%)	8246 (44·3%)	7796 (36·2%)	5965 (35·6%)
Female sex	1017695	553775 (54·4%)	512199 (54·0%)	2066 (63·5%)	4613 (52·6%)	10359 (55·7%)	13731 (63·8%)	10807 (64·4%)
Current smoker	945856	267678 (28·3%)	252507 (28·7%)	914 (28·9%)	2583 (30·6%)	4763 (26·6%)	4422 (21·1%)	2489 (15·3%)
Systolic blood pressure, mm Hg	753256	135 (19)	134 (19)	135 (19)	138 (19)	142 (19)	143 (19)	146 (20)
BMI, kg/m^2	890293	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	594679	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	398521	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	196159	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_{1c}, %	96802	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	1017695	73091 (7·2%)	63734 (6·7%)	422 (13·0%)	1097 (12·5%)	2256 (12·1%)	2820 (13·1%)	2762 (16·5%)
Medication use†	614036	84056 (13·7%)	66186 (11·6%)	1060 (52·8%)	2610 (47·3%)	4777 (41·5%)	5261 (37·8%)	4162 (32·9%)
Vocational or university education level	389924	99850 (25·6%)	94710 (25·9%)	313 (23·4%)	775 (23·2%)	1578 (22·8%)	1583 (21·4%)	891 (15·8%)
Non-White ethnic group	534131	71348 (13·4%)	61154 (12·4%)	617 (35·0%)	1781 (32·8%)	3378 (30·5%)	2817 (22·1%)	1601 (15·3%)
UK Biobank								
Number of participants	498023	498023 (100·0%)	471223 (94·6%)	1550 (0·3%)	5859 (1·2%)	11041 (2·2%)	7406 (1·5%)	944 (0·2%)
Prevalent diabetes	498023	24981 (5·0%)	..	1550 (100·0%)	5810 (99·2%)	10798 (97·8%)	6818 (92·1%)	5 (0·5%)
Incident diabetes	498023	1819 (0·4%)	..	0	49 (0·8%)	243 (2·2%)	588 (7·9%)	939 (99·5%)
Age at baseline, years	498023	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	498023	226676 (45·5%)	210224 (44·6%)	882 (56·9%)	3560 (60·8%)	6889 (62·4%)	4508 (60·9%)	613 (64·9%)
Female sex	498023	271347 (54·5%)	260999 (55·4%)	668 (43·1%)	2299 (39·2%)	4152 (37·6%)	2898 (39·1%)	331 (35·1%)
Current smoker	497789	52494 (10·5%)	49497 (10·5%)	243 (15·7%)	815 (14·0%)	1193 (10·8%)	665 (9·0%)	81 (8·6%)
Systolic blood pressure, mm Hg	497112	138 (19)	137 (19)	137 (17)	138 (17)	141 (17)	144 (17)	145 (18)
BMI, kg/m^2	495426	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	465833	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	426110	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	17712	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_{1c}, %	462791	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	498023	69693 (14·0%)	62346 (13·2%)	363 (23·4%)	1316 (22·5%)	3122 (28·3%)	2344 (31·7%)	202 (21·4%)
Medication use†	490758	135849 (27·7%)	113681 (24·5%)	1364 (90·0%)	4707 (82·3%)	9453 (87·1%)	6173 (84·8%)	471 (51·1%)
Vocational or university education level	494242	298113 (60·3%)	284262 (60·7%)	875 (58·3%)	3237 (56·7%)	5811 (53·7%)	3362 (46·0%)	566 (60·1%)
Non-White ethnic group	496231	26390 (5·3%)	23052 (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**

