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## A systematic review of trends in all-cause mortality among people with diabetes

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### Abstract

**Aims/hypothesis**—We examined all-cause mortality trends in people with diabetes and compared them with trends among people without diabetes.

**Methods**—MEDLINE, EMBASE and CINAHL databases were searched for observational studies published from 1980 to 2019 reporting all-cause mortality rates across 2 time periods in people with diabetes. Mortality trends were examined by ethnicity, age and sex within comparable calendar periods.

**Results**—Of 30,295 abstracts screened, 35 studies were included, providing data on 69 separate ethnic-specific or sex-specific populations with diabetes since 1970. Overall, 43% (3/7), 53% (10/19) and 74% (32/43) of the populations studied had decreasing trends in all-cause mortality

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**Contribution statement** DJM, JES, MEP and EWG conceived the project. LC, RMI, MT, DNK and JLH are postdoctoral fellows who screened abstracts for selection into the systematic review. JW, JWS, ELMB, JES and DJM also screened abstracts. LC, RMI, JW and DJM extracted data. LC, TRH, DJM and JES applied the quality criteria to selected articles. LC and DJM performed the statistical analysis, drafted the report, reviewed/edited the manuscript and revised the report for important intellectual content. AS provided statistical advice and commented on statistical analyses. JES, MEP and EWG reviewed/edited the manuscript and provided intellectual input throughout the process. All authors reviewed/edited the manuscript and approved the version to be published. DJM and JES are the guarantors of this work and, as such, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Dianna J. Magliano and Jonathan E. Shaw are joint senior authors.

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rates in people with diabetes in 1970–1989, 1990–1999 and 2000–2016, respectively. In 1990–1999 and 2000–2016, mortality rates declined in 75% (9/12) and 78% (28/36) of predominantly Europid populations, and in 14% (1/7) and 57% (4/7) of non-Europid populations, respectively. In 2000–2016, mortality rates declined in 33% (4/12), 65% (11/17), 88% (7/8) and 76% (16/21) of populations aged <40, 40–54, 55–69 and ≥ 70 years, respectively. Among the 33 populations with separate mortality data for those with and without diabetes, 60% (6/10) of the populations with diabetes in 1990–1999 and 58% (11/19) in 2000–2016 had an annual reduction in mortality rates that was similar to or greater than in those without diabetes.

**Conclusions/interpretation**—All-cause mortality has declined in the majority of predominantly Europid populations with diabetes since 2000, and the magnitude of annual mortality reduction matched or exceeded that observed in people without diabetes in nearly 60% of populations. Patterns of diabetes mortality remain uncertain in younger age groups and non-Europid populations.

Registration—PROSPERO registration ID CRD42019095974.

## Keywords

Diabetes; Epidemiology; Mortality; Systematic review; Trends

## Introduction

Over the past three decades, the number of people with diabetes has more than doubled globally and this trend is projected to continue, making diabetes a key health priority [1]. Presently, more than one in three people are expected to develop diabetes in their lifetimes [2, 3]. These people will have nearly twofold higher mortality from any cause compared with people without diabetes [4], and a shorter life expectancy (~6–7 years less than the general population) [2, 3]. Nonetheless, an increasing number of reports indicate that mortality among people with diabetes is declining, paralleling trends observed in general populations [5–8]. In the USA, for example, all-cause mortality has decreased in people both with and without diabetes, mainly due to reduction in cardiovascular fatalities [8, 9]. However, it remains unclear how consistent mortality trends are among various populations with diabetes, and whether these simply reflect similar change in the general population.

Mortality trends in diabetes provide a key metric of the burden of diabetes-related complications and comorbidities, and are an important long-term indicator of healthcare, access to care and other socioeconomic and genetic factors. There is considerable international variation in mortality rates among populations with diabetes; however, the overall magnitude and variability of trends in mortality rates remain unknown.

Therefore, we conducted a systematic review of observational studies reporting all-cause mortality rates across 2 time periods among people with diabetes. In addition to overall mortality trends over time, we examined the patterns of mortality trends in people with diabetes by ethnicity, age and sex within comparable calendar times, and differences in trends between people with and without diabetes.

## Methods

This systematic review is reported in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [10] and was registered on PROSPERO (CRD42019095974).

### Search strategy and selection criteria

We searched MEDLINE ([www.ovid.com/product-details.901.html](http://www.ovid.com/product-details.901.html)), EMBASE ([www.ovid.com/product-details.903.html](http://www.ovid.com/product-details.903.html)) and CINAHL ([www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete](http://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete)) databases (all accessed 6 February 2020) from January 1980 to December 2019, using the following combined free text and medical subject heading search strategy: (Diabetes OR Diabetes Mellitus OR ‘Diabetes Mellitus, Type 2’) AND (Mortality OR ‘Cause of death’ OR ‘Child mortality’ OR Death OR Trends). We limited the search to articles published in English (Electronic supplementary material [ESM] Table 1). The reference lists of identified articles were also screened and we undertook a Google search to identify any relevant government reports.

To be included in this review, studies needed to report all-cause mortality rates in populations with diabetes in two or more separate time periods such that a trend could be calculated. Studies only reporting death attributable specifically to diabetes were excluded. A detailed explanation of inclusion and exclusion criteria is provided in the ESM Methods.

Studies that were derived from nationally representative data were prioritised over studies that were based on regional or selected groups. Where there were multiple publications using the same data source, we chose the publication that covered the longest time. Each title and abstract was screened by at least two authors (D. J. Magliano, D. N. Koye, E. L. M. Barr, J. L. Harding, J. W. Sacre, J. Wang, L. Chen, M. Tabesh, J. E. Shaw and R. M. Islam) and discrepancies were resolved by discussion.

### Assessment of diabetes status at baseline

We categorised the definition of diabetes that was reported in the original publications into one of five groups: self-report of physician-diagnosed diabetes, linkage to medication or reimbursement registries, measurement of blood glucose or HbA<sub>1c</sub>, clinical diagnosis by physicians or from International Classification of Disease codes, or administrative algorithm derived.

### Outcome measure

Death was determined by linkage to the national death registries within the respective country.

### Data extraction and quality assessment

Extracted data included study and population characteristics, crude or standardised mortality rate (per 1000 person-years) or cumulative mortality (% per year) during each time period or annual mortality rate (per 1000 people) among people with diabetes and those without diabetes (if available) (including number of deaths and the corresponding number of people

with and without diabetes, respectively), and the reported pattern of the trend (increasing, decreasing or unchanged mortality [i.e. no statistically significant ( $p < 0.05$ ) evidence of changing mortality rates]) over the study's observation period (Table 1 and ESM Table 2). Each study's observation period was the time interval between the first and last calendar years that mortality rates were reported. If mortality rates were reported for a multi-year time period, instead of by individual calendar year, the mortality rate was attributed to the calendar year that corresponded to the midpoint of the time period.

From each study, we extracted data from each subpopulation reported, such that a study that reported mortality trends in men and women separately contributed two populations (ESM Table 2). To avoid double counting, when the data were reported in the total population and by sex and ethnic groups, we included data only once and prioritised ethnic-specific data over sex-specific and total population data. We classified studies as two major ethnic categories, i.e. Europid and non-Europid populations, based on the predominant ethnicity of the country where they were conducted. Studies from the indigenous populations were included in the non-Europid category, irrespective of the country where they were conducted.

