Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data

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Summary

Background Large reductions in diabetes complications have altered diabetes-related morbidity in the USA. It is unclear whether similar trends have occurred in causes of death.

Methods Using data from the National Health Interview Survey Linked Mortality files from 1985 to 2015, we estimated age-specific death rates and proportional mortality from all causes, vascular causes, cancers, and non-vascular, non-cancer causes among US adults by diabetes status.

Findings From 1988–94, to 2010–15, all-cause death rates declined by 20% every 10 years among US adults with diabetes (from 23·1 [95% CI 20·1–26·0] to 15·2 [14·6–15·8] per 1000 person-years), while death from vascular causes decreased 32% every 10 years (from 11·0 [9·2–12·2] to 5·2 [4·8–5·6] per 1000 person-years), deaths from cancers decreased 16% every 10 years (from 4·4 [3·2–5·5] to 3·0 [2·8–3·3] per 1000 person-years), and the rate of non-vascular, non-cancer deaths declined by 8% every 10 years (from 7·7 [6·3–9·2] to 7·1 [6·6–7·5]). Death rates also declined significantly among people without diagnosed diabetes for all four major mortality categories. However, the declines in death rates were significantly greater among people with diabetes for all-causes ($p_{interaction}<0·0001$), vascular causes ($p_{interaction}=0·0214$), and non-vascular, non-cancer causes ($p_{interation}<0·0001$), as differences in all-cause and vascular disease death between people with and without diabetes were reduced by about a half. Among people with diabetes, all-cause mortality rates declined most in men and adults aged 65–74 years of age, and there was no decline in death rates among adults aged 20–44 years. The different magnitude of changes in cause-specific mortality led to large changes in the proportional mortality. The proportion of total deaths among adults with diabetes from vascular causes declined from 47·8% (95% CI 38·9–58·8) in 1988–94 to 34·1% (31·4–37·1) in 2010–15; this decline was offset by large increases in the proportion of deaths from non-vascular, non-cancer causes, from 33·5% (26·7–42·1) to 46·5% (43·3–50·0). The proportion of deaths caused by cancer was relatively stable over time, ranging from 16% to 20%.

Interpretation Declining rates of vascular disease mortality are leading to a diversification of forms of diabetes-related mortality with implications for clinical management, prevention, and disease monitoring.

Funding None.

Introduction

Diabetes has been associated with an approximate 75% increase in mortality rate in adults, and the average 60 year old person diagnosed with diabetes loses 5 years of his or her life to the disease.[1–4] Although cardiovascular diseases have historically accounted for the largest number of those deaths, diabetes is associated with increased risk of death from a wide range of additional causes, including diabetes itself, renal disease, cancers, infections, liver disease, and external causes.[1,3–6] Some population-based studies suggest that the character of diabetes-related complications could be changing.[4,7,8] In US adults diagnosed with diabetes, the rate of cardiovascular disease-related complications declined more than other types of morbidities from 1990, to 2010, potentially increasing the relative importance of other complications and conditions, including chronic kidney disease, cancer, and ageing-related conditions.[2,8–10] It is possible that these shifts in morbidity are accompanied by changes in the causes of death among people with diabetes, as has been reported in the general population.[11] However, no studies have assessed cause-specific mortality among people with diabetes in the USA.[7]

National Vital Statistics data[12] suggest that the mortality rate attributed to diabetes decreased by 16% from 2000, to 2010. However, deaths caused by diabetes itself are difficult to interpret because of awareness, changing prevalence, and under-reporting of diabetes as a contributing cause.[13,14] Thus, determination of the causes and trends in death associated with diabetes requires follow-up mortality data based on cohorts of people with and without diabetes. In this study, we assembled data from two nationally representative datasets to assess the mortality burden associated with diagnosed diabetes, and to determine whether the magnitude and causes of death associated with

Research in context

Evidence before this study
We searched PubMed for English-language reports of population-based studies of trends in causes of death in populations with diagnosed diabetes published from Jan 1, 1990, to June 1, 2017, using the terms "mortality trends", and "diabetes mellitus" and separately "cause-specific mortality" and "diabetes mellitus". Previous studies indicate that all-cause mortality among populations with diabetes has declined in several countries but no studies had examined trends in cause-specific mortality among people with diabetes or how those causes differ from populations without diagnosed diabetes.

Added value of the study
This study is the first nationally representative study of trends in the specific causes of death in adults with diagnosed diabetes and compares them to trends in those without diagnosed diabetes. Death rates due to vascular disease have declined more steeply among people with diabetes than in those without diabetes and decreased from about half of all deaths among people with diabetes in the 1990s, to about one-third in 2010–15. At the same time, the decrease in non-vascular, non-cancer deaths was modest and they now account for almost half of deaths in people with diabetes. Several of these causes, including renal disease, influenza and pneumonia, sepsis, and chronic liver disease, were significantly higher in people with diabetes than in those without.

Implications of all the available evidence
The disproportionate shift in causes of death from vascular and non-vascular causes has led to a diversification of causes of death, indicating a need to attend to clinical management, prevention, and monitoring of a more diverse range of diabetes-related conditions.

diabetes are changing in concert with trends in diabetes complications.

Methods

Study design and population

We used data from the National Health Interview Survey, an annual cross-sectional survey of the health status, health-care access, and behaviours of US civilians conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics.[15,16] The survey uses multistage probability sampling to select around 35 000 households from randomly selected clusters of addresses within census tracts, counties, and metropolitan statistical areas that serve as the primary sampling units. One sample adult and one child are selected from each household. Household response rates ranged from 78% to 97% between 1980, and 2014. All survey participants provided informed consent before participation in the study.

The National Health Interview Survey Linked Mortality files include data from all surveys between 1985, and 2014, linked to the National Death Index, with follow-up to date of death or Dec 31, 2015.[15,17] 4% of those surveyed were excluded because of inadequate data to provide linkage to the National Death Index, resulting in a sample of 677 060 adults aged 18 years and older at baseline (age >20 years at follow-up), followed up to Dec 31, 2015, among whom 50 200 had diagnosed diabetes.

Measurements

Interviewers assessed diabetes status by asking participants if a doctor or other health professional had ever told them they had diabetes or sugar diabetes. The design of the National Health Interview Survey was revised in 1997; before 1997, a sixth of participants were asked about diabetes and other health conditions, whereas starting with 1997, all participants were asked whether a doctor had ever told them they had diabetes.

Underlying causes of death before 1999 were classified according to the 9th revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-9) and from 1999 onwards according to the ICD-10 guidelines. All underlying causes of death were grouped into four general categories: all-causes, all vascular causes, all cancers, and all non-cancer and non-vascular causes. We also assessed death rates for the 15 leading causes in the general population (diseases of the heart, malignant neoplasms, chronic lower respiratory disease, unintentional accidents; cerebrovascular disease; Alzheimer's disease; diabetes mellitus; influenza and pneumonia; nephritis and nephrotic syndrome; intentional self-harm; sepsis; chronic liver disease; essential hypertension or renal; Parkinson's disease; pneumonitis).[18] The appendix (p 1) shows specific codes for causes of death.

See Online for appendix

Statistical analysis

We had two objectives: (1) to examine the association of diagnosed diabetes with specific causes of death, including a comparison with death rates in people without diabetes; and (2) to examine trends from 1990, to 2015, in cause-specific mortality according to diabetes status, including an assessment of whether the proportion of major causes of mortality has changed in the people with and without diagnosed diabetes.

