Sex differences in the association between diabetes and risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality: a systematic review and meta-analysis of 5,162,654 participants

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Abstract

Background: Studies have suggested sex differences in the mortality rate associated with diabetes. We conducted a meta-analysis to estimate the relative effect of diabetes on the risk of all-cause, cancer, cardiovascular disease (CVD), infectious disease, and respiratory disease mortality in women compared with men.

Methods: Studies published from their inception to April 1, 2018, identified through a systematic search of PubMed and EMBASE and review of references. We used the sex-specific RRs to derive the women-to-men ratio of RRs (RRR) and 95% CIs from each study. Subsequently, the RRR for each outcome was pooled with random-effects meta-analysis weighted by the inverse of the variances of the log RRRs.

Results: Forty-nine studies with 86 prospective cohorts met the inclusion criteria and were eligible for analysis. The pooled women-to-men RRR showed a 13% greater risk of all-cause mortality associated with diabetes in women than in men (RRR 1.13, 95% CI 1.07 to 1.19; P < 0.001). The pooled multiple-adjusted RRR indicated a 30% significantly greater excess risk of CVD mortality in women with diabetes compared with men (RRR 1.30, 95% CI 1.13 to 1.49; P < 0.001). Compared with men with diabetes, women with diabetes had a 58% greater risk of coronary heart disease (CHD) mortality, but only an 8% greater risk of stroke mortality (RRR CHD 1.58, 95% CI 1.32 to 1.90; P < 0.001; RRR stroke 1.08, 95% CI 1.01 to 1.15; P < 0.001). However, no sex differences were observed in pooled results of populations with or without diabetes for all-cancer (RRR 1.02, 95% CI 0.98 to 1.06; P = 0.21), infectious (RRR 1.13, 95% CI 0.90 to 1.38; P = 0.33), and respiratory mortality (RRR 1.08, 95% CI 0.95 to 1.23; P = 0.26).

Conclusions: Compared with men with the same condition, women with diabetes have a 58% and 13% greater risk of CHD and all-cause mortality, respectively, although there was a significant heterogeneity between studies. This points to an urgent need to develop sex- and gender-specific risk assessment strategies and therapeutic interventions that target diabetes management in the context of CHD prevention.

Keywords: Diabetes, Sex difference, Mortality, Meta-analysis

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Background
According to the Global Burden of Disease Study (GBD), non-communicable diseases (NCDs) are the main cause of premature deaths amongst the world’s population [1]. As one of four main NCDs, diabetes affected an estimated 387 million people throughout the world and caused around 1.3 million deaths worldwide in 2010 alone [2–4]. With the increasing prevalence of physical inactivity and obesity, the burden of diabetes is predicted to increase to 592 million by 2035, making it a major contributor to the global burden of disease [5].

Type 2 diabetes mellitus is associated with an approximate twofold increase in the risk of all-cause mortality as well as death from cardiovascular disease (CVD), kidney disease, infectious disease, respiratory disease, and several specific forms of cancer [6]. Previous meta-analyses, through internal, within-study comparisons of female and male participants, have observed that women with diabetes are at substantially higher risk of coronary heart disease (CHD), stroke, and gastric cancer compared to affected men. On the other hand, no sex differences were found between diabetes and the risk of esophageal cancer, colorectal cancer, and pancreatic cancer [7–9]. However, the magnitude of the excess risk of these and other cause-specific outcomes that are conferred by diabetes for men and women is unknown. Furthermore, it is unclear whether important confounders (e.g., age) and methodological heterogeneity (duration of follow-up, method of diabetes classification or assessment) would modify any such sex differential in the association between diabetes and mortality. It is also unclear whether such a difference might be more pronounced in recent years with the growing obesity epidemic (e.g., year of publication).

Accordingly, we sought to conduct a meta-analysis of prospective cohort studies in order to (i) calculate any sex differential in the association between diabetes and risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality for the general population and (ii) to determine whether these associations are modified by demographics, setting, length of follow-up, diabetes measurement, and recency of publication.

Methods
Search strategy
The meta-analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology guidelines [10] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [11] (Additional file 1: Table S1). We searched the PubMed and EMBASE databases from their inception to April 1, 2018. Details of the search strategy using a combined text word and medical subject heading are displayed in Additional file 1. The articles were restricted to English language studies. Moreover, the reference lists of the retrieved publications and reviews were checked for other potentially relevant studies.

Study selection
Studies were included if they met the following criteria: (1) the study was a prospective cohort design; (2) the outcomes included all-cause mortality, cancer mortality, CVD mortality, CHD mortality, stroke mortality, infectious disease mortality, and/or respiratory disease mortality; (3) the studies provided odds ratio (OR), relative risk (RR), or hazard ratio (HR) with 95% confidence intervals (CI) for the associations between diabetes and mortality disaggregated for men and women participants; and (4) when multiple publications reported on the same population or subpopulation, the study with the most recent or most informative data was included. The exclusion criteria were as follows: (1) matched prospective cohort study design, (2) studies reporting only estimates for type 1 diabetes, (3) studies not adjusting for age, and (4) studies of populations that predominantly consisted of individuals with underlying pathological disorders, such as cardiovascular disease or cancer. We also used individual participant data from the America’s National Health Interview Surveys (1997 to 2009) linked to the National Death Index records through December 31, 2011. Extensive details about the questionnaire, methodology, data, and documentation are available on the NHIS website. [https://www.cdc.gov/nchs/nhis/about_nhis.htm].

Data extraction and study quality assessment
Two investigators (YFW and YRJ) independently reviewed all potentially eligible studies using predefined criteria and extracted the data from each paper. In case of incomplete or unclear data, the authors were contacted where possible. The cohort study quality was estimated using the nine-star Newcastle-Ottawa quality assessment Scale (NOS) ranging from zero to nine stars [12]. Disagreements were resolved by consensus between the authors.

Statistical analysis
The RR was used as a measure of the association between diabetes and outcome risk. For individual participant data, we used Cox proportional hazards regression to obtain HRs (regarded as RRs). If the included studies did not report the RRs, the HRs were directly considered as RRs and the ORs were converted into RRs using the formula: \( RR = \frac{OR}{(1 - Po) + (OR \times Po)} \), in which Po was the incidence of the outcome of interest in the non-diabetes group [13]. For studies that reported RRs in different age groups, we pooled these RRs with inverse variance random-effect models, and then we used
combined estimates for that study. For the primary analysis, we used the sex-specific RRs to derive the women-to-men ratio of RRs (RRR) and 95% CIs from each study, as previously described [14]. Subsequently, the RRR for each outcome was pooled with random-effects meta-analysis weighted by the inverse of the variances of the log RRRs. We also pooled RRs for men and women separately, using an identical approach. The heterogeneity among the included studies was evaluated by the $Q$ test and $I^2$ statistic [15].