Age-specific mortality rates for each time period and the reported pattern of mortality trends by age group were also extracted where available (ESM Table 2) and then categorised into four age groups (<40, 40–54, 55–69 and ≥ 70 years). In studies where numbers of deaths and numbers with diabetes were reported by smaller age groups, we re-calculated mortality rates across our specified larger age groups. Where there were multiple age groups within any of our broader age groups, but insufficient information to combine the data into a new category, only data from the one age group that was most representative of the broader age group were used.

Data were extracted independently by pairs of authors (L. Chen and R. M. Islam or J. Wang) and were checked for any errors (D. J. Magliano). Data reported only in graphs were extracted using DigitizeIt software [11]. The study quality of all included studies was assessed by two authors (L. Chen and T. R. Hird) using a modified Newcastle–Ottawa scale for assessing the risk of bias of cohort studies [12] (details in the ESM Methods). Any disagreements were discussed between two authors (L. Chen and D. J. Magliano), and another author (J. E. Shaw) gave a final judgement if no consensus could be reached.

### Data synthesis and analysis

The primary analysis was to investigate the proportions of populations reporting increasing, decreasing and unchanged mortality rates in people with diabetes within comparable calendar times. We allocated the reported trend of each population to the midpoint of each study's observation period, and then assigned this trend to one of four pre-specified calendar periods: 1970–1979, 1980–1989, 1990–1999 and from 2000 onwards.

Where a test of significance of trends was not reported or when a study's observation period was longer than 10 years (ESM Table 3), we used joinpoint regression to identify the years or time periods where linear trends changed significantly either in direction or in magnitude, and calculated an annual per cent change (APC) for each segment identified and the average

annual per cent change (AAPC) over the study's whole observation period with the weights equal to the length of each segment [13, 14] (details in the ESM Methods). For studies reporting mortality rates in only two time periods, we performed log-linear regression to determine the difference in mortality rates between the two time periods and to calculate the APC in mortality rates. We classified the mortality trend as 'increasing' if the point estimate of the APC was positive and this value was statistically significant based on the 95% CI of the APC, i.e. the 95% CI excluded the null value of zero. Conversely, a trend was defined as 'decreasing' if the point estimate of the APC was negative and its 95% CI excluded the null value of zero. When the 95% CI of the APC included the null value of zero, we classified the trend as without statistical significance, or 'unchanged'. If two different trends (either direction or magnitude) were detected over two different segments/parts of the study period in one population, we considered these as two separate populations.

We examined the variance in the APC in mortality rates in people with diabetes using random-effects meta-analysis weighted by the inverse of the variance of the APC, and we used the  $I^2$  statistic to estimate the percentage of variability caused by between-population heterogeneity [15]. We conducted subgroup analyses among populations with data on APC in mortality rates according to the following variables: predominant ethnicity (Europid, non-Europid); sex (men, women and total); year of study midpoint (1970–1989, 1990–1999 and 2000–2016); number of time periods with mortality rates reported (<4 and ≥ 4 time periods); whether the studies were of high quality (greater than 6 out of a maximum of 11 points) vs low quality (a score of 6 or below) on the Newcastle–Ottawa scale; and whether the data were sourced from an administrative or health insurance or registry database vs from a survey database. Random-effects metaregression analyses were used to test differences across subgroups. Subgroup analyses were also conducted by restricting to those studies based on administrative or health insurance or registry database.

We examined whether people with diabetes had a greater or lesser reduction in mortality rates than those without diabetes over each study's whole observation period among studies with available data for comparison. If a statistical test of difference in mortality trends between diabetes and non-diabetes was not reported in the study, we calculated the  $z$  score using the point estimate and its variance for the difference in the APCs in mortality rates between those with and without diabetes [16].

To test whether use of multiple populations per study was driving our primary results, we conducted a sensitivity analysis in which we examined the patterns of mortality trends among the total population with diabetes in each study. We also investigated the patterns of mortality trends in people with diabetes after excluding studies with quality scores in the lowest quartile. Analyses were conducted using Stata software version 15.1 (Stata Corporation, College Station, TX, USA) and the Joinpoint Regression Program, version 4.7.0.0 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, MD, USA).

## Results

### Characteristics of included studies

A total of 30,295 abstracts published between 1 January 1980 and 31 December 2019 were identified. Among these, 89 papers described mortality trends among people with diabetes, of which 36 met all inclusion criteria (ESM Fig. 1). Of the 36 articles, two reported crude mortality rates by age groups and sex and age-and sex-adjusted mortality rates, respectively, but were based on the same data source and thus were treated as one study [17, 18]. Another article reported mortality trends using data from two countries (Canada and the UK) [6], and was treated as one study with two data sources. Therefore, 35 studies (36 data sources) from 17 countries/regions reporting mortality trends since 1970 contributed to the analysis; all were from high-income countries (Table 1 and ESM Table 2). Only 17% (6/35) of studies provided data on predominantly non-Europid populations [8, 19–23], including two (6%) in indigenous people [20, 21].

The most common data source was administrative data (47% of the 36 sources), followed by registry data (28%), health surveys linked to a mortality database (17%) and health insurance data (8%); 64% (23/36) of the data sources were based on national data. These data sources employed various definitions of diabetes, i.e. clinical diagnosis (33%), diabetes medication (via linkage to medication registries) (8%), an algorithm (incorporating at least two different criteria) (42%), measurement of blood glucose or HbA<sub>1c</sub> (3%) and self-report (11%). The sample sizes of the populations were greater than 10,000 per time period in 75% (27/36) of the data sources and greater than 150,000 per time period in 50% of the sources. Eleven studies (31%) restricted the population to type 2 diabetes while the remainder included all people with diabetes. Annual and standardised mortality rates were reported in 69% (24/35) and 71% (25/35) of the studies, respectively.

### Overall trends of all-cause mortality among populations with diabetes

We separated the data into populations based on ethnicity and sex, and performed joinpoint or log-linear regression in those populations without reported mortality trends or with study periods longer than 10 years, generating 69 separate populations with a single trend over the whole or part of a study's observation period (Table 2). Overall, all-cause mortality rates in people with diabetes declined in 43% (3/7), 53% (10/19) and 74% (32/43) of the populations studied in 1970–1989, 1990–1999 and 2000–2016, respectively (Fig. 1).

ESM Fig. 2 shows the APCs in mortality rates by sex and the midpoint of the study period among the 67 separate populations (APC data unavailable in two populations). We found that 81% (54/67) of the populations had a negative change in mortality rates (the point estimate of the APC less than zero), of which the 95% CI of the APC was less than zero in 42/54 (ESM Fig. 3). The proportion of populations with small sample sizes (i.e. <10,000 per time period) was similar between those with unchanged and those with significantly decreasing mortality rates (47% [9/19] vs 27% [12/45],  $p = 0.11$ ). There was significant heterogeneity in the APCs in mortality rates among the 67 populations ( $I^2 = 95.1\%$ ,  $p < 0.001$ ; ESM Fig. 2) and across different subgroups ( $I^2 = 37.1\text{--}97.4\%$ ; ESM Figs 4 and 5).

## Patterns of all-cause mortality trends among populations with diabetes by ethnicity, age and sex

Figure 1 summarises the findings from Tables 2 and 3, stratifying by predominant ethnicity, pre-specified age groups and sex within comparable calendar periods. The proportion of populations with declining mortality rates was higher in predominantly Europid populations than in non-Europid populations in 1990–1999 (75% [9/12] vs 14% [1/7],  $p = 0.01$ ), but was not statistically different in 2000–2016 (78% [28/36] vs 57% [4/7],  $p = 0.25$ ).