We used weighted discrete Poisson regression to calculate death rates and compare yearly rates according to baseline diagnosed diabetes status and time period.[19] We used robust variance estimation to account for over-dispersion of data. These analyses divided the continuous time-to-event survival data into discrete survival years from the date at

	Diabetes						No diabetes					
	1985–89	1990–94	1995–99	2000–04	2005–09	2010–14	1985–89	1990–94	1995–99	2000–04	2005–09	2010–14
Average total population (million)	6·2	7·1	9·2	12·8	17·5	21·1	165·5	174·3	178·7	181·9	197·2	208·9
Mean age (SE; years)	60·1 (0·4)	59·9 (0·4)	60·0 (0·3)	59·6 (0·2)	59·4 (0·2)	60·6 (0·2)	42·9 (0·2)	43·5 (0·1)	43·9 (0·1)	44·2 (0·1)	44·7 (0·1)	45·3 (0·1)
Female (%)	54·6%	55·2%	54·0%	49·8%	51·1%	50·0%	52·5%	52·2%	51·9%	52·1%	51·7%	51·9%
Ethnic origin (%)												
Non-Hispanic white	74·3%	72·5%	67·9%	68·7%	66·1%	63·4%	79·6%	76·3%	75·6%	73·7%	70·3%	67·8%
Non-Hispanic black	16·7%	16·5%	17·2%	15·7%	15·8%	15·8%	10·5%	10·8%	10·7%	10·9%	11·3%	11·6%
Hispanic	6·9%	8·3%	10·9%	11·5%	13·0%	15·1%	7·2%	8·8%	9·7%	11·2%	13·2%	14·7%
Other	2·1%	2·7%	3·9%	4·1%	5·1%	5·7%	2·6%	4·1%	4·0%	4·2%	5·2%	6·0%
Education (%)												
Less than high school	44·8%	40·9%	34·7%	29·5%	25·5%	22·8%	23·0%	20·5%	18·6%	17·0%	15·7%	13·6%
High school	32·9%	35·2%	32·7%	31·5%	32·3%	30·2%	38·8%	37·9%	32·5%	29·4%	28·1%	25·9%
More than high school	22·4%	29·3%	32·6%	39·0%	42·2%	47·1%	38·2%	41·6%	48·9%	53·6%	56·2%	60·5%
Body-mass index (%)												
<25 kg/m²	33·5%	28·9%	25·0%	19·2%	17·0%	15·6%	58·4%	54·0%	47·9%	43·0%	40·2%	39·0%
25–30 kg/m²	38·3%	36·1%	35·4%	32·8%	31·1%	31·1%	30·4%	32·3%	34·5%	35·6%	35·5%	35·0%
>30 kg/m²	28·1%	35·0%	39·6%	48·0%	51·9%	53·3%	11·2%	13·7%	17·6%	21·5%	24·3%	26·1%
Mean duration of diabetes												
<1 year	10·4	9·7	13·5	16·5	15·8	12·9	··	··	··	··	··	··
1<5 years	27·6	28·0	27·2	27·7	26·7	23·5	··	··	··	··	··	··
≥5 years	62·0	62·2	59·3	55·8	57·5	63·6	··	··	··	··	··	··

***Table 1:* Characteristics of US adults aged 18 years or older with and without diabetes, 1985–2014**

interview to date of death or censoring on Dec 31, 2015. We used year and age of follow-up and event status as time-dependent variables. These analyses account for the fact that cohorts overlap across calendar years and make the estimates representative of the US population by stratifying each overlapping cohort by diabetes status, sex, race, and age for each year using US population weights. We used the marginal rate from the Poisson regression to estimate crude and adjusted mortality rates. Using calendar years as a continuous variable, we calculated absolute changes (average differences) and relative changes (percentage), a derivative, expressed in rate per 10-year period.[20] We used the delta method, a first-order Taylor expansion, to compute standard errors and CIs for differences and ratios.[21] We further assessed the linear trend of estimated death rates by five time periods by use of orthogonal polynomial contrasts using the middle point of the time period. We tested period-by-diabetes status interaction terms to determine whether mortality rates declined by a greater magnitude in the population with diabetes than in those without diabetes. We evaluated quadratic and cubic terms for calendar year but they were not statistically significant and excluded from final models. For descriptive purposes, we also portray rates for five periods (1988–94, 1995–99, 2000–04, 2005–09, and 2010–15), to represent the early and late period of each decade.

To reduce potential selection bias due to people with acute and life-threatening illness being less likely to be interviewed at baseline, all follow-up time of participants was excluded up to the end of second year of follow-up.[22] To minimise misclassification bias associated with lack of assessment of incident diabetes after baseline, we limited follow-up duration to 10 years. We did several sensitivity analyses, including an assessment of the impact of not limiting follow-up duration and of excluding people with possible type 1 diabetes (defined by being on insulin and having an age of onset <30 years). To assess the potential effect of a progressive increase in detection over time, we did sensitivity analyses incrementally excluding people with newly diagnosed diabetes in later time periods. This analysis changed the diabetes status of people with diabetes to no diabetes in the first 2 years, 3 years, 4 years, and 5 years of follow-up over the four baseline survey periods (1997–99, 2000–04, 2005–09, 2010–14), respectively, and recalculated rates to examine whether similar trends existed. This analysis simulates a scenario wherein people in later years are identified at an earlier and healthier state. We used Stata (version 15.1) to account for the complex multistage sampling design and produce weighted estimates, 95% CIs, and total case estimates. We used a p value of less than 0·05 as an indication of statistical significance.

Role of the funding source

EWG—a representative of one of the co-sponsors—had the idea for and led the study design, data analyses, data

	1988–94	1995–99	2000–04	2005–09	2010–15	Average 10-year difference	10-year percentage change	p value for linear trend
Deaths from all causes								
No diabetes								
Annual deaths (n)	1 574 760	1 815 287	1 810 927	1 817 651	1 918 198	..	..	..
Death rate (per 1000 person-years)	11·8 (11·3 to 12·3)	11·4 (11·1 to 11·8)	10·8 (10·5 to 11·1)	9·9 (9·7 to 10·1)	9·3 (9·1 to 9·5)	–1·2 (–1·4 to –1·0)	–10·7 (–12·4 to –8·9)	<0·0001
Diabetes								
Annual deaths (n)	278 401	414 035	519 839	568 665	658 479	..	..	..
Death rate (per 1000 person-years)	23·1 (20·1 to 26·0	23·6 (21·8 to 25·4)	21·4 (20·0 to 22·7)	17·6 (16·8,18·5)	15·2 (14·6 to 15·8)	–4·4 (–5·5 to –3·3)	–20·1 (–24·1 to –15·9)	<0·0001
Excess rate (*vs* no diabetes)	11·3 (8·5 to 14·1)	12·2 (10·4 to 14·0)	10·6 (9·3 to 11·9)	7·7 (6·9 to 8·6)	5·9 (5·3 to 6·5)	..	..	..
Relative risk (*vs* no diabetes)	2·0 (1·7 to 2·2)	2·1 (1·9 to 2·2)	2·0 (1·9 to 2·1)	1·8 (1·7 to 1·9)	1·6 (1·6 to 1·7)	..	..	..
Vascular disease deaths								
No diabetes								
Annual deaths (n)	679 082	761 957	691 895	583 750	594 894	..	..	..
Death rate (per 1000 person-years)	5·2 (4·9 to 5·6)	4·8 (4·6 to 5·1)	4·2 (4·0 to 4·4)	3·2 (3·1 to 3·3)	2·9 (2·8 to 3·0)	–1·2 (–1·3 to –1·0)	–25·5 (–28·0 to –22·9)	<0·0001
Diabetes								
Annual deaths (n)	135 729	199 166	213 969	217 170	233 722	..	..	..
Death rate (per 1000 person-years)	11·0 (9·2 to 12·2)	11·0 (9·9 to 12·2)	8·6 (7·8 to 9·4)	6·6 (6·1 to 7·1)	5·2 (4·8 to 5·6)	–3·1 (–3·8 to –2·4)	–31·9 (–36·5 to –26·8)	<0·0001
Excess rate (*vs* no diabetes)	5·8 (4·0 to 7·6)	6·2 (5·0 to 7·4)	4·4 (3·6 to 5·2)	3·4 (2·9 to 3·9)	2·3 (1·9 to 2·7)	..	..	
Relative risk (*vs* no diabetes)	2·1 (1·8 to 2·5)	2·3 (2·0 to 2·5)	2·1 (1·9 to 2·3)	2·0 (1·9 to 2·2)	1·8 (1·7 to 2·0)	..	..	
Cancer deaths								
No diabetes								
Annual deaths (n)	432 827	456 487	466 966	482 250	487 522	..	..	..
Death rate (per 1000 person-years)	3·2 (2·9 to 3·4)	2·8 (2·7 to 3·0)	2·7 (2·6 to 2·9)	2·6 (2·5 to 2·7)	2·4 (2·3 to 2·5)	–0·3 (–0·4 to –0·2)	–11·8 (–15·0 to –8·5)	<0·0001
Diabetes								
Annual deaths (n)	51 044	63 201	89 320	106 833	125 163	..	..	..
Death rate (per 1000 person-years)	4·4 (3·2 to 5·5)	3·8 (3·0 to 4·4)	3·8 (3·2 to 4·4)	3·4 (3·0 to 3·8)	3·0 (2·8 to 3·3)	–0·6 (–1·1 to –0·2)	–15·7 (–24·7 to –5·7)	0·0199
Excess rate (*vs* no diabetes)	1·2 (0·1 to 2·4)	0·9 (0·2 to 1·6)	1·0 (0·4 to 1·6)	0·8 (0·4 to 1·2)	0·7 (0·4 to 0·9)	..	..	..
Relative risk (*vs* no diabetes)	1·4 (1·0 to 1·8)	1·3 (1·1 to 1·6)	1·4 (1·2 to 1·6)	1·3 (1·2 to 1·5)	1·3 (1·2 to 1·4)	..	..	..
Non-cancer, non-vascular deaths								
No diabetes								
Annual deaths (n)	462 851	596 843	652 067	751 651	835 781	..	..	..
Death rate (per 1000 person-years)	3·4 (3·2 to 3·7)	3·7 (3·5 to 3·9)	3·9 (3·7 to 4·0)	4·1 (3·9 to 4·2)	4·0 (3·9 to 4·2)	0·3 (0·2 to 0·4)	8·3 (5·0 to 11·6)	<0·0001
Diabetes								
Annual deaths (n)	91 628	151 667	216 549	244 661	299 594	..	..	..
Death rate (per 1000 person-years)	7·7 (6·3 to 9·2)	8·8 (7·7 to 10·0)	9·1 (8·3 to 9·9)	7·7 (7·2 to 8·2)	7·1 (6·6 to 7·5)	–0·7 (–1·3 to –0·1)	–8·2 (–14·5 to –1·5)	0·1707
Excess rate (*vs* no diabetes)	4·3 (2·9 to 5·7)	5·1 (3·9 to 6·3)	5·2 (4·4 to 6·0)	3·6 (3·1 to 4·2)	3·0 (2·6 to 3·5)	..	..	..
Relative risk (*vs* no diabetes)	2·3 (1·9 to 2·7)	2·4 (2·0 to 2·7)	2·4 (2·1 to 2·6)	1·9 (1·8 to 2·0)	1·7 (1·6 to 1·9)	..	..	..