Subsequently, where the number of included studies was more than 10 for each outcome of interest, sensitivity analyses were performed by mean age ($\leq 60$ versus $> 60$ years), region (Asia versus Europe versus America versus others), publish year ($\leq 2000$ versus $2001–2009$ versus $\geq 2010$), length of follow-up ($\leq 10$ versus $> 10$ years), and ascertainment of diabetes (known diabetes versus newly diagnosed diabetes versus both). Random-effects meta-regression analyses were used to evaluate whether the differences in the mean/medium duration of study follow-up and mean age of participants at baseline contributed to the heterogeneity between the studies. Publication bias was assessed by Begg’s rank correlation test and its funnel plots of the natural log of the RRR against its standard error [16]. Where publication bias was detected, trim and fill analyses were used to adjust the RRs or ratio of RRs. All statistical analyses were performed with Stata version 13.0 (StataCorp, College Station, TX, USA).

**Results**

Of the 24,303 references identified through the systematic search, 375 were examined in the full-text review (Fig. 1). In addition, 6 articles were retrieved from the reference lists of relevant articles and reviews. Subsequently, individual participant data from NHIS were
added to these published results. Finally, 49 studies with 86 prospective cohorts met the inclusion criteria and [17–63] were eligible for analysis (Table 1).

The characteristics of the included studies are described in Table 1. Baseline surveys were conducted between 1950 and 2014, and the number of participants ranged from 379 to 1,298,358. The mean/median duration of follow-up ranged from 6.0 to 21.4 years, while the average baseline age was between 33.3 and 80.0 years. The quality of all included studies based on NOS was high (Additional file 1: Table S2). All studies adjusted for age and most of the studies also controlled for smoking \((n = 77)\), hypertension \((n = 71)\), and body mass index \((n = 68)\).

Twenty-eight studies with 3,887,585 participants were included to assess the sex-specific association between diabetes and all-cause mortality. For cause-specific mortality, 14 studies with 4,482,501 reported on cancer mortality, 23 studies with 2,067,486 reported on CVD mortality, 23 studies with 2,050,929 reported on CHD mortality, 15 studies with 2,292,387 reported on stroke mortality, 4 studies with 1,633,520 reported on respiratory disease mortality, and 3 studies with 1,638,651 reported on infectious disease mortality.

**Sex-specific association between diabetes and risk of all-cause, cancer, CVD, infectious disease, and respiratory disease mortality**

The pooled multiple-adjusted RRs of all-cause mortality associated with diabetes compared with no diabetes were 1.93 (95% CI 1.80 to 2.06; Fig. 2) in women and 1.74 (1.67 to 1.82) in men. The pooled women-to-men RRR showed a 13% greater risk of all-cause mortality associated with diabetes in women than in men (RRR 1.13, 95% CI 1.07 to 1.19; \(P < 0.001\); Figs. 3 and 4). There was, however, a significant heterogeneity between the studies \(I^2 = 60\%\), \(P < 0.001\); Fig. 2).

The pooled multiple-adjusted RRs showed that diabetes was associated with a 26% (1.16 to 1.36) increased risk for cancer mortality in women and a 29% (1.18 to 1.42; Additional file 1: Figure S1) increased risk in men. There was no evidence of a sex difference in the association between diabetes and cancer mortality; the pooled multiple-adjusted RRR of cancer mortality for diabetes was 1.02 (0.98 to 1.06; \(P = 0.21\); Fig. 4; Additional file 1: Figure S2). No evidence of significant between-study heterogeneity was found \(I^2 = 0\%\); \(P = 0.60\).

Compared with unaffected individuals, the pooled RR for CVD mortality in people with diabetes was 2.42 (2.10 to 2.78; Additional file 1: Figure S3) in women and 1.86 (1.70 to 2.03) in men. Overall, the pooled multiple-adjusted RRR indicated a 30% significantly greater excess risk of CVD mortality in women with diabetes compared with men (RRR 1.30, 95% CI 1.13 to 1.49; \(P < 0.001\); Fig. 4; Additional file 1: Figure S4), but with significant heterogeneity between the studies \(I^2 = 78\%\), \(P < 0.001\).

In addition, the pooled RR of CHD mortality for individuals with diabetes compared with those without diabetes was higher in women than in men [women, 3.16 (2.61 to 3.82); men, 2.11 (1.98 to 2.25); both \(P < 0.001\); Additional file 1: Figure S5]. Compared with men with diabetes, women with diabetes had a 58% greater risk of CHD mortality, but only an 8% greater risk of stroke mortality [CHD mortality (RRR 1.58, 95% CI 1.32 to 1.90; \(P < 0.001\); Additional file 1: Figure S6); stroke mortality (RRR 1.08, 95% CI 1.01 to 1.15; \(P < 0.001\); Additional file 1: Figure S7); Fig. 4]. Moreover, there was no heterogeneity between the studies examining stroke mortality, but significant heterogeneity between the studies for CHD mortality [CHD mortality \(I^2 = 67\%\), \(P < 0.001\); stroke mortality \(I^2 = 0\%\), \(P = 0.74\)].

Compared with those without, women and men with diabetes had approximately 31% and 22% greater risk of respiratory disease mortality, respectively (Additional file 1: Figure S8). However, no sex differences were observed (RRR 1.08, 95% CI 0.95 to 1.23; \(P = 0.26\); Fig. 4) nor significant heterogeneity \(I^2 = 0\%\); \(P = 0.98\).

Diabetes was associated with an approximately twofold increase in the risk of infectious disease-related mortality [women, 2.13 (1.89 to 2.42); men, 1.94 (1.66 to 2.26); both \(P < 0.001\); (Additional file 1: Figure S9)]. There was no evidence of sex differences (RRR 1.11, 95% CI 0.90 to 1.38; \(P = 0.33\); Fig. 4).

**Subgroup, meta-regression, and publication bias analyses**

We performed subgroup analyses for cancer, CHD, stroke, CVD and all-cause mortality outcomes. Results showed no evidence of heterogeneity between the subgroups stratified by study characteristics including age, geographical location, duration of follow-up, publish year, and method of diabetes ascertainment (Table 2). For the method of diabetes ascertainment, sex differences for CVD, CHD, and all-cause mortality conferred by diabetes were only significant in self-reported diagnosis (all-cause mortality: RRR 1.17, 95% CI 1.07 to 1.27; \(P < 0.001\); CVD mortality: RRR 1.20, 95% CI 1.02 to 1.42, \(P < 0.001\); CHD mortality: RRR 1.52, 95% CI 1.20 to 1.92, \(P < 0.001\)). The pooled RRR for CHD, stroke, CVD, and all-cause mortality did not vary by mean age of the participants at baseline, mean/median duration of follow-up, baseline prevalence of diabetes, and women-to-men ratio of diabetes prevalence (all \(P > 0.1\)). We found no evidence of publication bias for cancer, CHD, stroke, CVD, respiratory disease, infectious disease, and all-cause mortality \(P > 0.10\).