Among two US studies reporting mortality trends among different ethnic groups with diabetes, an earlier study showed significant declining mortality rates in predominantly Europids, while mortality rates were unchanged among US black, Hispanic and Asian people in 1994–2001 [19]; another recent US study reported declining mortality rates in Europids and black people, but not in other US ethnic groups from 1988 to 2015 [8]. Another study did not show that trends differed between Canadian indigenous and non-indigenous populations with diabetes in 1995–2007 [21].

Of the 14 studies reporting age-specific mortality trends, six described trends in the period earlier than 2000 [6, 19, 24–27] and no clear patterns of trends were observed during this period (Table 3, Fig. 1 and 2). In 2000–2016, the proportion of populations reporting declining mortality rates was lower in those aged <40 years than in those aged 55–69 years (33% vs 88%,  $p = 0.02$ ) and in those aged 70 years (33% vs 76%,  $p = 0.02$ ).

Among studies that directly compared mortality trends among different age groups, a Scottish study reported reductions of similar magnitudes in all age groups [28]. In contrast, greater reductions in mortality rates were observed in younger adults in a study from Canada [18], and in 65–74 years olds compared with those aged 75 years in an Italian population [29].

A total of 15 studies provided data on mortality trends by sex, mainly in 2000–2016 (Table 2, Fig. 1). Similar proportions of populations with declining mortality rates were observed for men (75%) and women (69%) in 2000–2016. Among six studies specifically comparing men and women, four showed greater mortality declines in men [8, 29–31], while the remaining two reported no significant difference [18, 32].

## Comparison of all-cause mortality trends between people with and without diabetes

A total of 44 populations either reported a difference in mortality trends between people with and without diabetes or had data available comparing the difference in the APCs in mortality rates between these two groups in each study. Of these, 17% (1/6), 60% (6/10) and 71% (20/28) showed that the reduction in mortality rates in diabetes was at least as great among those with diabetes as among those without diabetes in 1970–1989, 1990–1999 and 2000–2016, respectively (ESM Table 4).

Figure 3 shows the APCs in mortality rates by diabetes status in the 33 populations that had data available for calculating the APC separately for those with and without diabetes. In 1970–1989, 1990–1999 and 2000–2016, 25% (1/4), 60% (6/10) and 58% (11/19) of

populations had a more negative or similar APC estimate in diabetes compared with non-diabetes (ESM Table 5).

Trends in the excess risk of mortality from diabetes, as measured by mortality rate ratio or standardised mortality ratio, were compared between men and women in two studies, both showing similar declines in men and women over time [6, 32]. One study reported that the mortality rate ratios became lower over time for all age groups except for the group aged <44 years in the Canadian and UK cohorts [6].

### Sensitivity analyses

When the patterns of mortality trends were examined based on individual studies, declining mortality rates in people with diabetes was observed in 82% (23/28) of studies in 2000–2016, which was similar to the 74% (32/43) of separate ethnic-specific or sex-specific populations showing decreasing trends in this time period.

The median quality score was 8 out of 11 (interquartile range: 6.5–9) (ESM Table 6). We repeated the analyses reported in Fig. 1 after excluding studies with quality scores in the lowest quartile (i.e. a score of 6 or below), and observed similar patterns in the 26 studies that were deemed high quality, with 77% (30/39) of populations showing declining mortality trends in people with diabetes in 2000–2016.

## Discussion

In this systematic review of mortality trends in people with diabetes, we present three key findings. First, among those with diabetes, all-cause mortality rates declined in nearly 80% of the reported populations with a predominantly European background since 2000. Second, among the limited studies in non-Europid populations, 57% of populations showed a significantly declining mortality since 2000. Third, a greater or similar annual mortality reduction was observed among people with diabetes compared with those without diabetes in nearly 60% of populations from 1990 onwards.

Examining mortality trends is crucial for understanding the health burden associated with diabetes. Our data provide important context to concurrent changes in the prevalence of diabetes. Indeed, the falling mortality in a number of settings reported here will likely lead to increasing prevalence despite a stable or even declining incidence of diabetes [33].

We noted that the magnitude of mortality reduction in diabetes matched or exceeded that observed in people without diabetes in around 60% of populations from 1990 to 2016. This finding is in line with a recent analysis of the US National Health Interview Survey, which demonstrated a nearly 50% reduction in the excess mortality risk associated with diabetes from 1988–1994 to 2010–2015 [8]. More aggressive management of risk factors with statins and anti-hypertensive medications [34, 35] and improvements in glycaemic control [36] may have contributed to the substantial reductions in the rates of diabetes-related complications [8, 37, 38] and, ultimately, improved survival rate. Because people with diabetes started with a higher mortality risk than those without diabetes, population-wide changes in risk

factors [39–41] are likely to have led to a greater absolute risk reduction among people with diabetes than in those without.

Several factors, including population-level health promotion of tobacco cessation and lifestyle modification, have led to reduction in risk factors for mortality [39–41]. Other factors may also have contributed to the apparent declining mortality trends. Changing diagnostic criteria over the last two decades, particularly lowering the diagnostic threshold for fasting glucose, likely identifies people at an earlier stage in the natural history of diabetes who have an inherently lower mortality risk. However, the reduction in the fasting glucose diagnostic criterion took place over 20 years ago, and the more recent shift towards HbA<sub>1c</sub> as a diagnostic test may lead to diagnoses later in the disease course [42]. Irrespective of diagnostic criteria, increases in screening activity might also lead to more 'early' diagnoses of diabetes, again resulting in falling mortality due to lead-time bias. Data from the US National Health and Nutrition Examination Survey have indicated that the mean age at diagnosis of type 2 diabetes decreased from 52 to 46 years [43]. Younger age of diabetes onset could lower overall absolute mortality rate. However, as most of the included studies (25/35) reported change in age-standardised mortality rates over time, the declining mortality trends reported in these studies are not likely to be due to changes in the age profile of the populations studied over time. Furthermore, analysis of age-specific mortality trends confirms that reductions in mortality rates were present in most age groups during recent years (2000–2016).

Data on mortality trends in predominantly non-Europid populations are limited and, therefore, the patterns of mortality trends in these populations are uncertain. Three non-Europid populations with unchanged mortality rates since 2000 included Canadian indigenous people [21] and US ethnic groups other than Europid or black [8]. Evidence shows that limited access to healthcare facilities and lower socioeconomic status contribute to the sub-optimal diabetes management, indicated by high HbA<sub>1c</sub> levels and higher rates of diabetes-related complications, in indigenous people and some ethnic groups [44].

We found that mortality rates declined in a third of populations aged <40 years in 2000–2016, a lower proportion than that observed in older age groups. The lack of decline in all-cause mortality rates, particularly cardiovascular mortality, in young individuals in recent decades [37] may be related to the increase in the prevalence of obesity, diabetes and CVD in this age group [45, 46]. Compared with late-onset type 2 diabetes, young-onset type 2 diabetes is associated with worse metabolic control and an increased risk of chronic complications and all-cause mortality [47–49].