All estimates are adjusted for age, sex, and ethnic origin, except for annual deaths, which are weighted absolute numbers of deaths across all ages. Data in parentheses are 95% CIs. p value for time by diabetes interaction (p<0·0001 for all cause; 0·0214 for cardiovascular disease; 0·9318 for cancer; <0·0001 for all non-cancer, non-vascular.

Table 2: **Adjusted cause specific mortality rates, by cohort and diagnosis of diabetes**

	1988–94	1995–99	2000–04	2005–09	2010–15	Average 10-year difference	10-year percentage change	p value for linear trend
Diabetes								
Sex								
Men	30·8 (25·7 to 35·9)	29·3 (26·2 to 32·5)	25·3 (23·0 to 27·6)	21·8 (20·1 to 23·4)	20·4 (19·1 to 21·7)	–5·2 (–7·0 to –3·4)	–12·4 (–22·9 to –0·4)	<0·0001
Women	19·3 (16·1 to 22·5)	22·4 (20·4 to 24·8)	22·0 (20·0 to 24·2)	18·3 (17·0 to 19·6)	16·7 (15·6 to 17·8)	–2·1 (–3·4 to –0·8)	–3·3 (–14·8 to 9·8)	0·0141
Age (years)								
20–44	5·1 (2·1 to 8·1)	3·5 (1·5 to 5·5)	5·3 (3·0 to 7·6)	5·3 (3·3 to 7·6)	4·9 (3·4 to 6·3)	0·4 (–0·8 to 1·7)	9·2 (–16·4 to 42·8)	0·7297
45–64	17·5 (12·2 to 22·7)	18·9 (15·6 to 22·1)	18·0 (15·4 to 20·5)	13·8 (12·3 to 15·2)	13·8 (12·3 to 15·2)	–2·9 (–5·0 to –0·8)	–16·1 (–25·4 to –5·8)	0·0408
65–74	47·3 (39·7 to 54·8)	51·4 (44·9 to 58·0)	37·1 (32·7 to 41·5)	30·6 (27·6 to 33·5)	26·5 (24·4 to 28·7)	–11·4 (–14·7 to –8·2)	–25·9 (–31·3 to –20·1)	<0·0001
≥75	90·0 (74·8 to 105·2)	91·9 (82·3 to 101·4)	87·8 (80·9 to 94·6)	74·9 (70·3 to 79·5)	68·3 (64·7 to 71·9)	–12·1 (–17·8 to –6·3)	–13·5 (–18·9 to –7·7)	0·0004
Ethnic origin								
Non-Hispanic white	24·8 (21·5 to 28·1)	27·1 (24·8 to 29·5)	23·9 (22·0 to 25·8)	20·6 (19·2 to 22·0)	19·2 (18·1 to 20·3)	–3·4 (–4·7 to –2·0)	–6·0 (–16·7 to 6·0)	<0·0001
Non-Hispanic black	26·8 (19·9 to 33·6)	19·0 (15·6 to 22·5)	24·7 (21·3 to 28·2)	21·3 (18·7 to 23·9)	17·8 (16·1 to 19·4)	–3·2 (–5·7 to –0·7)	–6·1 (–19·3 to 2·0)	0·0357
Other	20·5 (10·7 to 30·4)	20·0 (15·1 to 25·0)	20·0 (16·6 to 23·3)	13·6 (11·9 to 15·3)	13·3 (11·9 to 14·7)	–4·5 (–7·8 to –1·2)	–16·1 (–31·0 to 2·0)	0·0507
Without diabetes								
Sex								
Men	14·3 (13·6 to 15·1)	13·7 (13·1 to 14·3)	12·9 (12·4 to 13·4)	12·1 (11·7 to 12·4)	11·4 (11·1 to 11·7)	–1·4 (–1·7 to –1·0)	–3·6 (–7·9 to –0·2)	<0·0001
Women	9·0 (8·5,9·5)	9·2 (8·8,9·6)	9·0 (8·6,9·3)	8·5 (8·2,8·7)	8·4 (8·2,8·7)	–0·3 (–0·6 to –0·1)	3·6 (–0·6 to 7·9)	0·0065
Age (years)								
20–44	1·1 (1·0 to 1·3)	1·4 (1·2 to 1·5)	1·4 (1·2 to 1·5)	1·4 (1·3 to 1·5)	1·5 (1·3 to 1·6)	0·1 (0·1 to 0·2)	12·3 (5·5 to 19·6)	0·0011
45–64	5·2 (4·7 to 5·7)	4·3 (4·0 to 4·6)	4·4 (4·1 to 4·7)	4·5 (4·3 to 4·7)	4·5 (4·3 to 4·7)	–0·2 (–0·5 to 0·0)	–3·9 (–8·5 to 1·0)	0·0561
65–74	19·4 (17·6 to 21·2)	17·9 (16·6 to 19·1)	15·9 (14·9 to 16·9)	13·2 (12·4 to 14·0)	12·0 (11·4 to 12·7)	–3·6 (–4·4 to –2·7)	–19·8 (–23·7 to –15·7)	<0·0001
≥75	58·3 (55·1 to 61·5)	59·7 (57·2 to 62·1)	57·8 (55·7 to 60·0)	54·2 (52·6 to 55·8)	52·4 (50·9 to 53·9)	–3·0 (–4·6 to –1·5)	–4·5 (–7·0 to –1·9)	<0·0001
Ethnic origin								
Non-Hispanic white	11·1 (10·5 to 11·6)	11·1 (10·7 to 11·5)	10·4 (10·1 to 10·7)	9·9 (9·6 to 10·1)	9·6 (9·3 to 9·9)	–0·7 (–1·0 to –0·5)	–0·1 (–3·3 to 3·5)	<0·0001
Non-Hispanic black	15·2 (13·7 to 16·6)	13·0 (11·9 to 14·0)	14·1 (13·0 to 15·2)	12·5 (11·7 to 13·3)	11·2 (10·5 to 11·9)	–1·5 (–2·2 to –0·9)	–4·5 (–10·3 to 1·3)	<0·0001
Other	9·8 (7·6 to 12·0)	9·7 (8·6 to 10·9)	9·9 (9·0 to 10·8)	9·0 (8·4 to 9·6)	9·2 (8·7 to 9·8)	–0·3 (–1·2 to 0·5)	3·7 (–5·5 to 13·8)	0·4719

Data are deaths per 1000 person-years (95% CIs) unless stated otherwise, adjusted for sex, age group, and ethnic origin.