**Discussion**

This systematic review and meta-analysis of 49 studies with 86 prospective cohorts found that diabetes conferred
| Author                  | Study location | Study name                      | Mean baseline age (years) | No. of participants | No. of diabetes | Ascertainment of diabetes | Outcome                              | Mean follow-up years | Maximum adjustment available                                                                 |
|------------------------|----------------|---------------------------------|---------------------------|---------------------|-----------------|---------------------------|--------------------------------------|---------------------|---------------------------------------------------------------------------------------------|
| Jousilahti et al. 1999 | Finland        | Pekka et al-Finnish             | 44.4                      | 14,786              | NA              | Self-reported             | CHD mortality                        | NA                  | Age, study year, area, smoking, HDL, HDL/cholesterol ratio, SBP, BMI                        |
| Oba et al. 2008         | Japan          | Takayama study                  | 54.6                      | 29,079              | 1217            | Self-reported             | All-cause mortality, cancer mortality, CVD mortality, CHD mortality, stroke mortality | 7                   | Age, smoking, BMI, physical activity, length of education in years, history of hypertension, total energy intake, intake of vegetables, fat, and alcohol |
| Hu et al. 2005          | Finland        | Kuopio and North Karelia study  | 44.3                      | 50,281              | 962             | Self-reported             | All-cause mortality, CVD mortality, CHD mortality, stroke mortality | 17.2                | Age, study year, BMI, SBP, TC, smoking                                                   |
| Madssen et al. 2012     | Norway         | HUNT 1 study                    | 74.6                      | 47,586              | 2421            | Self-reported, measured  | CHD mortality                        | NA                  | Age, BMI, hypertension, CVD, smoking, physical activity                                  |
| DECODE Study Group 2001 | Europe         | DECODE Study                    | 53.2                      | 22,514              | 1807            | Self-reported, measured  | All-cause mortality, CVD mortality, CHD mortality, stroke mortality | 8.8                 | Age, center, TC, BMI, SBP, smoking                                                      |
| Keli et al. 1993        | USA            | Charleston Heart Study          | 50                        | 2181                | NA              | Self-reported             | All-cause mortality, CHD mortality    | 30                  | Age, SBP, serum cholesterol, smoking, BMI, years of education, history of diabetes         |
| Friberg et al. 2004     | Denmark        | Copenhagen City Heart Study     | 58.4                      | 29,310              | 1072            | Self-reported, measured  | CVD mortality                        | 4.7                 | Age, AF, arterial hypertension, SBP, MI, ELVH, smoking, FEV2                            |
| VR et al. 1996          | Pacific island nation of Fiji | NA                             | 50.5                      | 2546                | 2638            | Self-reported, measured  | All-cause mortality, CVD mortality, CHD mortality, stroke mortality | 11                  | Age, SBP, BMI, TC, smoking, survey area                                                     |
| Bozorgmanesh et al. 2011| Iran           | Tehran Lipid and Glucose Study  | 47                        | 6331                | 897             | Self-reported, measured  | All-cause mortality                  | 8.6                 | Age, smoking, SBP, WC, TC, TG, HDL-C, non-HDL-C, CVD, intervention                         |
| Kleinman et al. 1988    | USA            | First National Health and Nutrition Examination Survey | 58.1                      | 7381                | 407             | Self-reported, measured  | All-cause mortality, CVD mortality, CHD mortality | 10                  | Age, SBP, serum cholesterol, BMI, smoking                                                 |
| Magliano et al. 2010    | Mauritius      | NA                              | 40.9                      | 9559                | NA              | Self-reported, measured  | All-cause mortality, CVD mortality, CHD mortality | 15                  | Age, WC, HIP, smoking, hypertension, ethnicity, CVD, education, HDL-C, TG, TC             |
| Elizabeth et al. 1991   | USA            | The Rancho Bernardo Study       | 61.9                      | 2471                | 334             | Self-reported, measured  | CHD mortality                        | 14.4                | Age, SBP, cholesterol, BMI, smoking                                                       |
| Fraser et al. 1992      | USA            | The Adventist Health Study      | 52.8                      | 27,658              | NA              | Self-reported, measured  | CHD mortality                        | 6                   | Age, hypertension, smoking, physical activity, BMI                                       |
| Sievers et al. 1992     | India          | NA                              | 49.5                      | 5131                | 1266            | Measured                  | All-cause mortality, cancer mortality, IHD mortality, stroke mortality, infections mortality | 10                  | Age                                                                                      |
| Seeman et al. 1993      | USA            | The New Haven EPESE cohort      | NA                        | 2812                | 386             | Self-reported             | CHD mortality                        | 6                   | Age, education, BMI, smoking, alcohol, vegetable intake, red meat intake, physical activity, aspirin use |
| Author                     | Study location | Study name                                      | Mean baseline age (years) | No. of participants | No. of diabetes | Ascertainment of diabetes | Outcome                                                                 | Mean follow-up years | Maximum adjustment available                                                                 |
|---------------------------|----------------|-----------------------------------------------|---------------------------|---------------------|-----------------|---------------------------|----------------------------------------------------------------------|---------------------|---------------------------------------------------------------------------------------------|
| Campbell et al. 2012 [6]  | USA            | Cancer Prevention Study-II                    | NA                        | 1,053,831           | 52,655          | Self-reported             | All-cause mortality, cancer mortality, CVD mortality, CHD mortality, stroke mortality, respiratory system mortality, infections mortality | 26                  | Age, high blood pressure, BMI, smoking, elevated serum cholesterol, elevated serum triglycerides, elevated serum uric acid, IGT, obesity, hyperuricemia |
| Wang et al. 2012 [32]     | Taiwan         | Taiwan Survey of Hypertension, Hyperglycemia, and Hyperlipidemia | 45.6                      | 4289                | 335             | Measured                 | All-cause mortality, CVD mortality                                   | 7.7                 | Age, education, marital status, housing tenure, car ownership                                |
| Natarajan et al. 2003 [33]| USA            | Framingham Heart Study and the Framingham Offspring Study | 52.2                      | 5243                | 229             | Measured                 | CHD mortality                                                        | 20                  | Age strata, CAD, stroke, BMI, alcohol, smoking, betel nut chewing, physical activity, income |
| Vilbergsson et al. 1998 [34]| Iceland      | The Reykjavik Study                           | 52.8                      | 18,912              | 477             | Self-reported, measured  | All-cause mortality, CVD mortality                                   | 17                  | Age, smoking, hypertension, TC, HDL-C, BMI                                                  |
| Qvist et al. 1996 [35]    | Sweden         | NA                                            | 59.1                      | 5306                | NA              | Self-reported             | CVD mortality, stroke mortality                                      | 10                  | Age, smoking, hypertension, BMI                                                            |
| Tunstall-Pedoe et al. 1997 [36]| England | Edinburgh and north Glasgow MONICA population surveys | 49.5                      | 11,629              | NA              | Self-reported             | All-cause mortality, CHD mortality                                   | 7.6                 | Age, smoking, BMI, hypertension, TC, TG, calendar year                                      |
| Nilsson et al. 1998 [37]  | Sweden         | Swedish Annual Level-of-Living Survey          | NA                        | 39,055              | 776             | Self-reported             | All-cause mortality, CVD mortality, CHD mortality, stroke mortality   | 16                  | Age                                                                                         |
| Imazu et al. 2002 [38]    | USA            | The Hawaii-Los Angeles-Hiroshima study         | 60.9                      | 927                 | 169             | Measured                 | CVD mortality, CHD mortality                                        | 14                  | Age, BMI, serum uric acid, TC, TG, hypertension, ECG (abnormal Q), ECG (ST-T changes), smoking |
| Hart et al. 1999 [39]     | England        | The Renfrew/ Paisley general population study  | NA                        | 15,406              | NA              | Self-reported             | Stroke mortality                                                     | 20                  | Age, DBP, smoking, FEV1, height, BMI, diabetes, preexisting CHD                                |
| Bragg et al. 2014 [40]    | China          | The China Kadoorie Biobank                    | 51.5                      | 512,869             | 512,869         | Self-reported             | All-cause mortality, cancer mortality, IHD mortality, stroke mortality, respiratory disease mortality, infections mortality | 7                   | Age                                                                                         |
| Kato et al. 2015 [41]     | Japan          | Japan Public Health Center-based prospective study | 50.2                      | 99,584              | 4286            | Self-reported             | All-cause mortality, cancer mortality, IHD mortality, stroke mortality | 20                  | Age, BMI, alcohol, smoking, hypertension, physical activity, area                             |
| Johansen et al. 1987 [42]| Canada         | The Nutrition Canada survey                   | NA                        | 8094                | NA              | Self-reported             | All-cause mortality                                                  | 10                  | Age, respondent status, smoking, DBP, history of diabetes or presence of glucose in the urine, BMI, serum cholesterol level, |
### Table 1 Characteristics of studies included in the meta-analysis (Continued)