### Strengths and weaknesses

A key strength of this work is its systematic approach and robust methodology, though several potential limitations deserve consideration. First, there was variation among studies in the definition of diabetes and not all studies differentiated between type 2 and type 1 diabetes. Since less than 10% of all cases of diabetes are due to type 1 diabetes, our findings should only be generalised to type 2 diabetes. Second, we used joinpoint regression to detect changes in trends over a long study period, and when more than one segment was detected, we reported the trend separately for each different segment. Joinpoint regression uses a

robust permutation test to detect the number of segments and has been previously shown to yield an acceptable type I error [14], which means that the probability of ‘false-positive’ detection of multiple segments when none exist is unlikely to be beyond the type I error used (5% in our analysis). However, the power of the test for detecting segments is a function of several factors, namely the magnitude of change in trends between segments, the number of measured time-points and the size of the underlying population, which means that there is a possibility we may have missed more subtle changes in trends in studies conducted in smaller populations with fewer follow ups. However, we noted that the 19 populations with unchanged mortality rates had a similar distribution of sample size to the other 45 populations reporting decreasing trends. Moreover, as 75% of the data sources had sample sizes greater than 10,000 in each time period, the likelihood of misclassification would be small. Third, as the number of deaths among younger adults with diabetes, particularly with type 2 diabetes, was small (reflected by the wide CI of the APC in mortality rates in age group <40 years), it is possible that there was inadequate power to detect real mortality trends in some younger populations. Fourth, the use of multiple populations (ethnic-specific or sex-specific) per study may lead to bias. However, our sensitivity analysis conducted among the total population with diabetes in each study demonstrated similar patterns of mortality change compared with the results based on separate ethnic-specific or sex-specific populations. Fifth, no estimates of mortality trends in diabetes have been reported from low- or middle-income countries. Among the limited studies in non-Europid populations, we found that 86% (6/7) and 43% (3/7) of the populations studied in 1990–1999 and 2000–2016 did not have statistical evidence for a declining mortality, including indigenous populations [20, 21] and US ethnic groups (black, Asian and Hispanic) [8, 19]. This suggests that people with diabetes living in low- and middle-income countries, which share a similar demographic background to the non-Europid populations included in this review, may not have the declining mortality trends found here. Sixth, this review focused on published data and is, therefore, subject to potential publication bias, in which only increasing or only decreasing mortality rates could be perceived as worth publishing. However, since there is a reasonable spread of increasing, decreasing and unchanged mortality trends, it would appear that such a publication bias is not a major issue. Seventh, despite excluding closed cohort studies from our review, the selection bias related to diabetes duration may not be completely removed even in open cohort studies, because surviving participants who were recruited during earlier periods of the study might have a longer duration of diabetes than those recruited from later periods. Eighth, lack of available data precluded analyses relating to cause-specific mortality, diabetes duration or age at diabetes onset, and we were not able to source unit record data by age and sex on all populations studied; therefore, it is not possible to standardise the mortality rates from each individual study to a specific external population. Ninth, the Newcastle–Ottawa scale for assessing the quality of cohort studies was not designed for studies of trends, and may not perform ideally [50]. It is therefore possible that the sensitivity analysis that excluded the studies with scores in the bottom quartile did not correctly identify all of the lowest-quality studies. Tenth, considering the significant heterogeneity observed among the 67 separate ethnic-specific or sex-specific populations and across different subgroups, we did not report the pooled estimates of annual mortality change in people with diabetes or without diabetes. It is also worth noting that since we report multiple trends from within a particular population, the overall heterogeneity

shown by our trend estimates represents both within- and between-population heterogeneity and it will be larger than the between-population heterogeneity alone. Finally, although we did not formally search the grey literature, a Google search identified only one additional article, which was from Russia and was of low quality [51].

## Conclusions

This systematic review shows that in most high-income countries for which data are available, mortality among those with diabetes has declined in the majority of predominantly Europid populations since 2000. However, it remains uncertain how widespread these patterns are, given the limited data on younger age groups and non-Europid populations. Considering that nearly 80% of people with diabetes live in low-and middle-income countries [1], it is imperative to examine patterns of diabetes mortality in such countries.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data availability

Data may be obtained from the corresponding author upon request.

## Abbreviation

APC Annual per cent change

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### Research in context

#### What is already known about this subject?

- Understanding the mortality patterns in people with diabetes has become increasingly important as more than one in three people are expected to develop diabetes in their lifetimes
- Some studies have reported decreasing mortality in people with diabetes, but it remains unclear how consistent this is among various populations with diabetes

#### What is the key question?

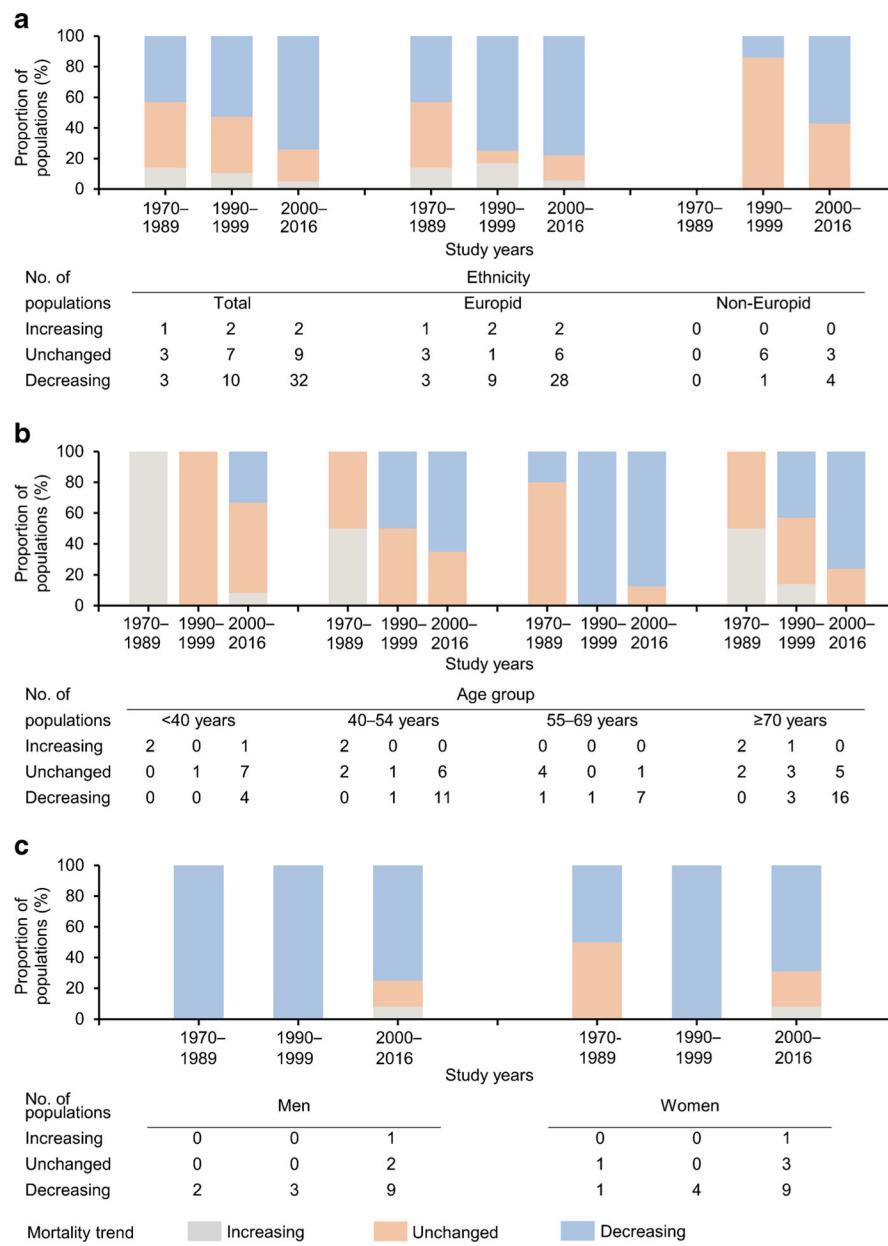
- What was the overall magnitude and variability of trends in all-cause mortality rates among people with diabetes, and did these trends reflect a similar mortality change in the general population?