Table 3: **Trends in all-cause mortality according to diabetes status**

interpretation, and wrote the report. EWG and YJC had full access to all the data in the study, and EWG had final responsibility for the decision to submit for publication.

Results

Between the late 1980s and the early 2010s, the total number of adults with diagnosed diabetes in the USA more than tripled, from 6·2 million to 21·1 million. Among people with diabetes there was a decrease in the proportion of women and of non-Hispanic whites and an increase in the proportion of people with more than a high school education and with a body-mass index more than 30 kg/m², while there was little change in mean age (table 1). However, compared with adults without diagnosed diabetes over the study period, those with diabetes were older, less likely to be white, had lower levels of education, and higher levels of obesity ($p<0.05$ for each).

Compared with adults without diabetes, adults with diabetes had significantly higher death rates from all-causes, vascular causes, cancers, and non-cancer, non-vascular causes throughout the period of evaluation (table 2). The hazard ratios (HRs) of death associated with diagnosed diabetes (*vs* no diabetes) declined over time for all-causes (HRs ranged from 1·6 to 2·1; $p_{interaction}$ of diabetes status and period <0·0001), for vascular causes (HR range 1·8 to 2·3, $p_{interaction}$=0·0214), and non-vascular, non-cancer causes (HR range 1·7 to 2·4, $p_{interaction}$<0·0001), and were lower and stable for cancer (HR range 1·3 to 1·4, $p_{interaction}$=0·913; table 2).

From 1988–94 to 2010–15, among the population with diabetes, all-cause mortality rates declined by 20% every 10 years, while death from vascular causes declined by 32% every 10 years, and cancers declined by 16% every 10 years (table 2). For non-vascular, non-cancer deaths, there was an 8% overall reduction in death rates every 10 years, but the test for linear trends was not significant (p=0·1707) as a decrease in death rates occurred mainly in the last three time periods.

Among people without a diagnosis of diabetes, death rates also declined significantly for all major mortality

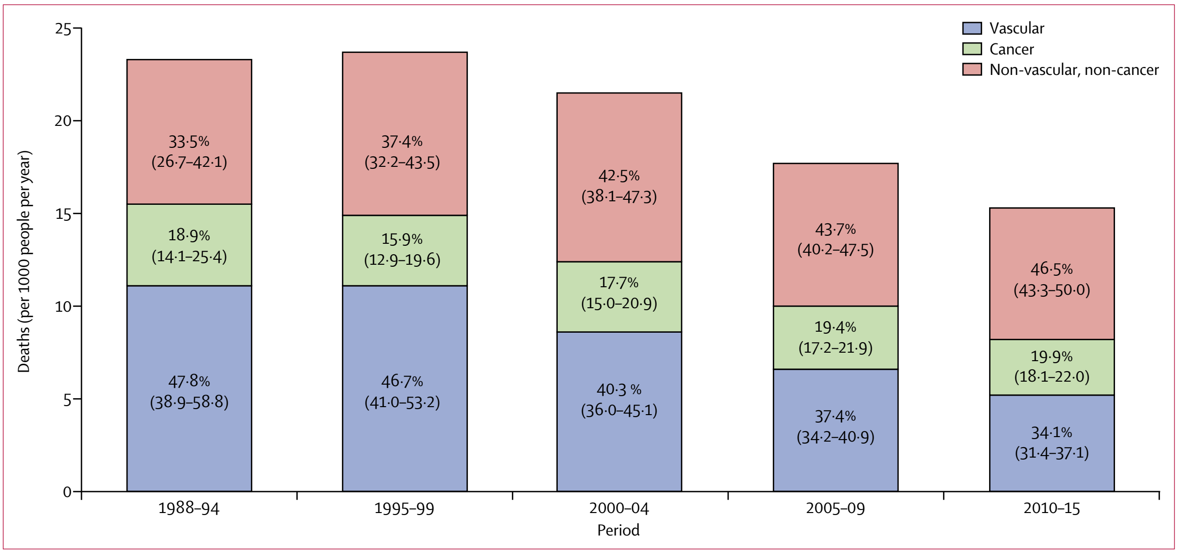

Figure 1: **Deaths due to vascular, cancer, and non-vascular, non-cancer causes among US adults diagnosed with diabetes**
Numbers in bars represent % of total deaths (95% CI).

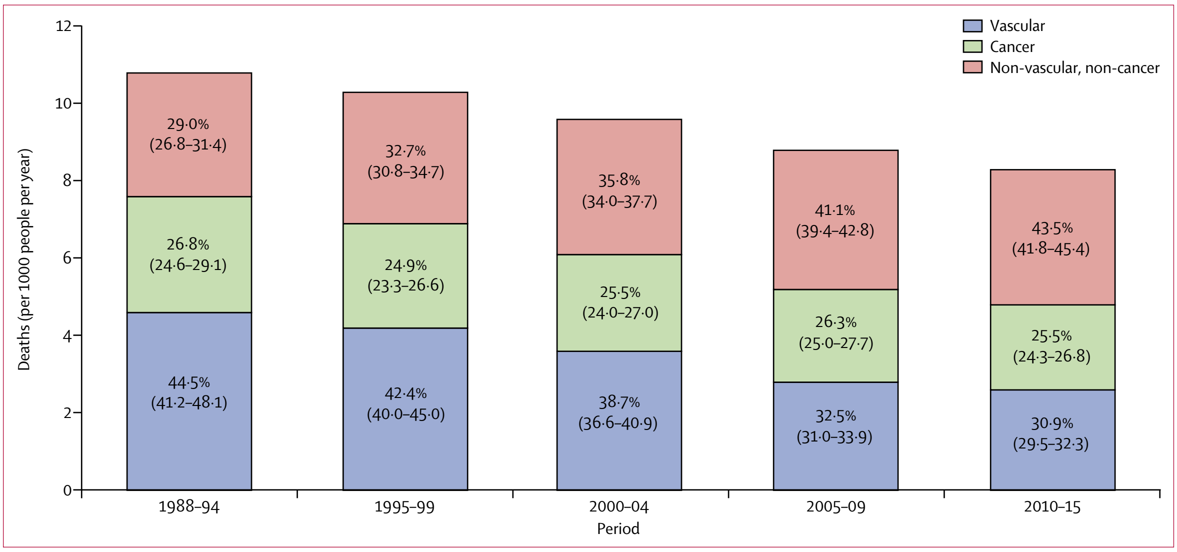

Figure 2: **Deaths due to vascular, cancer, and non-vascular, non-cancer causes among US adults without diagnosed diabetes**
Numbers in bars represent % of total deaths (95% CI).

categories except non-cancer, non-vascular deaths for which there was an 8% increase every 10 years. However, the rates of decline were significantly greater for those with diabetes than those without diabetes for all causes ($p<0·0001$), vascular disease causes ($p=0·0214$), and non-vascular, non-cancer causes ($p<0·0001$), but not for deaths due to cancer ($p=0·93$; table 2). Sensitivity analyses accounting for the possibility of earlier detection in later years yielded similar findings (appendix p 2).

All-cause mortality rates decreased for both sexes but most notably in men (table 3). There was a narrowing of the age-related differences in death rates, as the magnitude of decline was greatest in adults aged 65–74 years and did not decrease significantly in young adults (age 20–44 years) with diabetes (table 3). Patterns of declines in mortality rates were similar in people with and without diabetes (table 3).