| Author        | Study location | Study name                                                                 | Mean baseline age (years) | No. of participants | No. of diabetes | Ascertainment of diabetes | Outcome                          | Mean follow-up years | Maximum adjustment available                                                                 |
|---------------|----------------|----------------------------------------------------------------------------|----------------------------|---------------------|------------------|--------------------------|----------------------------------|----------------------|---------------------------------------------------------------------------------------------|
| Suemoto et al. 2014 [43] | Brazil         | The SABE Study                                                            | 71                         | 1882                | 312              | Self-reported            | All-cause mortality              | 7                    | Alcohol consumption, age, race, marital status, years of education, childhood socioeconomic status, occupation, income, heart disease, lung disease, stroke, arthritis, depressive symptoms, alcohol smoking, BMI, physical activity, frailty, nutritional status, year of entry in the study |
| Jee et al. 2005 [44]       | Korea          | The National Health Insurance Corp                                          | 46.9                       | 1,298,358           | 62,924           | Self-reported, measured | All-cause mortality, all-cancer mortality | 10                   | Age, age squared, smoking, alcohol                                                                 |
| Fraser et al. 1997 [45]    | Spain          | Non-Hispanic white Seventh-Day Adventists from California                   | NA                         | 603                 | NA               | Self-reported            | All-cause mortality, CHD mortality  | 12                   | Age, smoking, physical activity, nuts per week, fruit per day, bread, sweet desserts per week, beef per week |
| Moe et al. 2013 [46]       | Norway         | HUNT 2                                                                     | 46.5                       | 53,587              | 1195             | Self-reported, measured | CVD mortality                    | 12                   | Age, physical activity, smoking, alcohol, education, BMI, SBP, TC                                                                                           |
| Liu et al. 2011 [47]       | USA            | The LSOA II study                                                          | 80                         | 9246                | NA               | Self-reported            | All-cause mortality              | 8                    | Age, marital status, living arrangement, educational attainments, hypertension, CHD, stroke |
| Vimalananda et al. 2014 [48] | USA           | The Cardiovascular Health Study                                             | 72.6                       | 4817                | 681              | Self-reported, measured | All-cause mortality              | 12.5                 | Age, clinical site, HDL-C, LDL-C, SBP, antihypertensive medication use, CRP                                                                              |
| Echner et al. 2010 [49]    | USA            | The Strong Heart Study                                                     | 56                         | 4293                | 265              | Self-reported, measured | CVD mortality                    | 17                   | Age, BMI, LDL-C, HDL-C, physical activity, hypertension, diabetes, macro- and microalbuminuria |
| Bozorgmanesh et al. 2012 [50] | Iran         | The Tehran lipid and glucose study                                          | 33.3                       | 8795                | 1449             | Self-reported, measured | All-cause mortality, CVD mortality | 9                    | Age, smoking, SBP, using antihypertensive drugs, TC, HDL-C                                                                                               |
| Moe et al. 2013 [51]       | Norway         | HUNT 1 study                                                               | 47.9                       | 56,170              | 1105             | Self-reported            | CVD mortality, IHD mortality     | 24                   | Age, birth, smoking, education, alcohol, SBP, BMI, physical activity                                                                                     |
| Kakehi et al. 2014 [52]    | Japan          | The Jichi Medical School Cohort Study                                       | 55.1                       | 11,998              | 2706             | Measured                | All-cause mortality, cancer mortality, CVD mortality, stroke mortality | 10.7                 | Age, BMI, SBP, TC, HDL-C, smoking, alcohol                                                                                                           |
| Shen et al. 2014 [53]      | China          | Elderly health centers in Hong Kong                                         | 69.5                       | 66,820              | 9225             | Self-reported            | All-cause mortality, cancer mortality, IHD mortality, stroke mortality | 12.5                 | Age, alcohol, smoking, physical activity, education, housing, monthly expenditure                                                                   |
| Hiltunen et al. 2005 [54]  | Finland        | Kempele, Oulunsalo and Hailuoto study                                       | 76                         | 379                 | 98               | Self-reported, measured | All-cause mortality              | 9.8                  | Age, BMI, CVD, hypertension, physical activity, self-rated health                                                                                |
| Gordon-Dseagu et al. 2014 [55] | England      | The Health Survey for England or Scottish Health                            | 47                         | 204,533             | 7199             | Self-reported            | All-cause mortality, cancer mortality, CVD mortality | 10                   | Age, sex, smoking, BMI                                                                                                                                   |
| Author         | Study location | Study name | Mean baseline age (years) | No. of participants | No. of diabetes | Ascertainment of diabetes | Outcome                | Mean follow-up years | Maximum adjustment available                                      |
|---------------|----------------|------------|---------------------------|---------------------|----------------|--------------------------|------------------------|---------------------|-----------------------------------------------|
| Yeh et al. 2012 [56] | USA            | The CLUE II (Give Us a Clue to Cancer and Heart Disease) cohort | 51.8               | 18,280               | 599            | Treated diabetes          | All-cancer mortality  | 17                  | Age, BMI, smoking, education level, hypertension treatment, and high cholesterol treatment, menopausal status, history of use of oral contraceptives, history of use of hormone replacement therapy |
| Chen et al. 2017 [57] | Asia           | The ACC    | 53.9               | 771,297              | NA             | Self-reported             | All-cancer mortality  | 12.7                | Age, BMI, smoking, alcohol, educational attainment, urban residence |
| Zhou et al. 2010 [58] | Europe         | The DECODE study | 53.4               | 44,655               | NA             | Self-reported, measured   | All-cancer mortality  | 21.4                | Age, study cohort, BMI, SBP, cholesterol, smoking |
| Drake et al. 2017 [59] | Sweden         | The MDCS   | 57.9               | 26,953               | 21,940         | Self-reported             | Cancer mortality     | 17                  | Age, calendar year of study entry, height, smoking, physical activity, alcohol, educational level, past food habit change, hypertension, use of lipid-lowering drugs, family history of cancer, BMI |
| Preis et al. 2009 [60] | USA            | The Framingham Heart Study | 58.1               | 10,333               | NA             | Self-reported, measured   | All-cause mortality, CVD mortality | 25                  | Age                                                                 |
| NHIS          | USA            | NHIS       | 46.8               | 339,113              | 26,039         | Self-reported             | All-cause mortality, cancer mortality, CVD mortality, stroke mortality | 6.6                  | Age, race, BMI, smoking, drinking, education level, hypertension, physical activity, marital status, CVD, cancer |
| Natarajan et al. 2005 [61] | USA           | National Health and Nutrition Examination Survey Epidemiologic Follow-up Study | 52.4               | 10,871               | 539            | Measured                 | CHD mortality         | NA                  | Age, race, smoking, hypertension, serum cholesterol level, body mass index |
| Hirakawa et al. 2017 [62] | Japan         | EPOCH-JAPAN study | 58.2               | 38,854               | 1867           | Measured                 | All-cause mortality, CVD mortality, CHD mortality, stroke mortality | 10.3                 | Age, SBP, serum total cholesterol, BMI, current smoking status, habitual alcohol intake |
| Alegre-Díaz et al. 2016 [63] | Mexico         | Mexico City Study | 51.7               | 146,046              | 17,411         | Self-reported             | All-cause mortality   | 12                  | Age, smoking, district, education level, height, weight, WC, Hip |