#### What are the new findings?

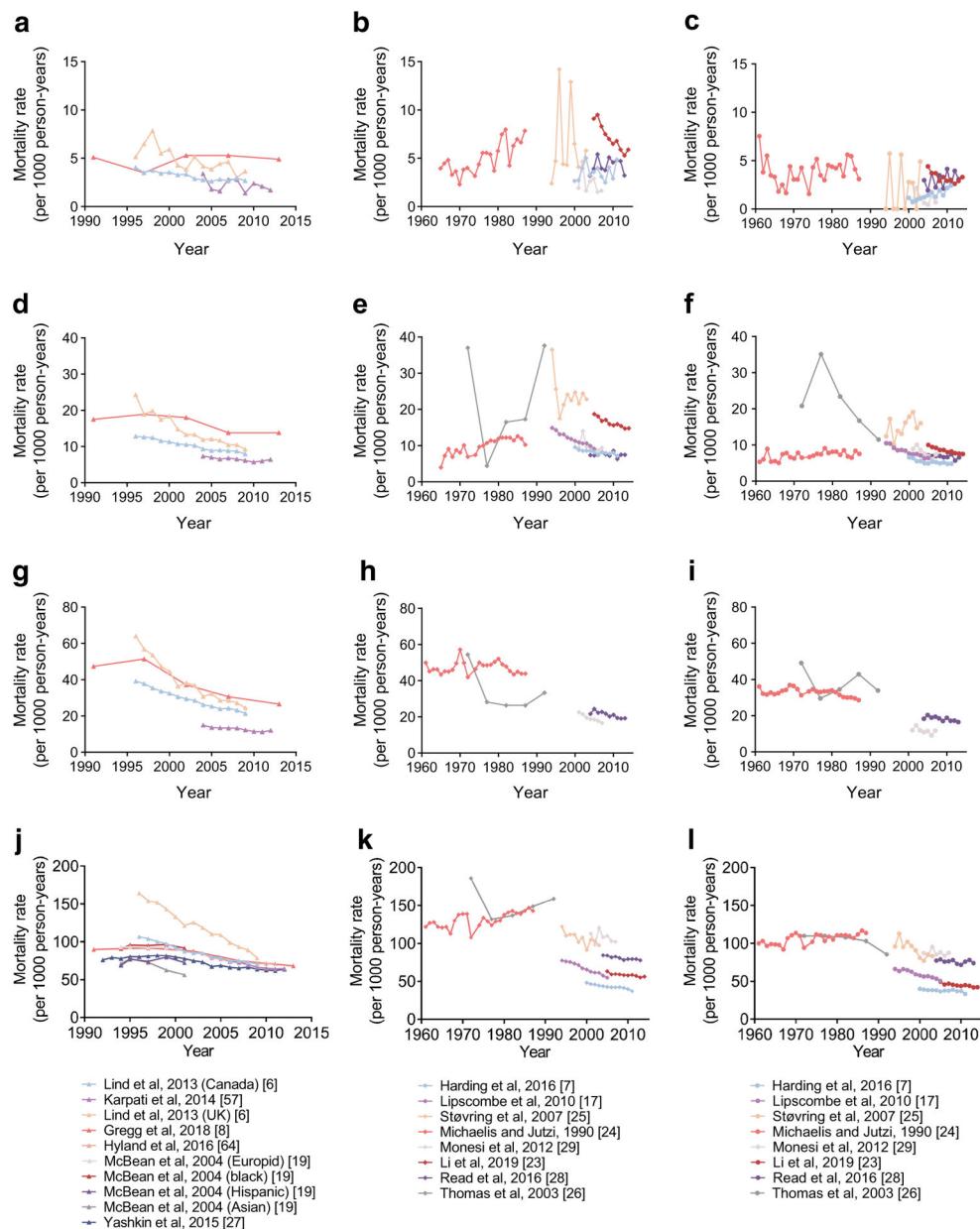
- From 2000 to 2016, all-cause mortality rates in people with diabetes declined in nearly 75% of the populations studied. This was particularly evident in predominantly Europid populations
- Nearly 60% of the reported populations with diabetes had a greater or similar annual mortality reduction as compared with those without diabetes from 1990 to 2016

#### How might this impact on clinical practice in the foreseeable future?

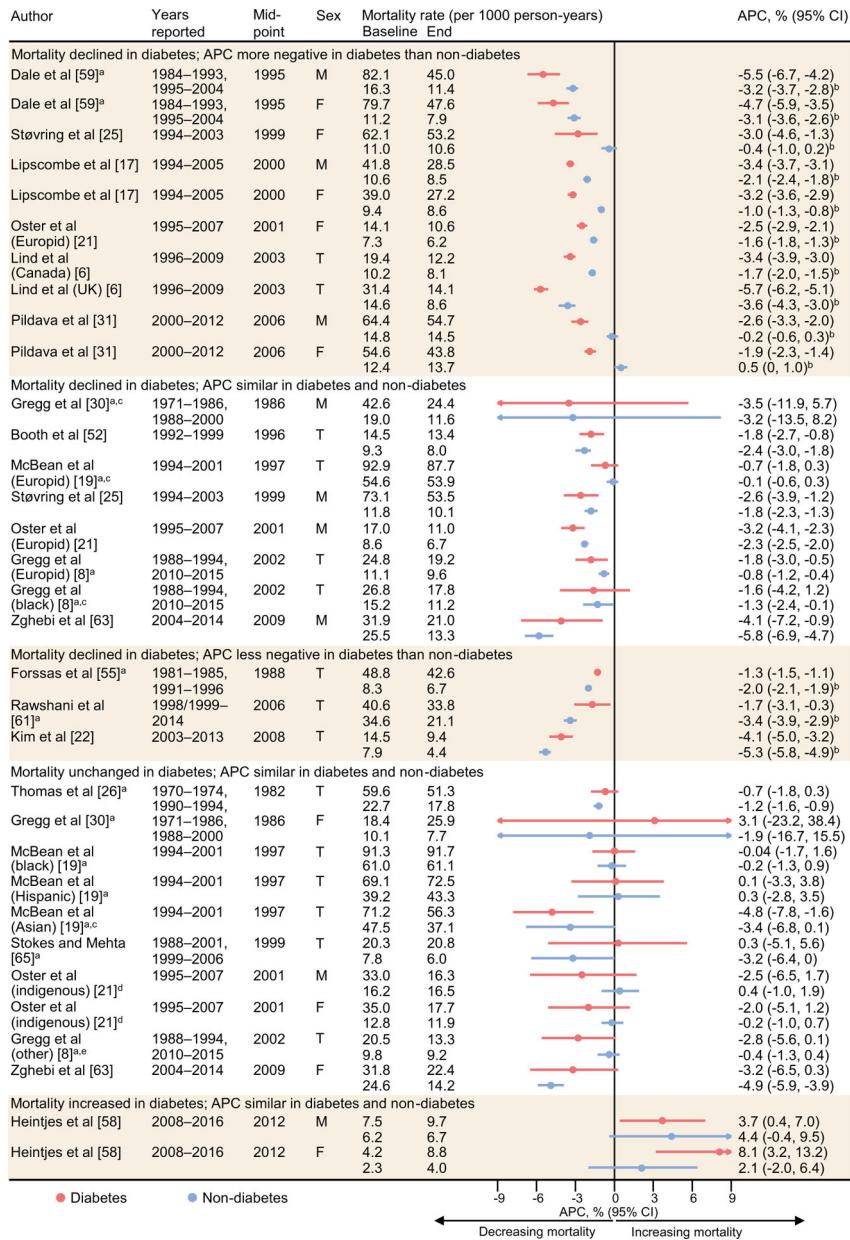
- Public health and clinical practice should continue to pursue, and expand on, recent measures to maintain cardiometabolic control in diabetes, in order to achieve on-going reductions in mortality