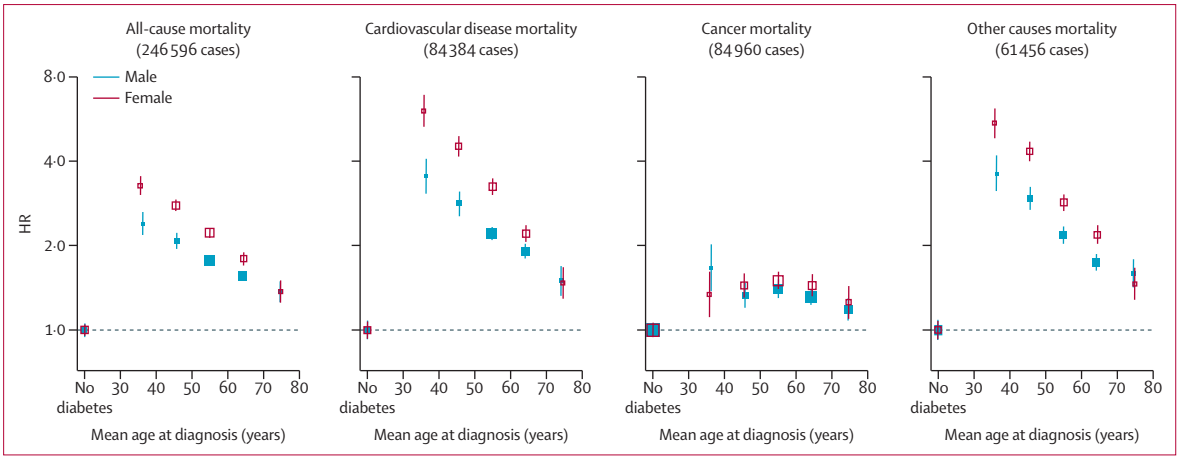

Figure 1: **Sex-specific HRs for all-cause and cause-specific mortality according to age at diagnosis of type 2 diabetes**
The mean age at diagnosis for the categories 30 to <40 years, 40 to <50 years, 50 to <60 years, 60 to <70 years and ≥70 years is plotted on the x axis. HRs are adjusted for age, 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 possilibilty 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_{1c}), 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*
All-cause mortality				
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^2 (95% CI)	..	67 (59–74)	68 (60–74)	67 (60–74)
Cardiovascular disease mortality				
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^2 (95% CI)	..	58 (47–67)	59 (48–67)	59 (48–67)
Cancer mortality				
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^2 (95% CI)	..	26 (2–44)	24 (0–43)	24 (0–43)
Other causes mortality				
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^2 (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.[3]

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 previous been observed for other cardiovascular risk factors, including blood pressure[40] and LDL-cholesterol.[41] 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[42] (characterised by higher BMI, higher blood pressure, higher concentrations of proatherogenic lipids,[43] and faster deterioration in glycaemic control[24,44]) than individuals who develop diabetes at older ages, potentially leading to premature mortality.[45] 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.[46–48]

Our study had several strengths and is distinctive and complimentary to previous studies.[7–19,26–29] 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)[49] and in defining the duration of diabetes (which could be confounded by the timing of entry into, and 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

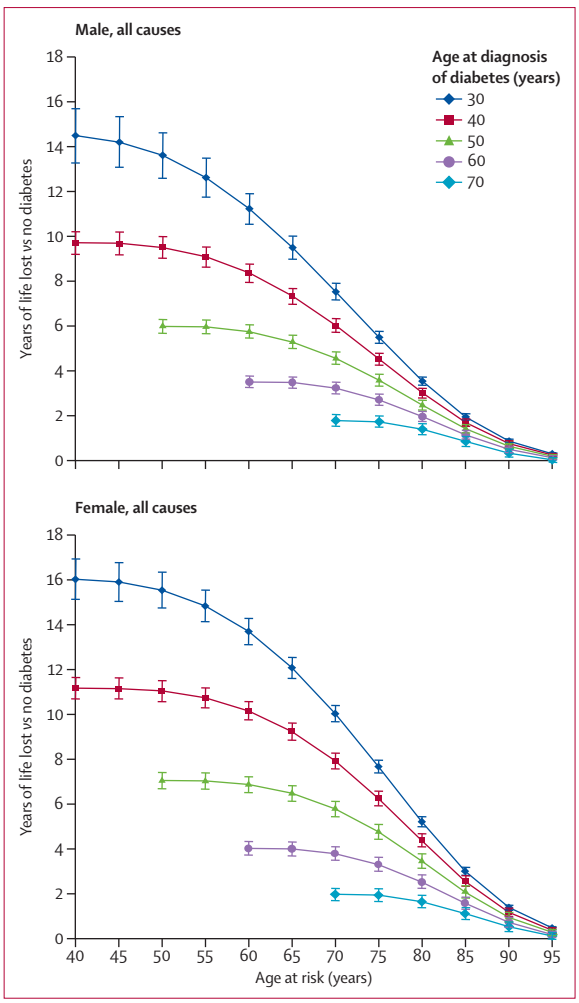

Figure 2: **Estimated years of life lost by age at diagnosis of type 2 diabetes compared with people without diabetes**

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.

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.[50] 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.[51] However, non-competing risk-adjusted models might be subject to selection bias, because HRs are calculated conditional on those who have survived.[52]

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.

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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

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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.

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