The different magnitude of changes in cause-specific mortality led to large changes in the proportional mortality, particularly among adults with diabetes (figure 1). The proportion of total deaths from vascular causes among people with diabetes decreased from 47·8% (95% CI 38·9–58·8) in 1988–94 to 34·1% (31·4–37·1) in 2010–2015. This decrease was offset by large increases in the proportion of deaths from non-vascular, non-cancer

	1988–94	1995–99	2000–04	2005–09	2010–15	Average 10-year difference	10-year percentage change	p value for linear trend
Diseases of the heart								
Diabetes	9·1 (7·7 to 10·6)	9·0 (7·9 to 10·6)	7·1 (6·3 to 7·8)	5·1 (4·6 to 5·5)	4·1 (3·8 to 4·5)	−2·6 (−3·2 to −2·1)	−33·2 (−37·7 to −28·3)	<0·0001
No diabetes	4·1 (3·8 to 4·4)	3·7 (3·5 to 3·9)	3·1 (2·9 to 3·2)	2·4 (2·3 to 2·5)	2·2 (2·1 to 2·3)	−0·9 (−1·0 to −0·8)	−26·6 (−29·4 to −23·8)	<0·0001
Relative risk (95% CI)	2·2 (1·9 to 2·6)	2·4 (2·1 to 2·8)	2·3 (2·0 to 2·6)	2·1 (1·9 to 2·3)	1·9 (1·7 to 2·1)	..	..	..
Malignant neoplasms								
Diabetes	4·4 (3·2 to 5·5)	3·7 (3·0 to 4·5)	3·8 (3·2 to 4·4)	3·4 (3·0 to 3·8)	3·0 (2·8 to 3·3)	−0·6 (−1·1 to −0·2)	−15·7 (−25·7 to −5·7)	0·0199
No diabetes	3·2 (2·9 to 3·4)	2·8 (2·7 to 3·0)	2·8 (2·6 to 2·9)	2·6 (2·5 to 2·7)	2·4 (2·3 to 2·5)	−0·3 (−0·4 to −0·2)	−11·8 (−15·0 to −8·5)	<0·0001
Relative risk (95% CI)	1·4 (1·1 to 1·8)	1·3 (1·1 to 1·6)	1·4 (1·2 to 1·6)	1·3 (1·2 to 1·5)	1·3 (1·2 to 1·4)	..	..	..
Chronic lower respiratory disease								
Diabetes	0·4 (0·1 to 0·6)	0·7 (0·4 to 1·1)	0·7 (0·5 to 0·9)	0·9 (0·7 to 1·1)	0·8 (0·7 to 0·9)	0·2 (0·0 to 0·3)	25·2 (4·5 to 50·1)	0·0023
No diabetes	0·5 (0·5 to 0·6)	0·6 (0·5 to 0·7)	0·6 (0·6 to 0·7)	0·7 (0·6 to 0·7)	0·6 (0·6 to 0·7)	0·0 (−0·0 to 0·1)	5·3 (−1·7 to 12·9)	0·1798
Relative risk (95% CI)	0·7 (0·3 to 1·3)	1·2 (0·7 to 1·9)	1·1 (0·8 to 1·5)	1·4 (1·1 to 1·7)	1·3 (1·1 to 1·6)	..	..	..
Accidents								
Diabetes	0·2 (0·0 to 0·4)	0·3 (0·1 to 0·5)	0·5 (0·3 to 0·8)	0·6 (0·4 to 0·7)	0·6 (0·4 to 0·7)	0·1 (0·0 to 0·2)	38·2 (6·8 to 78·9)	0·0001
No diabetes	0·3 (0·3 to 0·4)	0·4 (0·3 to 0·4)	0·4 (0·3 to 0·4)	0·4 (0·4 to 0·5)	0·4 (0·4 to 0·5)	0·1 (0·0 to 0·1)	18·9 (9·1 to 29·6)	0·0007
Relative risk (95% CI)	0·7 (0·2 to 1·9)	0·8 (0·4 to 1·6)	1·4 (0·8 to 2·2)	1·4 (1·0 to 1·8)	1·2 (0·9 to 1·7)	..	..	..
Cerebrovascular diseases								
Diabetes	1·4 (0·8 to 2·1)	1·6 (1·2 to 2·0)	1·2 (0·9 to 1·4)	1·1 (0·9 to 1·3)	0·8 (0·6 to 0·9)	−0·4 (−0·6 to −0·2)	−28·7 (−40·1 to −15·0)	0·0071
No diabetes	0·8 (0·7 to 0·9)	0·9 (0·8 to 1·0)	0·8 (0·7 to 0·9)	0·6 (0·5 to 0·6)	0·5 (0·4 to 0·5)	−0·2 (−0·2 to −0·1)	−24·7 (−29·6 to −19·3)	<0·0001
Relative risk (95% CI)	1·7 (1·1 to 2·7)	1·9 (1·4 to 2·6)	1·5 (1·2 to 2·0)	1·9 (1·6 to 2·4)	1·6 (1·3 to 2·0)	..	..	..
Alzheimer's disease								
Diabetes	0·2 (0·0 to 0·3)	0·3 (0·1 to 0·6)	0·3 (0·1 to 0·4)	0·3 (0·2 to 0·4)	0·3 (0·2 to 0·4)	0·1 (−0·0 to 0·1)	22·2 (−10·8 to 67·4)	0·2069
No diabetes	0·1 (0·1 to 0·2)	0·1 (0·1 to 0·2)	0·3 (0·2 to 0·3)	0·3 (0·3 to 0·3)	0·3 (0·3 to 0·3)	0·1 (0·1 to 0·1)	53·6 (34·9 to 74·9)	<0·0001
Relative risk (95% CI)	1·5 (0·4 to 4·7)	2·6 (1·0 to 6·5)	1·1 (0·6 to 1·9)	1·1 (0·8 to 1·6)	1·1 (0·8 to 1·4)	..	..	..
Diabetes mellitus								
Diabetes	3·5 (2·6 to 4·5)	3·2 (2·6 to 3·9)	3·3 (2·8 to 3·9)	2·1 (1·8 to 2·4)	1·7 (1·5 to 1·9)	−1·0 (−1·3 to −0·6)	−30·1 (−37·5 to −21·9)	<0·0001
No diabetes	0·1 (0·0 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·0 (−0·0 to 0·0)	11·3 (−6·3 to 32·1)	0·1281
Relative risk (95% CI)	56·1 (31·8 to 99·1)	28·8 (20·1 to 41·3)	27·9 (20·6 to 37·8)	17·0 (13·4 to 21·6)	19·0 (15·1 to 23·9)	..	..	..
Influenza or pneumonia								
Diabetes	0·6 (0·3 to 0·9)	0·6 (0·3 to 0·9)	0·5 (0·3 to 0·7)	0·4 (0·3 to 0·5)	0·3 (0·2 to 0·4)	−0·2 (−0·3 to −0·1)	−32·2 (−46·1 to −14·8)	0·0168
No diabetes	0·4 (0·3 to 0·5)	0·5 (0·4 to 0·5)	0·3 (0·2 to 0·3)	0·2 (0·2 to 0·2)	0·2 (0·2 to 0·2)	−0·1 (−0·1 to −0·1)	−30·3 (−39·1 to −20·2)	<0·0001
Relative risk (95% CI)	1·6 (0·9 to 3·0)	1·3 (0·8 to 2·2)	1·8 (1·1 to 2·8)	1·8 (1·3 to 2·4)	1·4 (1·0 to 2·0)	..	..	..
Nephritis or nephrotic syndrome								
Diabetes	0·4 (0·2 to 0·7)	0·5 (0·3 to 0·8)	0·8 (0·6 to 1·0)	0·7 (0·5 to 0·9)	0·4 (0·3 to 0·5)	−0·1 (−0·2 to 0·1)	−8·9 (−24·6 to 10·0)	0·7057
No diabetes	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·2)	0·0 (0·0 to 0·1)	24·0 (6·9 to 43·9)	0·0008
Relative risk (95% CI)	4·2 (2·0 to 8·9)	5·2 (3·0 to 9·1)	5·0 (3·5 to 7·2)	3·6 (2·7 to 4·8)	2·9 (2·2 to 3·8)	..	..	..
Intentional self-harm								
Diabetes	0·1 (0·0 to 0·3)	0·1 (0·0 to 0·2)	0·2 (0·0 to 0·3)	0·1 (0·0 to 0·2)	0·1 (0·1 to 0·2)	0·0 (−0·1 to 0·1)	1·3 (−44·3 to 84·4)	0·9836
No diabetes	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·2)	0·0 (−0·0 to 0·0)	11·9 (−4·4 to 30·9)	0·1750
Relative risk (95% CI)	1·3 (0·3 to 5·3)	0·6 (0·2 to 2·6)	1·7 (0·8 to 3·5)	0·8 (0·3 to 2·2)	0·9 (0·5 to 1·7)	..	..	..