**Fig. 1.**

Patterns of all-cause mortality trends among people with diabetes by ethnicity (a), age group (b) and sex (c). The graph in (a) includes 55 predominantly Europid and 14 non-Europid populations from 35 studies; (b) includes 15 populations aged <40 years, 23 populations aged 40–54 years, 14 populations aged 55–69 years and 32 populations aged ≥70 years from 14 studies with data on age-specific mortality trends; (c) includes 17 male and 19 female populations from 15 studies with data on sex-specific mortality trends. Only the patterns of mortality trends in three calendar periods, i.e. 1970–1989, 1990–1999 and 2000–2016, are summarised. Blank columns indicate that data were not available for some calendar periods

**Fig. 2.**

Age-specific mortality rates among 26 populations with diabetes over time. Only populations reporting mortality in three or more time periods are plotted. (a, d, g, j) Mortality trends among the total population who were aged <40 (a), 40–54 (d), 55–69 (g) and 70 years (j). (b, e, h, k) Mortality trends among men who were aged <40 (b), 40–54 (e), 55–69 (h) and 70 years (k). (c, f, i, l) Mortality trends among women who were aged <40 (c), 40–54 (f), 55–69 (i) and 70 years (l)

**Fig. 3.**

APC in mortality rates by diabetes status among 33 populations. Only the 33 populations with mortality data available for computing the APC in mortality rates separately for those with and without diabetes are plotted. Populations are grouped according to the pattern of mortality trends in people with diabetes and the difference in mortality trends between populations with diabetes and without diabetes. <sup>a</sup>Studies did not measure mortality rates in continuous years; <sup>b</sup> $p < 0.05$  for the difference in the APCs in mortality rates between people with and without diabetes; <sup>c</sup>classification of mortality trends in diabetes was determined according to statistical significance reported in the original paper, not according to the CIs

of the APC shown in the figure; <sup>d</sup>Canadian indigenous population; <sup>e</sup>people not from a European or black background in the USA. F, female; M, male; T, total

Characteristics of studies included in the systematic review, listed by location

**Table 1**

Author, publication year	Years reported	Location	Origin of data source	Type of data	Diabetes definition	Age (years)
Harding et al, 2016 [7]	2000–2011	Australia	National Diabetes Register	Registry	Clinical diagnosis	0
Booth et al, 2006 [52]	1992–1999	ON, Canada	Population-based diabetes database	Administrative	Administrative algorithm	20
Lind et al, 2013 [6]	1996–2009	ON, Canada	Population-based diabetes database	Administrative	Administrative algorithm	20
Lipscombe et al, 2007 [18]; 2010 [17]	1994–2005 [17], 1995–2005 [18]	ON, Canada	Population-based diabetes database	Administrative	Administrative algorithm	20 [18]; 30 [17]
Oster et al, 2011 [21]	1995–2007	AB, Canada	Provincial administrative health records	Administrative	Administrative algorithm	20
Pohar et al, 2007 [53] <sup>a</sup>	1993, 2001	SK, Canada	Provincial administrative health records	Administrative	Administrative algorithm	0
Carstensen et al, 2008 [5]	1995–2006	Denmark	National Diabetes Register	Registry	Administrative algorithm	0
Færch et al, 2014 [32]	2002–2010	Denmark	Patient records at the Steno Diabetes Centre	Administrative	Clinical diagnosis	0
Green et al, 2015 [54]	2000–2011	Denmark	National Diabetes Register	Registry	Administrative algorithm	0
Stovring et al, 2007 [25]	1994–2003	Funen County, Denmark	Population-based medication database	Registry	Diabetes medications	0
Michaelis and Juizi, 1990 [24]	1961–1987	East Germany	National Diabetes Register	Registry	Clinical diagnosis	0
Forsas et al, 2003 [55] <sup>a</sup>	1981–1985, 1991–1996	Finland	The Finnish Study linkage to death index	Survey	Diabetes medications	30–74
Forsas et al, 2010 [56] <sup>a</sup>	1991–1994, 1995–1999, 2000–2003	Finland	National health register	Administrative	Clinical diagnosis (ICD) plus treatment	30–79
Karpati et al, 2014 [57]	2004–2012	Israel	Clalit Health Services	Health insurance	Administrative algorithm	26
Monesi et al, 2012 [29]	2001–2007	Lombardy, Italy	Administrative health databases	Administrative	Clinical diagnosis	0
Kim et al, 2018 [22]	2003–2013	Korea	National Health Insurance Service-National Sample Cohort	Health insurance	Clinical diagnosis (ICD)	30
Pildava et al, 2014 [31]	2000–2012	Latvia	National Diabetes Register	Registry	Clinical diagnosis	0
Heintjes et al, 2019 [58]	2008–2016	the Netherlands	PHARMO Database Network	Administrative	Diabetes medications	18
Dale et al, 2008 [59] <sup>a</sup>	1984–1993, 1995–2004	Norway	Nord-Trøndelag health study linked to death registry	Survey	Self-report	20
Dedov et al, 2017 [51]	2013–2016	Russia	Federal diabetes registry	Registry	No data	0
Evans et al, 2007 [60]	1993–2003	Tayside, Scotland	DARTS clinical system (Tayside)	Administrative	Administrative algorithm	0
Read et al, 2016 [28]	2004–2013	Scotland	Scottish Care Information-Diabetes database	Registry	Clinical diagnosis (ICD)	40–89
Rawshani et al, 2017 [61] <sup>a</sup>	1998/1999–2014	Sweden	National Diabetes Register	Registry	Clinical diagnosis	18