Abbreviations: BMI body mass index (Quetelet index), BP blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure, TC total cholesterol, HDL high-density lipoprotein, LDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TG triglyceride, TGMDL-C triglyceride-to-high-density lipoprotein cholesterol ratio, ELVF electrocardiographic left ventricular hypertrophy, AF atrial fibrillation, MI myocardial infarction, FEV1 forced expiratory volume in 1 s, FEV2 forced expiratory volume in 2 s, CVD cardiovascular disease (angina, coronary heart disease, stroke, or amputation) (family history of premature CVD), IHD ischemic heart disease, CHD coronary heart disease, WC waist circumference, Hip hip circumference, IGT impaired glucose tolerance, CRP C-reactive protein, NA not available.
Fig. 2 Pooled RRs for risk of all-cause mortality
a greater risk for almost all outcomes of interest. Diabetes appears to be a stronger risk factor for CHD, CVD, and all-cause mortality in women than in men. Of note, compared to men with diabetes, women with the same condition had 57% excess risk for CHD. Although diabetes was associated with a higher risk of cancer mortality, infectious disease, and respiratory disease mortality, we did not observe a sex difference between diabetes and mortality. Interestingly, however, these results were only upheld in studies that used self-reporting measures to identify diabetes cases.

Diabetologists and epidemiologists have long been aware that diabetes has pronounced cardiovascular consequences for women, irrespective of diabetes type [10, 28, 64]. Indeed, CVD is the leading cause of morbidity and mortality for individuals with diabetes, which accounts for >50% of all deaths [65]. We found that for women, diabetes confers a 54% excess risk of CHD death. While such sex-specific differences are of increasing interest in cardiology and medical fields, the underpinning mechanisms driving this association are not entirely clear. The pathogenesis seems to be multifactorial with contributions from sex differences in genetic and biological factors, gender disparities from cultural and environmental factors, and the well-documented differences in the diagnosis, management, and treatment of DM and CVD of women and men [66–68].

The putative biological mechanisms have centered on the effects of estrogen which can deplete during menopause to elevate women’s CHD risk [69]. Testosterone

![Fig. 3 Pooled women-to-men RRRs for risk of all-cause mortality](image-url)
may be involved in different mechanisms attributed to sex differential in CHD risk [70–72]. In men, higher total testosterone levels are associated with reduced risk of future CHD and ischemic stroke. Testosterone has anabolic effects, promoting muscle mass and strength [73]. The recent prospective cohort study of half a million UK Biobank participants showed that higher grip strength was associated with a lower risk of incidence of and mortality from CVD [74]. Compared with men, women with lower testosterone levels have low mass and strength of muscle, which also partially explain greater risk for CHD death conferred by diabetes in women compared with men.