(Table 4 continues on next page)

causes: from 33·5% (26·7–42·1) to 46·5% (43·3–50·0). The proportion of deaths from cancer was relatively stable over time, ranging from 15·9% to 19·9% (figure 1).

Similar shifts occurred in people without diabetes (figure 2) although the overall proportion of deaths that were caused by cancer was larger among people without diabetes (ranging from 24·9% to 26·8%).

Compared with adults without diabetes, adults with diagnosed diabetes had significantly higher risk over most or all of the time periods for eight of the top 15 specific causes of death (diseases of the heart, malignant neoplasms, cerebrovascular disease, diabetes mellitus, influenza or pneumonia, nephrotic syndrome, sepsis, chronic liver disease; table 4, figure 3). HRs for death associated with diagnosed diabetes (*vs* persons without diabetes) were (apart from diabetes itself) highest for nephritis and nephrotic causes (HRs ranged from 2·9 to 5·2 across the five periods), sepsis (HRs from 1·4 to 2·9), chronic liver disease (HRs from 1·8 to 3·9), diseases of the heart (HRs from 1·9 to 2·4), and cerebrovascular disease (HRs from 1·6 to 1·9; table 4). Death rates due to diseases of the heart,

	1988–94	1995–99	2000–04	2005–09	2010–15	Average 10-year difference	10-year percentage change	p value for linear trend
(Continued from previous page)								
Sepsis								
Diabetes	0·1 (0·0 to 0·3)	0·3 (0·1 to 0·5)	0·3 (0·1 to 0·4)	0·4 (0·2 to 0·5)	0·3 (0·2 to 0·3)	0·0 (–0·0 to 0·1)	10·4 (–15·4 to 44·1)	0·0889
No diabetes	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·2 (0·1 to 0·2)	0·1 (0·1 to 0·1)	0·0 (–0·0 to 0·0)	16·5 (–3·0 to 40·0)	0·0503
Relative risk (95% CI)	1·4 (0·5 to 4·0)	2·9 (1·5 to 5·8)	2·4 (1·4 to 4·2)	2·4 (1·6 to 3·5)	2·1 (1·5 to 3·0)	..	..	..
Chronic liver disease								
Diabetes	0·4 (0·1 to 0·8)	0·4 (0·1 to 0·7)	0·2 (0·1 to 0·4)	0·2 (0·1 to 0·4)	0·2 (0·1 to 0·3)	–0·1 (–0·3 to 0·0)	–29·2 (–53·9 to 8·6)	0·1596
No diabetes	0·1 (0·1 to 0·2)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·0 (–0·0 to 0·0)	5·9 (–11·3 to 26·3)	0·7520
Relative risk (95% CI)	3·9 (1·5 to 10·3)	3·8 (1·8 to 7·7)	2·2 (1·3 to 3·7)	2·2 (1·3 to 3·8)	1·8 (1·2 to 2·7)	..	..	..
Essential hypertension or renal								
Diabetes	0·1 (0·0 to 0·1)	0·1 (0·0 to 0·1)	0·1 (0·0 to 0·2)	0·2 (0·1 to 0·3)	0·2 (0·1 to 0·2)	0·1 (0·0 to 0·1)	66·8 (13·4 to 145·3)	0·0010
No diabetes	0·1 (0·0 to 0·1)	0·1 (0·0 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·0 (0·0 to 0·0)	36·3 (8·7 to 70·9)	0·0011
Relative risk (95% CI)	1·0 (0·2 to 4·5)	0·9 (0·3 to 3·0)	0·9 (0·4 to 2·0)	2·4 (1·5 to 3·7)	1·3 (0·9 to 2·0)	..	..	..
Parkinson's disease								
Diabetes	0·0 (0·0 to 0·1)	0·0 (0·0 to 0·1)	0·2 (0·1 to 0·3)	0·1 (0·0 to 0·2)	0·1 (0·0 to 0·1)	0·0 (–0·0 to 0·0)	23·1 (–16·0 to 80·3)	0·0179
No diabetes	0·0 (0·0 to 0·1)	0·1 (0·0 to 0·1)	0·1 (0·0 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·1 to 0·1)	0·0 (0·0 to 0·0)	30·9 (7·6 to 59·2)	0·0024
Relative risk (95% CI)	0·5 (0·1 to 4·0)	0·6 (0·1 to 2·8)	2·3 (1·1 to 5·2)	1·2 (0·6 to 2·1)	0·9 (0·5 to 1·6)	..	..	..
Pneumonitis								
Diabetes	0·1 (0·0 to 0·2)	0·1 (0·0 to 0·2)	0·2 (0·1 to 0·3)	0·1 (0·0 to 0·1)	0·1 (0·0 to 0·1)	–0·0 (–0·0 to 0·0)	–2·5 (–34·9 to 46·1)	0·7414
No diabetes	0·0 (0·0 to 0·1)	0·1 (0·0 to 0·1)	0·1 (0·1 to 0·1)	0·1 (0·0 to 0·1)	0·1 (0·1 to 0·1)	0·0 (–0·0 to 0·0)	27·4 (–3·8 to 68·8)	0·0131
Relative risk (95% CI)	2·3 (0·5 to 10·0)	1·3 (0·4 to 4·3)	2·4 (1·2 to 4·7)	1·2 (0·6 to 2·4)	1·2 (0·6 to 2·2)	..	..	..

Data are age-adjusted sex-adjusted mortality rates per 1000 person-years (95% CI), unless otherwise stated.

Table 4: **Cause-specific mortality rates by diabetes status and time period**

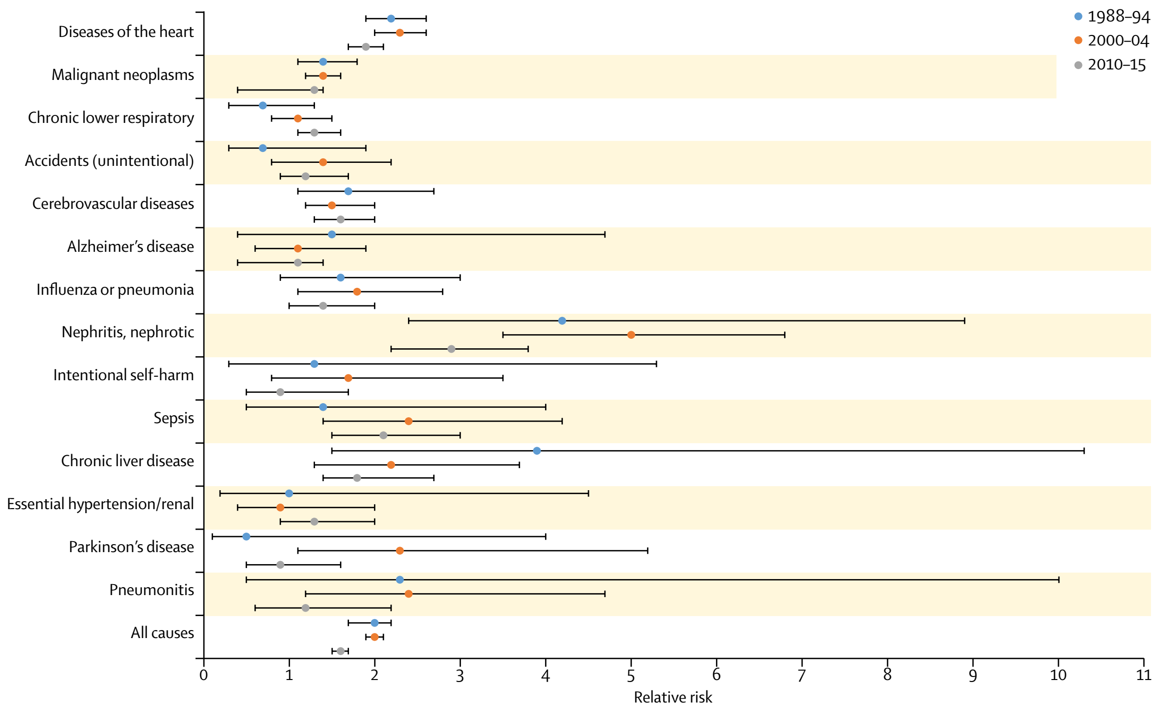

Figure 3: **Relative risks of death among people diabetes versus those without, according to specific causes of death**

malignant neoplasms, cerebrovascular disease, diabetes mellitus, and influenza or pneumonia decreased significantly over time in adults with diabetes (table 3). However, death rates in adults with diabetes tripled for unintentional accidents (with an average 38% increase every 10 years), and increased significantly for chronic lower respiratory disease, Parkinson's disease, and essential hypertension and renal disease (table 3).