Author, publication year	Years reported	Location	Origin of data source	Type of data	Diabetes definition	Age (years)
Ringborg et al, 2008 [62]	1996–2003	Uppsala County, Sweden	RECAP-DM (26 primary healthcare providers)	Administrative	Administrative algorithm	30
Li et al, 2019 [23]	2005–2014	Taiwan	National Health Research database	Health insurance	Administrative algorithm	0
Lind et al, 2013 [6]	1996–2009	UK	The Health Improvement Network database	Administrative	Clinical diagnosis	20
Zghebi et al, 2017 [63]	2004–2014	UK	Clinical Practice Research Database	Administrative	Clinical diagnosis	16
Gregg et al, 2007 [30] <sup>a</sup>	1971–1986, 1976–1992, 1988–2000	USA	NHANES linkage to death index	Survey	Self-report	35–74
Gregg et al, 2018 [8] <sup>a</sup>	1988–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2015	USA	NHIS linkage to death index	Survey	Self-report	>20
Hyland et al, 2016 [64]	2002–2011	USA	Medicare administrative database	Administrative	Administrative algorithm	65
McBean et al, 2004 [19] <sup>a</sup>	1994, 1995, 1997, 1999, 2001	USA	Medicare administrative database	Administrative	Administrative algorithm	67
Narayanan et al, 2010 [20] <sup>a</sup>	1986–1990, 2002–2006	AK, USA	Alaska Native Diabetes Registry	Registry	Clinical diagnosis (ICD)	0
Stokes and Mehta, 2013 [65] <sup>a</sup>	1988–2001, 1999–2006	USA	NHANES linkage to death index	Survey	Glucose (HbA <sub>1c</sub> ) plus treatment	35–74
Thomas et al, 2003 [26] <sup>a</sup>	1970–1974, 1975–1979, 1980–1984, 1985–1989, 1990–1994	Rochester, NY, USA	Rochester Epidemiology Project	Administrative	Administrative algorithm	45
Tierney et al, 2004 [66]	1997–2002	ND, USA	North Dakota Behavioral Risk Factor Surveillance System	Survey	Self-report	18
Yashkin et al, 2015 [27]	1992–2012	USA	Medicare administrative database	Administrative	Administrative algorithm	65

At least two different criteria were included in the administrative algorithm for identifying a person as having diabetes in each individual study

<sup>a</sup>Studies did not measure mortality rates in continuous years

DARTS, Diabetes Audit and Research in Tayside Scotland; ICD, International Classification of Diseases; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey; RECAP-DM, Real-Life Effectiveness and Care Patterns in Diabetes Management

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**Table 2**  
 Summary of patterns of mortality trends in people with diabetes based on analyses reported in each publication, listed by the midpoint of the years reported ( $n = 69$ )

Author, publication year	Years reported	Midpoint		Location	Predominant ethnicity	Age (years)	Mortality trends in diabetes	
		Men	Women				Men	Women
1970–1979								
Michaelis and Jutzi, 1990 [24]	1961–1981	1971	East Germany	Europid		0		
1980–1989								
Thomas et al, 2003 [26] <sup>b</sup>	1970–1974, 1990–1994	1982	USA	Europid		45		NS <sup>a</sup>
Michaelis and Jutzi, 1990 [24]	1981–1987	1984	East Germany	Europid		0		NS <sup>a</sup>
Gregg et al, 2007 [30] <sup>b</sup>	1971–1986, 1976–1992, 1988–2000	1986	USA	Europid		35–74	↓	NS
Forsas et al, 2003 [55] <sup>b</sup>	1981–1985, 1991–1996	1988	Finland	Europid		30–74	↓	↓
1990–1999								
Dale et al, 2008 [59] <sup>b</sup>	1984–1993, 1995–2004	1995	Norway	Europid		20	↓ <sup>a</sup>	↓ <sup>a</sup>
Booth et al, 2006 [52]	1992–1999	1996	Canada	Europid		20		↓
Narayanan et al, 2010 [20] <sup>b</sup>	1986–1990, 2002–2006	1996	USA	Non-Europid (Eskimo)	0			NS
Narayanan et al, 2010 [20] <sup>b</sup>	1986–1990, 2002–2006	1996	USA	Non-Europid (Indian)	0			NS
Narayanan et al, 2010 [20] <sup>b</sup>	1986–1990, 2002–2006	1996	USA	Non-Europid (Aleut)	0			NS
Yashkin et al, 2015 [27]	1992–1999	1996	USA	Europid	65			↑ <sup>a</sup>
Forsas et al, 2010 [56] <sup>b</sup>	1991–1994, 1995–1999, 2000–2003	1997	Finland	Europid		30–79	↓	↓
Oster et al, 2011 [21]	1995–1998	1997	Canada	Non-Europid (indigenous)	20		↓ <sup>a</sup>	
Pohar et al, 2007 [53] <sup>b</sup>	1993, 2001	1997	Canada	Europid	0		↑	
McBean et al, 2004 [19] <sup>b</sup>	1994, 1995, 1997, 1999, 2001	1997	USA	Europid	67			
McBean et al, 2004 [19] <sup>b</sup>	1994, 1995, 1997, 1999, 2001	1997	USA	Non-Europid (black)	67			NS
McBean et al, 2004 [19] <sup>b</sup>	1994, 1995, 1997, 1999, 2001	1997	USA	Non-Europid (Hispanic)	67			NS
McBean et al, 2004 [19] <sup>b</sup>	1994, 1995, 1997, 1999, 2001	1997	USA	Non-Europid (Asian)	67			NS
Evans et al, 2007 [60]	1993–2003	1998	Scotland	Europid	0		↓	
Stokes and Mehta, 2013 [65] <sup>b</sup>	1988–2001, 1999–2006	1999	USA	Europid	35–74			NS

Author, publication year	Years reported	Midpoint	Location	Predominant ethnicity	Age (years)		Mortality trends in diabetes	
					Men	Women	Total	
Stovring et al, 2007 [25]	1994–2003	1999	Denmark	Europid	0	↓	↓	↓
2000–2016								
Lipscombe et al, 2010 [17]	1994–2005	2000	Canada	Europid	30	↓ <sup>a</sup>	↓ <sup>a</sup>	↓
Ringborg et al, 2008 [62]	1996–2003	2000	Sweden	Europid	30			
Tierney et al, 2004 [66]	1997–2002	2000	USA	Europid	18			NS
Carstensen et al, 2008 [5]	1995–2006	2001	Denmark	Europid	0	↓	↓	
Lind et al, 2013 [6]	1996–2005	2001	Canada	Europid	20			
Oster et al, 2011 [21]	1995–2007	2001	Canada	Europid	20	↓ <sup>a</sup>	↓ <sup>a</sup>	↓ <sup>a</sup>
Oster et al, 2011 [21]	1995–2007	2001	Canada	Non-Europid (indigenous)	20			
Gregg et al, 2018 [8] <sup>b</sup>	1988–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2015	2002	USA	Europid	>20			
Gregg et al, 2018 [8] <sup>b</sup>	1988–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2015	2002	USA	Non-Europid (black)	>20			↓
Gregg et al, 2018 [8] <sup>b</sup>	1988–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2015	2002	USA	Non-Europid (other)	>20			NS
Yashkin et al, 2015 [27]	1999–2004	2002	USA	Europid	65			↓ <sup>a</sup>
Pildava et al, 2014 [31]	2000–2004	2002	Latvia	Europid	0			NS <sup>a</sup>
Lind et al, 2013 [6]	1996–2009	2003	UK	Europid	20			↓ <sup>a</sup>
Oster et al, 2011 [21]	1998–2007	2003	Canada	Non-Europid (indigenous)	20			NS <sup>a</sup>
Rawshani et al, 2017 [61] <sup>b</sup>	1998/1999–2008/2009	2004	Sweden	Europid	18			↓ <sup>a</sup>
Monesi et al, 2012 [29]	2001–2007	2004	Italy	Europid	0			↓
Færch et al, 2014 [32]	2002–2010	2006	Denmark	Europid	0	↓	↓	
Green et al, 2015 [54]	2000–2011	2006	Denmark	Europid	0	↓ <sup>a</sup>	↓ <sup>a</sup>	
Harding et al, 2016 [7]	2000–2011	2006	Australia	Europid	0			↓ <sup>a</sup>
Pildava et al, 2014 [31]	2000–2012	2006	Latvia	Europid	0			
Hyland et al, 2016 [64]	2002–2011	2007	USA	Europid	65			↓
Lind et al, 2013 [6]	2005–2009	2007	Canada	Europid	20			↓ <sup>a</sup>
Kim et al, 2018 [22]	2003–2013	2008	Korea	Non-Europid (Korean)	30			↓
Zghebi et al, 2017 [63]	2004–2011	2008	UK	Europid	16			