Women with diabetes are more likely to have poor risk factor profiles and suffer greater disease risk owing to the effects of individual risk factors. A recent meta-analysis showed that smoking conferred 25% excess risk for CHD in women than in men [7]. In addition, women with diabetes remain less likely to achieve high-density lipoprotein cholesterol targets and have a higher prevalence of obesity than men [75–77]. Whether existing sex differences in diabetic heart disease are magnified by sex differences in traditional and modifiable cardiac risk factors requires consideration. Recently, a meta-analysis of individual data from 68 prospective studies showed that body mass index, blood pressure, and total cholesterol each had continuous log-linear associations with CHD or stroke mortality that were similar in strength among those with and those without diabetes, irrespective of sex [78]. Our other study found that compared with men with metabolic syndrome, women with metabolic syndrome had a significant 16% higher risk of CHD incidence (RRR 1.16, 95% CI 1.01 to 1.34; \( P = 0.04 \)), and the significant sex difference disappeared in non-diabetes population (RRR 0.92, 95% CI 0.73 to 1.17; \( P = 0.50 \)). This partly supported the hypothesis that the stronger detrimental effects of diabetes for women than for men in CVD could not be explained by the different levels of established major CVD risk factors and their clusters. Differences in the clinical manifestation of diabetes warrants further consideration. Prediabetes is associated with an increased risk of cardiovascular disease [79], and the sex differences in the non-physiological effects can be partly accounted for the diabetes-related excess risk of CVD in women. In the prediabetic state, impaired glucose tolerance may be more serious in women than in men [80, 81].
| Event                  | Individuals | N   | RRR  | Lower  | Upper  | P value  | Test for heterogeneity | I² (%) | χ²    | P value for interaction |
|-----------------------|-------------|-----|------|--------|--------|----------|------------------------|--------|-------|------------------------|
| **All-cause mortality** | 3,887,585   | 28  |       |        |        |          |                        |        |       |                        |
| Age (years)           |             |     |      |        |        |          |                        |        |       |                        |
| < 60                  | 2,517,958   | 17  | 1.10 | 1.01   | 1.21   | 0.03     | 64.60                  | 45.24  | < 0.001 |
| ≥ 60                  | 268,044     | 7   | 1.10 | 1.04   | 1.18   | < 0.001  | 0.00                   | 3.00   | 0.81   |
| Others                | 1,101,583   | 4   | 1.19 | 0.91   | 1.57   | 0.21     | 84.30                  | 19.05  | < 0.001 |
| Location              |             |     |      |        |        |          |                        |        |       |                        |
| Asia                  | 1914.65     | 8   | 1.12 | 1.03   | 1.21   | 0.05     | 56.00                  | 15.89  | 0.03   |
| Western Europe        | 347,906     | 8   | 1.18 | 0.93   | 1.50   | 0.18     | 76.40                  | 29.69  | < 0.001 |
| North America         | 1,572,948   | 8   | 1.10 | 1.08   | 1.12   | < 0.001  | 0.00                   | 4.33   | 0.74   |
| Others                | 22,081      | 4   | 0.96 | 0.73   | 1.26   | 0.77     | 32.80                  | 4.47   | 0.22   |
| Follow-up years       |             |     |      |        |        |          |                        |        |       |                        |
| < 10                  | 908,252     | 9   | 1.12 | 1.02   | 1.22   | 0.02     | 38.00                  | 12.91  | 0.12   |
| ≥ 10                  | 2,979,333   | 19  | 1.13 | 1.06   | 1.21   | < 0.001  | 66.2                   | 53.32  | < 0.001 |
| Publication years     |             |     |      |        |        |          |                        |        |       |                        |
| ≤ 2000                | 95,532      | 9   | 1.1  | 0.9    | 1.4    | 0.5      | 64.50                  | 22.51  | < 0.001 |
| 2001–2009             | 1,381,865   | 5   | 1.3  | 1.0    | 1.6    | < 0.001  | 81.50                  | 21.60  | < 0.001 |
| ≥ 2010                | 2,410,188   | 14  | 1.1  | 1.0    | 1.2    | < 0.001  | 39.8                   | 21.59  | 0.06   |
| Method of diabetes ascertainment |     |     |      |        |        |          |                        |        |       |                        |
| KDM                   | 2,486,016   | 18  | 1.17 | 1.07   | 1.26   | < 0.001  | 74.2                   | 65.97  | < 0.001 |
| NDM                   | 590,506     | 6   | 1.05 | 0.90   | 1.21   | 0.20     | 32.10                  | 7.36   | 0.6    |
| KDM, NDM              | 1,363,765   | 9   | 1.05 | 0.97   | 1.15   | 0.3      | 16.40                  | 9.56   | < 0.001 |
| Cancer mortality      | 4,482,501   | 14  |      |        |        |          |                        |        |       |                        |
| Age (years)           |             |     |      |        |        |          |                        |        |       |                        |
| < 60                  | 3,361,850   | 12  | 1.01 | 0.95   | 1.07   | 0.75     | 0.00                   | 10.69  | 0.47   |
| ≥ 60                  | 66,820      | 1   | 1.02 | 0.88   | 1.18   | 0.81     | NA                     | 0.00   | NA     |
| Others                | 52,655      | 1   | 1.04 | 0.99   | 1.09   | 0.17     | NA                     | 0.72   | NA     |
| Location              |             |     |      |        |        |          |                        |        |       |                        |
| Asia                  | 2,795,136   | 8   | 1.01 | 0.96   | 1.08   | 0.65     | 0.00                   | 5.33   | 0.62   |
| Western Europe        | 276,141     | 3   | 0.94 | 0.58   | 1.51   | 0.80     | 53.50                  | 4.30   | 0.12   |
| North America         | 1,411,224   | 3   | 1.04 | 0.99   | 1.09   | 0.15     | 0.00                   | 0.03   | 0.98   |
| Others                | NA          |     |      |        |        |          |                        |        |       |                        |
| Follow-up years       |             |     |      |        |        |          |                        |        |       |                        |
| < 10                  | 881,061     | 3   | 1.08 | 0.94   | 1.23   | 0.29     | 0.00                   | 1.45   | 0.49   |
| ≥ 10                  | 3,601,440   | 11  | 1.02 | 0.98   | 1.06   | 0.32     | 0.00                   | 9.18   | 0.52   |
| Publication years     |             |     |      |        |        |          |                        |        |       |                        |
| ≤ 2000                | 5131        | 1   | 1.11 | 0.31   | 3.94   | 0.87     | NA                     | 0.00   | NA     |
| 2001–2009             | 1,327,437   | 2   | 1.05 | 0.91   | 1.20   | 0.50     | 5.10                   | 1.05   | 0.31   |
| ≥ 2010                | 3,149,933   | 11  | 1.02 | 0.98   | 1.06   | 0.30     | 0.00                   | 9.99   | 0.44   |
| Method of diabetes ascertainment |     |     |      |        |        |          |                        |        |       |                        |
| KDM                   | 2,094,903   | 9   | 1.03 | 0.90   | 1.19   | 0.65     | 77.90                  | 36.21  | < 0.001 |
| NDM                   | 557,524     | 2   | 1.07 | 0.96   | 1.18   | 0.22     | 0.00                   | 0.04   | 0.84   |
| KDM, NDM              | 2,369,318   | 4   | 1.03 | 0.99   | 1.08   | 0.16     | 0.00                   | 1.16   | 0.764  |
| Outcome                  | Individuals | N  | RRR | Lower | Upper | P value | Test for heterogeneity | I² (%) | χ²     | P value for interaction |
|--------------------------|-------------|----|-----|-------|-------|---------|-------------------------|--------|--------|------------------------|
| Treated diabetes         | 18,280      | 1  | 0.99| 0.56  | 1.74  | 0.96    | NA                      | 0      | NA     | NA                     |
| CVD mortality            | 2,067,486   | 23 | 23  |       |       |         |                         |        |        |                         |
| Age (years)              |             |    |     |       |       |         |                         |        |        |                         |
| < 60                     | 867,999     | 18 | 1.26| 1.01  | 1.56  | 0.04    | 72.20                   | 61.20  | < 0.001 |
| ≥ 60                     | 106,601     | 3  | 1.12| 0.98  | 1.29  | 0.10    | 5.70                    | 2.12   | 0.35    |
| Others                   | 1,092,886   | 2  | 1.53| 0.77  | 3.04  | 0.23    | 96.60                   | 29.05  | < 0.001 |
| Location                 |             |    |     |       |       |         |                         |        |        |                         |
| Asia                     | 159,835     | 6  | 1.08| 0.96  | 1.22  | 0.20    | 0.00                    | 4.95   | 0.42    |
| Western Europe           | 460,756     | 8  | 1.49| 1.17  | 1.90  | < 0.001 | 58.70                   | 16.96  | 0.02    |
| North America            | 1,415,878   | 6  | 1.33| 1.03  | 1.72  | 0.03    | 88.20                   | 42.22  | < 0.001 |
| Others                   | 31,017      | 3  | 1.12| 0.75  | 1.67  | 0.57    | 0.00                    | 0.53   | 0.77    |
| Follow-up years          |             |    |     |       |       |         |                         |        |        |                         |
| < 10                     | 433,100     | 6  | 1.08| 0.96  | 1.22  | 0.19    | 0.00                    | 4.13   | 0.53    |
| ≥ 10                     | 1,634,386   | 17 | 1.35| 1.13  | 1.62  | < 0.001 | 83.00                   | 93.96  | < 0.001 |
| Publication years        |             |    |     |       |       |         |                         |        |        |                         |
| ≤ 2000                   | 54,288      | 4  | 1.36| 0.75  | 2.47  | 0.31    | 79.10                   | 14.33  | < 0.001 |
| 2001–2009                | 142,444     | 6  | 1.63| 1.04  | 2.57  | 0.03    | 83.50                   | 30.31  | < 0.001 |
| ≥ 2010                   | 1,870,754   | 13 | 1.09| 1.06  | 1.12  | < 0.001 | 0.00                    | 4.62   | 0.97    |
| Method of diabetes ascertainment |             |    |     |       |       |         |                         |        |        |                         |
| KDM                      | 1,876,261   | 11 | 1.20| 1.02  | 1.42  | 0.03    | 85.10                   | 66.94  | < 0.001 |
| NDM                      | 42,944      | 3  | 1.40| 0.84  | 2.35  | 0.20    | 74.50                   | 7.85   | 0.02    |
| KDM, NDM                 | 152,371     | 11 | 1.31| 0.95  | 1.82  | 0.10    | 73.10                   | 37.23  | < 0.001 |
| Treated diabetes         | NA          |    |     |       |       |         |                         |        |        |                         |
| CHD mortality            | 2,050,929   | 23 | 23  |       |       |         |                         |        |        |                         |
| Age (years)              |             |    |     |       |       |         |                         |        |        |                         |
| < 60                     | 864,790     | 15 | 1.52| 1.22  | 1.90  | < 0.001 | 39.20                   | 23.02  | 0.06    |
| ≥ 60                     | 89,838      | 4  | 1.68| 1.22  | 2.30  | < 0.001 | 0.00                    | 2.69   | 0.44    |
| Others                   | 1,096,301   | 4  | 1.65| 0.90  | 3.04  | 0.11    | 89.70                   | 29.18  | < 0.001 |
| Location                 |             |    |     |       |       |         |                         |        |        |                         |
| Asia                     | 692,384     | 5  | 1.53| 0.99  | 2.38  | 0.06    | 61.10                   | 10.29  | 0.04    |
| Western Europe           | 242,624     | 8  | 1.86| 1.42  | 2.45  | < 0.001 | 41.60                   | 11.98  | 0.10    |
| North America            | 1,113,375   | 9  | 1.17| 1.13  | 1.22  | < 0.001 | 0.00                    | 7.26   | 0.51    |
| Others                   | 2546        | 1  | 3.11| 0.79  | 12.23 | 0.11    | NA                      | 0.00   | NA      |
| Follow-up years          |             |    |     |       |       |         |                         |        |        |                         |
| < 10                     | 606,561     | 6  | 1.23| 0.85  | 1.79  | 0.23    | 27.20                   | 6.87   | 0.27    |
| ≥ 10                     | 1,371,125   | 14 | 1.75| 1.33  | 2.31  | 0.00    | 78.50                   | 60.43  | < 0.001 |
| Others                   | 73,243      | 3  | 1.38| 0.95  | 2.02  | 0.10    | 0.00                    | 0.86   | 0.65    |
| Publication years        |             |    |     |       |       |         |                         |        |        |                         |
| ≤ 2000                   | 111,122     | 10 | 1.66| 1.21  | 2.27  | 0.00    | 41.90                   | 15.49  | 0.08    |
| 2001–2009                | 118,915     | 6  | 1.84| 1.25  | 2.71  | 0.00    | 32.80                   | 7.44   | 0.19    |
| ≥ 2010                   | 1,820,892   | 7  | 1.30| 1.12  | 1.52  | 0.00    | 41.00                   | 10.17  | 0.12    |
| Method of diabetes ascertainment |             |    |     |       |       |         |                         |        |        |                         |
| KDM                      | 1,457,769   | 14 | 1.52| 1.20  | 1.92  | 0.00    | 78.10                   | 59.23  | < 0.001 |