Discussion

This examination of cause-specific mortality in US adults diagnosed with diabetes shows important changes in both the type and magnitude of mortality risk, consistent with previous observations that the character of diabetes-related complications is changing.[7,8] Although vascular disease remains the largest single contributor to mortality, virtually all of the decline in death rate among adults with diabetes was caused by the reduction in vascular disease deaths: vascular disease accounted for almost half of deaths in people with diabetes in the early 1990s, falling to about one-third of deaths in 2010–15. Deaths from unintentional injuries, lower respiratory disease, and essential hypertension and renal disease increased over this period in people with diabetes. Non-vascular, non-cancer deaths now account for almost half of all deaths and also includes other causes that are consistently associated with diabetes, including sepsis, influenza, and liver diseases. Given the high prevalence of diabetes and the increased number of years of exposure to diabetes in the US,[2] the diversified causes of mortality could have important clinical and public health effects for diabetes in coming decades, indicating a need to identify and emphasise prevention approaches and epidemiological monitoring of a wider range of diabetes-related morbidity.

The reduction in deaths caused by vascular disease is consistent with previous reports of improved cardiovascular mortality rates, myocardial infarction, and stroke, which have been attributed to improvements in revascularisation, acute care, risk factor management, and behavioural changes.[8,23,24] Although mortality rates declined among people both with and without diabetes, the absolute reductions were greater for people with diabetes, resulting in a halving of the excess mortality risk associated with diabetes and a greater persistence of deaths due to diverse, non-vascular and non-cancer causes in people with diabetes. The particularly large reductions in all-cause and vascular disease mortality in the population diagnosed with diabetes could be a result of more aggressive management of risk factors among people diagnosed with diabetes. Levels of smoking, blood pressure, and lipid concentrations have improved more markedly in people with diabetes in recent decades, perhaps driven by observations that diabetes is a coronary risk equivalent.[25] Improvements in average glycaemic control during the 2000s[23] might have also reduced mortality risk among people with diabetes. Additional factors might have affected the risk of vascular disease mortality for the overall population both with and without diabetes, including reductions in trans fats and saturated fats, and new medical treatments following cardiovascular events.[24,26] Because people with diabetes had a high mortality rate to begin with, such population-wide changes in risk factors could have caused the greater absolute reduction among people with diabetes than in those without diabetes. Finally, the reduction in vascular disease deaths probably affected the rates of other causes, removing a competing risk and thus suppressing improvements in trends of other causes of death.

Young adults with diabetes were the exception to positive trends as there was no reduction in all-cause death rates among those aged 20–44 years. Among non-white young people, there has been a greater increase in type 2 than in type 1 diabetes along with a marked increase in obesity in people with diabetes, which, given the higher rate of complications in type 2 than in type 1 diabetes, could have suppressed improvements in mortality risk in young adulthood.[27] Diabetes complications and risk factor management have improved less in young adults than in other age groups,[8,28] and so young adults are an important group for future investigations.

Cancer-related deaths declined significantly among people both with and without diabetes, but declines were modest and its proportional contribution to overall deaths did not change. The findings of a 12–16% decrease in cancer-related deaths every 10 years among people without and with diabetes are consistent with those of the general population, in which rates decreased 18% every 10 years, from 1969, to 2013.[29] Diabetes is associated with an increased risk for liver, pancreas, endometrium, colon and rectum, breast, and bladder cancers.[3,30] Of these, death rates for colorectal and breast cancer have decreased overall in the USA, but deaths from pancreatic and liver cancers have increased.[31] Determining whether trends in the death rates for specific causes of cancer have also occurred in people with diabetes will depend on more in depth analysis and aggregation across years.

Diabetes as underlying cause of death in people with diagnosed diabetes declined substantially in the US from the early 1990s to 2015, consistent with observations of a decline in deaths, hospital admissions, and emergency room visits for hyperglycaemic crisis.[8,32] These trends could be due to improved management of diabetes and organisation of care that led to improved glycaemic control and risk factor control for other diabetes complications. However, diabetes as a contributing cause of death is under-reported on death certificates,[13] leaving open the possibility that changes in reporting practices could affect reports of diabetes-related deaths and its competing causes.[7,13,33] This limitation led us to assemble national cohorts to assess causes of death within people with diagnosed diabetes.

Non-vascular, non-cancer deaths included several less common, specific causes of death that have previously been associated with diabetes.[3] Risk ratios were highest for nephritis and nephrotic diseases, consistent with the effect of diabetes on nephropathy, as well as long-term exposure to hyperglycaemia and hypertension. Despite the improvements in the control of these major risk factors in people with diabetes and the increased use of renin-angiotensin-aldosterone system inhibitors from 1988–94 to 2005–08, the prevalence of kidney disease in individuals with diabetes in the US remained stable, which could also have suppressed improvements in mortality rates.[23,34–36] The increased risk of death from liver disease among people with diabetes (HRs ranged from 1·8 to 3·9 over the study period) could be bi-directional, as underlying fatty liver disease is a risk factor for type 2 diabetes, and diabetes is associated with an increased risk of cirrhosis, liver cancer, and hepatitis.[37] The increased risk of death from sepsis, influenza or pneumonia, and nephritis have also been reported previously[38,40] and are consistent with observations that deficiencies in the immune response (particularly neutrophil and humoral response) are associated with hyperglycaemia and may be exacerbated by the presence of vascular disease.[3,38–40]

Finally, the increasing mortality rate of unintentional injuries among people with diagnosed diabetes is concerning; the mechanisms for this association are unclear. Diabetes and its complications have been associated with an increased risk of injurious falls and fractures[41] and having severe hypoglycaemic episodes could increase the risk of motor vehicle accidents.[42]

There are several limitations in our analyses. First, cause of death reporting is affected by medical opinion and subjective judgement that could shift over time or by the transition from ICD-9 to ICD-10. However, with the exception of pneumonia and influenza, the causes with significant trends over time among people with diabetes were similar with ICD-9 and ICD-10.[43] We are not aware of research about the comparability of ICD reporting by diabetes status nor of studies that have validated cause-of-death reporting against adjudicated medical records over time to determine whether reporting is changing.

Second, diabetes was self-reported and changes in diabetes definitions could have affected the population with diagnosed diabetes, leading to detection of diabetes at earlier stages and lower mortality rates. However, there is not clear evidence that diabetes is being detected earlier, and there has been no change in the average age at diagnosis nationally.[44] Our sensitivity analyses, in which we simulated increased detection by excluding people with recent onset in recent cohorts, had little effect on our findings. Third, we lacked adequate information on diabetes type. The ratio of type 2 to type 1 diabetes has probably increased over time, which we think would favour an increasing risk of vascular disease death but have an unclear effect on other causes. Fourth, we lacked information after the baseline visit to ascertain incident cases of diabetes. Assuming the death rates among people newly diagnosed with diabetes are higher than that in people without diabetes but lower than those who already have diabetes, this limitation would lead to a slight overestimate of mortality rates for both the diabetic and non-diabetic populations but should have negligible effects on the relative risk.[45–47] Finally, our analyses did not adjust for multiple comparisons, and some of the trends in specific causes of death over time are based on fairly large confidence intervals and warrant replication and continued monitoring.