Author, publication year	Years reported		Midpoint	Location	Predominant ethnicity	Age (years)	Mortality trends in diabetes	
						Men	Women	Total
Karpati et al, 2014 [57]	2004-2012	2008	Israel	Europid	26		↓	
Pildava et al, 2014 [31]	2004-2012	2008	Latvia	Europid	0		↓ <sup>a</sup>	
Yashkin et al, 2015 [27]	2004-2012	2008	USA	Europid	65		↓ <sup>a</sup>	
Zghebi et al, 2017 [63]	2004-2012	2008	UK	Europid	16		↓ <sup>a</sup>	
Read et al, 2016 [28]	2004-2013	2009	Scotland	Europid	40-89		↓ <sup>a</sup>	
Li et al, 2019 [23]	2005-2014	2010	Taiwan	Non-Europid (Taiwan)	0	↓	↓	
Rawshani et al, 2017 [61] <sup>b</sup>	2008/2009-2014	2011	Sweden	Europid	18		NS <sup>a</sup>	
Heintjes et al, 2019 [58]	2008-2016	2012	the Netherlands	Europid	18	↑ <sup>a</sup>	↑ <sup>a</sup>	
Zghebi et al, 2017 [63]	2011-2014	2013	UK	Europid	16		NS <sup>a</sup>	
Zghebi et al, 2017 [63]	2012-2014	2013	UK	Europid	16		NS <sup>a</sup>	
Dedov et al, 2017 [51]	2013-2016	2015	Russia	Europid	0		NS <sup>a</sup>	

Where a cell is empty, this indicates that relevant data were not available in the study

<sup>a</sup>Trends were determined using joinpoint regression or log-linear regression analyses. ↑, increasing mortality rates over time; ↓, decreasing mortality rates over time; NS, no statistically significant change in mortality rates over time

<sup>b</sup>Studies did not measure mortality rates in continuous years

Summary of patterns of mortality trends in people with diabetes aged &lt;40, 40–54, 55–69 and 70 years, listed by the midpoint of the years reported

Author, publication year	Sex	<40 years		40–54 years		55–69 years		70 years		Trends
		Years reported	Midpoint	Years reported	Midpoint	Trends	Years reported	Midpoint	Trends	
Michaelis and Juizi, 1990 [24]	M	1965–1987	1976	↑	1965–1967	1966	NS	1961–1987	1974	NS
Michaelis and Juizi, 1990 [24]	F	1961–1966	1964	NS	1961–1987	1977	↑	1961–1963	1962	NS
Michaelis and Juizi, 1990 [24]		1966–1987	1977	↑			1963–1969	1966	NS	
							1969–1980	1975	NS	
							1980–1987	1984	↓	
Thomas et al, 2003 [26] <sup>a</sup>	M			1970–1974, 1990–1994	1982	NS	1970–1974, 1990–1994	1982	NS	1970–1974, 1990–1994
Thomas et al, 2003 [26] <sup>a</sup>	F			1970–1974, 1990–1994	1982	NS	1970–1974, 1990–1994	1982	NS	1970–1974, 1990–1994
McBean et al, 2004 (Europid) [19] <sup>a</sup>	T									1994–2001
McBean et al, 2004 (black) [19] <sup>a</sup>	T									1997
McBean et al, 2004 (Hispanic) [19] <sup>a</sup>	T									NS <sup>b</sup>
McBean et al, 2004 (Asian) [19] <sup>a</sup>	T									1997
Støvring et al, 2007 [25]	M	1994–2003	1999	NS	1994–1996	1995	↓	1994–2003	1999	↓
Støvring et al, 2007 [25]					1996–2003	2000	NS			
Lipscombe et al, 2010 [17]	F				1994–2003	1999	NS			1999
Lipscombe et al, 2010 [17]	M				1994–2005	2000	↓			2000
Lipscombe et al, 2010 [17]					1994–2005	2000	↓			2000
Gregg et al, 2018 [8] <sup>a</sup>	T	1988–1994, 2010–2015	2002	NS <sup>b</sup>	1988–1994, 2010–2015	2002	↓ <sup>b</sup>	1988–1994, 2010–2015	2002	1988–1994, 2010–2015
Lind et al, 2013 (Canada) [6]	T	1996–2009	2003	↓	1996–2009	2003	↓	1996–2009	2003	↓
Lind et al, 2013 (UK) [6]	T	1996–2009	2003	↓	1996–2009	2003	↓	1996–2001	1999	↓
							2001–2009	2005	↓	

Author, publication year	Sex	<40 years		40–54 years		55–69 years		70 years		Midpoint	Trends
		Years reported	Midpoint	Trends	Years reported	Midpoint	Trends	Years reported	Midpoint		
Monesi et al, 2012 [29]	M	2001–2007	2004	NS	2001–2007	2004	NS	2001–2007	2004	↓	2001–2007
Monesi et al, 2012 [29]	F	2001–2007	2004	NS	2001–2007	2004	↓	2001–2007	2004	NS	2001–2007
Harding et al, 2016 [7]	M	2000–2011	2006	NS	2000–2011	2006	↓				2000–2005
											2005–2009
											2009–2011
Harding et al, 2016 [7]	F	2000–2011	2006	↑	2000–2004	2002	↓				2009–2011
Hyland et al, 2016 [64]	T				2004–2011	2008	NS				2000–2011
Yashkin et al, 2015 [27]	T										2002–2011
											2007
Karpati et al, 2014 [57]	T	2004–2012	2008	NS	2004–2010	2007	↓	2004–2012	2008	↓	1992–1999
											1999–2004
Read et al, 2016 [28]	M	2004–2013	2009	NS	2004–2013	2009	NS	2004–2013	2009	↓	2004–2013
Read et al, 2016 [28]	F	2004–2013	2009	NS	2004–2013	2009	NS	2004–2013	2009	↓	2004–2013
Li et al, 2019 [23]	M	2005–2014	2010	↓ <sup>b</sup>	2005–2014	2010	↓ <sup>b</sup>				2005–2014
Li et al, 2019 [23]	F	2005–2014	2010	↓ <sup>b</sup>	2005–2014	2010	↓ <sup>b</sup>				2005–2014
											2010

Where a cell is empty, this indicates that relevant data were not available in the study

<sup>a</sup>Studies did not measure mortality rates in continuous years

<sup>b</sup>According to the trends reported in the original publications, all other trends were determined using joinpoint regression or log-linear regression analyses. ↑, increasing mortality rates over time; ↓, decreasing mortality rates over time; F, female; M, male; NS, no statistically significant change in mortality rates over time; T, total