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Biases embedded within health service need to be considered. There is evidence that women, compared to their male counterparts, are less likely to have their risk factors assessed by physicians when they present in primary care. Compared to older women at high risk of CVD, younger women at high risk were less likely to receive preventative treatment [82]. Indeed, women with diabetes or CVD are diagnosed later and have a lower frequency of statin therapy, aspirin use, and ACE inhibitor and β-blocker use than men [83]. Some studies observed lower medication adherence in women than in men [84, 85]. Where medication is adhered to, women do not always benefit to the same extent as men given the well-documented issues with under-representation of women in clinical trials [66]. What is more, younger women’s symptoms often present differently to those of men of the same age. There may be less myocardial ischemic preconditioning in women, and subsequently greater susceptibility to ischemia. Therefore, sex and gender disparities in treatment may exacerbate the sex differences in CVD owing to diabetes [86, 87].

Some studies show that the proportion of undiagnosed diabetes to total diabetes in men is higher than that in women [88, 89]. In studies that used self-reported measures to identify diabetes, there was a greater proportion of undiagnosed diabetes in men. It is possible that this concealed the true excess risk of mortality conferred by diabetes in men and subsequent sex-specific relative risk estimates that were calculated for women and men.

Our finding that diabetes elevates the risk of all-cancer mortality is in general agreement with previous reviews [90]. However, most have looked at site-specific cancers; sex-specific associations from which results have been inconsistent. One meta-analysis indicated that diabetes conferred a stronger positive relationship with kidney cancer mortality and gastric cancer risk in women than in men [91, 92].

### Table 2

Sensitivity analyses of women-to-men ratio of relative risks for the outcomes associated with diabetes (Continued)

| Individuals | N | RRR | Lower | Upper | P value | Test for heterogeneity | P value for interaction |
|-------------|---|-----|-------|-------|---------|------------------------|------------------------|
| NDM         | 119,825 | 4  | 1.90  | 0.98  | 3.70    | 0.06                  | 70.70                  | 10.26                  | 0.02                  |
| KDM, NDM    | 543,435 | 7  | 1.34  | 1.14  | 1.57    | 0.00                  | 0.00                  | 5.42                  | 0.49                  |
| Treated diabetes | NA          |     |       |       |         |                       |                       |                       |                       |

**Stroke mortality**

| NDM | 2,292,387 | 15 | 1.00  | 0.98  | 1.02    | 0.00                  | 0.00                  |

**Location**

| Asia       | 764,335 | 7  | 1.11  | 0.97  | 1.26    | 0.12                  | 0.00                  | 5.04                  | 0.54                  |
| Western Europe | 132,562 | 5  | 1.36  | 0.97  | 1.90    | 0.07                  | 0.00                  | 1.60                  | 0.81                  |
| North America | 1,392,944 | 2  | 1.06  | 0.98  | 1.13    | 0.13                  | 0.00                  | 0.08                  | 0.78                  |
| Others     | 2546    | 1  | 0.46  | 0.03  | 7.76    | 0.59                  | NA                    | 0.00                  | NA                    |