In summary, these nationally representative estimates of cause-specific mortality confirm a large excess risk of death due to diabetes across diverse causes and reflect the multiorgan effects of diabetes and its underlying risk factors. The reduction in relative risk of all-cause and vascular-disease death associated with diabetes should not be interpreted as an indication that the public health burden of diabetes is declining. One byproduct of the reduction in mortality has been the increase in lifetime risk and years spent with diabetes in the USA.[8] The diversification of morbidity and mortality associated with diabetes could take different forms in other countries where risk factors, health status, medical care, and health policies differ. The increasing diversification of the causes of death among people with diabetes will have important implications for the development of therapies and public health approaches to reduce diabetes-related morbidity. As such, this report serves an important national baseline for these efforts.

Contributors

EWG had the idea for the study, designed the study, and wrote the report. YJC did the primary analyses and data management and revised the report. MS and JL analysed data and revised the report. LSG, ALA, and GI analysed data, and wrote and reviewed of the report.

Declaration of interests

We declare no competing interests.

Acknowledgments

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

References

1 Seshasai SR, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *NEJM* 2011; **364:** 829–41.

2 Gregg EW, Zhuo X, Cheng YJ, Albright AL, Narayan KM, 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.

3 Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. *Diabetes Care* 2012; **35:** 1835–44.

4 Gordon-Dseagu VL, Shelton N, Mindell J. Diabetes mellitus and mortality from all-causes, cancer, cardiovascular and respiratory disease: evidence from the Health Survey for England and Scottish Health Survey cohorts. *J Diabetes Complications* 2014; **28:** 791–97.

5 Carstensen B, Jorgensen ME, Friis S. The epidemiology of diabetes and cancer. *Curr Diab Rep* 2014; **14:** 535.

6 Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. *NEJM* 2015; **373:** 1720–32.

7 Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S, Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997–2010. *Diabetes Care* 2014; **37:** 2579–86.

8 Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. *NEJM* 2014; **370:** 1514–23.

9 Lu FP, Lin KP, Kuo HK. Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. *PLoS One* 2009; **4:** e4144.

10 Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. *Lancet Diabetes Endocrinol* 2016; **4:** 537–47.

11 Sidney S, Quesenberry CP Jr, Jaffe MG, et al. Recent trends in cardiovascular mortality in the United States and public health goals. *JAMA Cardiol* 2016; **1:** 594–99.

12 Murphy SL, Kochanek KD, Xu J, Heron M. Deaths: final data for 2012. *Natl Vital Stat Rep* 2015; **63:** 1–117.

13 McEwen LN, Karter AJ, Curb JD, Marrero DG, Crosson JC, Herman WH. Temporal trends in recording of diabetes on death certificates: results from Translating Research Into Action for Diabetes (TRIAD). *Diabet Care* 2011; **34:** 1529–33.

14 Fedeli U, Zoppini G, Goldoni CA, Avossa F, Mastrangelo G, Saugo M. Multiple causes of death analysis of chronic diseases: the example of diabetes. *Popul Health Metr* 2015; **13:** 21.

15 Botman SL, Moore TF, Moriarty CL, Parsons VL. Design and estimation for the National Health Interview Survey, 1995–2004. *Vital Health Stat 2* 2000; **130:** 1–31.

16 Centers for Disease Control and Prevention. National Health Interview Survey: Methods. 2016. http://www.cdc.gov/nchs/nhis/methods.htm (accessed May 1, 2018).

17 National Center for Health Statistics Office of Analysis and Epidemiology. The National Health Interview Survey (1986-2004) Linked Mortality Files, mortality follow-up through 2006: Matching Methodology, May 2009. http://www.cdc.gov/nchs/data/datalinkage/matching_methodology_nhis_final.pdf (accessed May 1, 2018).

18 Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: final data for 2013. *Natl Vital Stat Rep* 2016; **64:** 1–119.

19 Cheng YJ, Gregg EW, Rolka DB, Thompson TJ. Using multi-year national survey cohorts for period estimates: an application of weighted discrete Poisson regression for assessing annual national mortality in US adults with and without diabetes, 2000–2006. *Popul Health Metr* 2016; **14:** 48.

20 Institute NC. Average Annual Percentage Change (AAPC). 2017. https://surveillance.cancer.gov/help/joinpoint/setting-parameters/advanced-tab/average-annual-percent-change-aapc (accessed Aug 24, 2017).

21 Parr WC. A note on the jacknife, the boostraap and the Delta method estimators of bias and variance. *Biometrika* 1983; 719–22.

22 Griffiths RI, O'Malley CD, Herbert RJ, Danese MD. Misclassification of incident conditions using claims data: impact of varying the period used to exclude pre-existing disease. *BMC Med Res Methodol* 2013; **13:** 32.

23 Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999–2010. *NEJM* 2013; **368:** 1613–24.

24 Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *NEJM* 2007; **356:** 2388–98.

25 Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *NEJM* 1998; **339:** 229–34.

26 Angell SY, Cobb LK, Curtis CJ, Konty KJ, Silver LD. Change in trans fatty acid content of fast-food purchases associated with New York City's restaurant regulation: a pre-post study. *Ann Intern Med* 2012; **157:** 81–86.

27 Dabelea D, Stafford JM, Mayer-Davis EJ, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. *JAMA* 2017; **317:** 825–35.

28 Chapter 9. In: Cowie CC, Casagrande SS, Menke A, et al, eds. Diabetes in America, 3rd edn. Bethesda, MD: National Institutes of Health, 2017: 1–55.

29 Ma J, Ward EM, Siegel RL, Jemal A. Temporal trends in mortality in the United States, 1969-2013. *JAMA* 2015; **314:** 1731–39.

30 Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010; **33:** 1674–85.

31 American Cancer Society. Cancer Facts and Figures 2016. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2016.html (accessed April 27, 2018).

32 Wang J, Geiss LS, Williams DE, Gregg EW. Trends in emergency department visit rates for hypoglycemia and hyperglycemic crisis among adults with diabetes, United States, 2006–2011. *PLoS One* 2015; **10:** e0134917.

33 Stokes A, Preston SH. Deaths attributable to diabetes in the United States: comparison of data sources and estimation approaches. *PLoS One* 2017; **12:** e0170219.

34 de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA* 2011; **305:** 2532–39.

35 Murphy D, McCulloch CE, Lin F, et al. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med* 2016; **165:** 473–81.

36 Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012; **380:** 1662–73.

37 Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes Care* 2007; **30:** 734–43.

38 Koh GC, Peacock SJ, van der Poll T, Wiersinga WJ. The impact of diabetes on the pathogenesis of sepsis. *Eur J Clin Microbiol Infect Dis* 2012; **31:** 379–88.

39 Magliano DJ, Harding JL, Cohen K, Huxley RR, Davis WA, Shaw JE. Excess risk of dying from infectious causes in those with type 1 and type 2 diabetes. *Diabetes Care* 2015; **38:** 1274–80.

40 Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. *NEJM* 1999; **341:** 1906–12.

41 Schwartz AV, Vittinghoff E, Sellmeyer DE, et al. Diabetes-related complications, glycemic control, and falls in older adults. *Diabetes Care* 2008; **31:** 391–96.

42 Lorber D, Anderson J, Arent S, et al. Diabetes and driving. *Diabetes Care* 2014; **37** (suppl 1): S97–103.

43 Anderson RN, Minino AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between ICD-9 and ICD-10: preliminary estimates. *Natl Vital Stat Rep* 2001; **49:** 1–32.

44 Centers for Disease Control and Prevention. National Diabetes Surveillance System. 2016. http://www.cdc.gov/diabetes/statistics/index.htm. (accessed Feb 25, 2016).

45 Head J, Fuller JH. International variations in mortality among diabetic patients: the WHO Multinational Study of Vascular Disease in Diabetics. *Diabetologia* 1990; **33:** 477–81.

46 Murray CJ, Kulkarni SC, Michaud C, et al. Eight Americas: investigating mortality disparities across races, counties, and race-counties in the United States. *PLoS Med* 2006; **3:** e260.

47 Chetty R, Stepner M, Abraham S, et al. The association between income and life expectancy in the United States, 2001–2014. *JAMA* 2016; **315:** 1750–66.