**Follow-up years**

| < 10      | 903,575 | 4  | 1.12  | 0.96  | 1.30    | 0.14                  | 0.00                  | 2.62                  | 0.45                  |
| ≥ 10      | 1,388,812 | 11 | 1.07  | 1.00  | 1.14    | 0.06                  | 0.00                  | 6.48                  | 0.77                  |
| Others    | NA      |    |       |       |         |                       |                       |                       |                       |

**Publication years**

| ≤ 2000    | 67,444  | 5  | 1.39  | 0.90  | 2.14    | 0.14                  | 0.00                  | 2.67                  | 0.62                  |
| 2001–2009 | 101,874 | 3  | 1.09  | 0.63  | 1.91    | 0.75                  | 23.90                 | 2.63                  | 0.27                  |
| ≥ 2010    | 2,123,069 | 7  | 1.07  | 1.00  | 1.14    | 0.04                  | 0.00                  | 2.66                  | 0.85                  |

**Method of diabetes ascertainment**

| KDM       | 1,720,989 | 10 | 1.06  | 1.00  | 1.13    | 0.07                  | 0.00                  | 8.36                  | 0.50                  |
| NDM       | 61,368    | 2  | 1.37  | 0.70  | 2.66    | 0.36                  | 24.80                 | 1.33                  | 0.25                  |
| KDM, NDM  | 532,544   | 4  | 1.18  | 0.98  | 1.42    | 0.09                  | 0.40                  | 3.01                  | 0.39                  |

**Treated diabetes**

Abbreviations: N number of studies, NA not available, CVD cardiovascular disease, CHD coronary heart disease
Others have found that diabetes increased the risk of esophageal cancer and leukemia in men, but not in women \[93, 94\]. Prospective studies showed that HRs for non-cancer, non-vascular deaths among participants with diabetes, as compared to those without diabetes, were also significantly higher among women (women: HR 2.20, 95% CI 1.91 to 2.52; men: HR 1.58, 95% CI 1.41 to 1.76; \( P_{\text{interaction}} < 0.001 \)). The absence of sex disparities for infectious disease and respiratory disease mortality did not contribute to the sex difference for non-cancer, non-vascular deaths \[95\]. Therefore, future research is needed to distinguish whether and to what extent the excess risk of cause-specific mortality from non-cancer, non-vascular deaths conferred by diabetes differs between the sexes, such as kidney disease mortality.

**Strengths and limitations**

The present meta-analysis has several main strengths. Firstly, the large number of participants ensured greater statistical power to detect sex differences than some previous individual studies. Secondly, using within-study comparisons to estimate sex-specific relationships between diabetes and cause-specific outcomes can minimize the role of extraneous, between-study factors. Thirdly, the study comprehensively evaluated the sex-specific associations for a range of important health outcomes: all-cause, all-cancer, CVD, and other cause-specific mortality. This has the potential to be more informative in aiding our understanding of the sex-specific burden of disease from diabetes. Fourthly, the detailed subgroup, sensitivity, and influence analyses ensure the robustness of the study findings.

There are also some specific limitations of this review that merit consideration. Firstly, there was some heterogeneity across studies for outcomes such as all-cause, CVD, and CHD mortality, but subgroup analyses and meta-regression analyses on study characteristics including age, geographical location, duration of follow-up, publish year, and method of diabetes ascertainment did not provide any evidence of a substantial effect of these differences on the results. Secondly, the present meta-analysis is based on prospective cohort studies, and the observational design is open to biases due to the residual confounding from incompletely measured factors and cannot elucidate causal relationship. Thirdly, the present meta-analysis did not include non-fatal events, which limited the ability to assess the presence of sex differences in risk for the incidence. Fourthly, differences in definition of diabetes, diabetes duration, duration of follow-up, and populations might have contributed to the sex differences in the association of diabetes with risk of death and CVD; although subgroup, meta-regression, and sensitivity analyses were conducted to explore the potential between-study heterogeneity, lack of individual participant data limited more in-depth sensitivity analyses than were reported here. Fifthly, our analysis cannot ascertain the underlying cause of the sex differences in the relationship between diabetes and the risk of CVD mortality. Finally, the potential publication bias was also a concern. Although we did not observe any apparent publication bias in our statistical tests, it was still difficult to completely rule this out.

**Conclusions**

Our study demonstrated that women with diabetes have a greater risk of all-cause mortality, particularly from CHD, compared with men with the same condition. An increased understanding and appreciation of sex differences in the relationship between diabetes and risk of all-cause and CHD mortality is required given the substantial global and regional burden of NCDs. Women with diabetes should be treated and managed throughout their life course with the view to reduce the burden of other diseases related to diabetes. In the future, in-depth sex-specific analyses from randomized trials and other studies using approaches like Mendelian randomization are needed to clarify the biological, behavioral, or social mechanisms involved.

**Additional file**

Additional file 1: contains additional information and analysis. Table S1. Study protocol: PRISMA 2009 Checklist. Table S2. Quality of included studies assessed with Newcastle-Ottawa Scale. Figure S1. Pooled RRs for the risk of cancer mortality. Figure S2. Pooled women-to-men RRRs for the risk of cancer mortality. Figure S3. Pooled RRs for the risk of CVD mortality. Figure S4. Pooled women-to-men RRRs for the risk of CVD mortality. Figure S5. Pooled RRs for the risk of CHD mortality. Figure S6. Pooled women-to-men RRRs for the risk of CHD mortality. Figure S7. Pooled women-to-men RRRs for the risk of stroke mortality. Figure S8. Pooled RRs for the risk of respiratory mortality. Figure S9. Pooled RRs for the risk of infectious mortality. (DOCX 1577 kb)

**Abbreviations**

BMI: Body mass index; CHD: Coronary heart disease; CI: Confidence intervals; CVD: Cardiovascular disease; GBD: Global Burden of Disease Study; HR: Hazard ratio; KDM: Known diabetes; N: Number of studies; NA: Not available; NCDs: Non-communicable diseases; NDM: Newly diagnosed diabetes; NOS: Newcastle-Ottawa quality assessment scale; OR: Odds ratio; RR: Relative risk; RRR: Ratio of RR

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**Authors’ contributions**

YW, AO, and CY were responsible for the conception and design of the study. YW, YJ, and LW were responsible for the acquisition of data and analysis. YJ and YW were responsible for the statistical analysis. YW, AO, YJ, JH, YI, YZ, and CY wrote and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data and materials analyzed in this manuscript are authentic and derived from published studies except data from NHS. For NHS, the data we used are publicly available. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This systematic review and meta-analysis includes previously published observational studies and public-use data from NHS. In addition, the NHS was approved by the National Center for Health Statistics ethics review board. We could not influence the design of the prior studies upon which this work is based and cannot comment on individual ethics approval or consent. Patients were not involved in the conduct of our epidemiological study, and there is no identifiable data.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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