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Association between diabetes mellitus and the risk for major cardiovascular outcomes and all-cause mortality in women compared with men: a meta-analysis of prospective cohort studies

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ABSTRACT

Objective Previous studies have reported sex differences in associations between diabetes mellitus (DM) and the risk of developing coronary heart disease (CHD) and stroke; however, the risk for cardiac death and all-cause mortality in women compared with men has not been reported. Therefore, this quantitative meta-analysis was performed to provide reliable estimates of sex differences in the effect of DM on major cardiovascular outcomes and all-cause mortality, irrespective of DM type.

Design Meta-analysis.

Data sources The PubMed, Embase and the Cochrane Library databases were systematically searched in April 2018.

Eligibility criteria Investigations designed as prospective cohort studies that examined the association between DM and major cardiovascular outcomes and all-cause mortality stratified according to sex were included.

Data extraction and synthesis Data extraction and quality assessment were independently performed by 2 of the authors, and the relative risk ratio (RRR) obtained using a random effects model was used to measure sex differences in the associations of DM with major cardiovascular outcomes and all-cause mortality.

Results Thirty prospective cohort studies that reported data from 1 148 188 individuals were included. The pooled women-to-men RRR suggested that female sex was associated with an increased risk for CHD (RRR 1.52(95% CI 1.32 to 1.76); p<0.001), stroke (RRR 1.23(95% CI 1.09 to 1.39); p=0.001), cardiac death (RRR 1.49(95% CI 1.11 to 2.00); p=0.009) and all-cause mortality (RRR 1.51(95% CI 1.23 to 1.85); p<0.001). In addition, sex differences for the investigated outcomes in the comparison between DM and non-DM patients were variable after stratification of studies according to publication year, country, sample size, assessment of DM, follow-up duration, adjustment for important cardiovascular risk factors and study quality.

Conclusions Findings of the present study suggested that women with DM had an extremely high risk for CHD, stroke, cardiac death and all-cause mortality compared with men with DM.

Strengths and limitations of this study

► Published studies with large sample sizes were included in the analysis, and findings of the present study were more robust than those of any individual study.
► All included studies were prospectively designed and population based, which mitigated, if not eliminated, the possibility of uncontrolled biases.
► Large studies with a diverse range of patient characteristics support the generalisability of the results because the populations included were distributed globally.
► Stratified results of sex differences between DM and major cardiovascular outcomes and all-cause mortality were calculated based on the study or patient characteristics.
► Heterogeneity of the included studies was resolved using multiple methods, and no publication bias was found, thus supporting the robustness of the pooled results.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide and accounts for 10.3% of the global disease burden, with a mortality rate of approximately 30% at the first CVD event.[1 2] Numerous studies have illustrated the risk for CVD and related factors in various populations.[3–7] It has been established that the morbidity and mortality of CVD risk are significantly increased in patients with diabetes mellitus (DM).[8–11] Furthermore, DM is an independent risk factor for CVD, all-cause mortality, blindness, kidney failure, amputation, fracture, frailty, depression, and cognitive decline,[12] thus emphasising the need to monitor high risk for CVD in patients with DM.

Sex differences in the effect of DM on the excess risk for coronary heart disease (CHD)

and stroke have been reported and vary based on several other risk factors.[13 14] These two large-scale quantitative meta-analyses reported that women with DM have a 44% and 27% greater risk for CHD and stroke, respectively. Although the mechanism of action remains unclear, the exposure effects may be influenced by non-DM women with persistently healthy lifestyles and are well controlled by other important cardiovascular risk factors.[15] However, to our knowledge, several other important outcomes, including cardiac death and all-cause mortality, have not been examined in previous studies.

Although previous meta-analyses have illustrated sex differences in the association between DM and CHD and stroke risk, the current study is the first meta-analysis to quantify potential sex differences in cardiac death and all-cause mortality. Clarifying sex differences in DM and major cardiovascular outcomes and all-cause mortality is particularly important to identify high-risk populations for the development of major cardiovascular outcomes and all-cause mortality, given that it has not been definitively determined. Therefore, we performed a large-scale examination of available prospective cohort studies that examined sex-specific effects of DM on the subsequent risk for CHD, stroke, cardiac death and all-cause mortality to determine sex differences in DM regarding major cardiovascular outcomes and all-cause mortality.

MATERIAL AND METHODS

Data sources, search strategy and selection criteria

This study was conducted and is reported according to the meta-analysis of observational studies in epidemiology protocol.[16] Studies with a prospective cohort design that analysed the associations between DM and CHD, stroke, cardiac death and all-cause mortality risk and were published in the English language were potentially eligible for inclusion in this meta-analysis. There were no restrictions on the publication status of the studies considered. Three electronic databases (PubMed, Embase and the Cochrane Library) were searched for studies published from inception to April 2018 using the following search terms: ('diabetes mellitus' OR 'diabetes') AND ('Coronary Disease' OR 'Coronary Artery Disease' OR 'Myocardial Ischemia' OR 'stroke' OR 'death' OR 'mortality') AND ('men' OR 'male') AND ('women' OR 'female') AND ('Cohort Studies' OR 'Prospective Studies') AND 'human' AND 'English'. The details of the strategy used to search PubMed are presented in online supplementary file 1. Additional eligible studies were identified by manual searches of the reference lists in the relevant original and review articles. The study title, design, exposure, control and outcomes of varying effects in men and women in these studies were separately considered in selecting relevant studies.

The literature search and study selection were performed independently by two reviewers; any disagreement between these reviewers was resolved by including the corresponding author in the discussion until consensus

was reached. The inclusion criteria were as follows: design: prospective cohort design; exposure and control: DM (irrespective of DM type) and non-DM; outcomes: CHD, stroke, cardiac death and all-cause mortality; and effect estimate: the relationship between DM and CHD, stroke, cardiac death, and all-cause mortality in men and women were reported separately. Studies examining single-sex populations, those with retrospective observational designs and reported with standard incidence/mortality ratio were excluded.

Data collection and quality assessment

Two independent reviewers performed data collection and quality assessment, and any inconsistencies was adjudicated by referring to the original studies. The collected data included the first author or study group's name, publication year, country, sample size, age range, percentage of women, number of DM subjects, assessment of DM, follow-up duration, adjusted factors and investigated outcomes. The effect estimate was selected and maximally adjusted for confounders if the study reported several multivariable adjusted effect estimates. Quality assessment was performed using the Newcastle-Ottawa Scale, which is based on selection (four items), comparability (one item) and outcome (three items).[17] A 'star system' (range: 0–9) was used to evaluate individual study quality.

Statistical analysis

Sex differences in the relationship between DM and CHD, stroke, cardiac death or all-cause mortality risk were based on the sex-specific effect estimate and corresponding 95% CI of each individual study. Given the low prevalence of CHD, stroke, cardiac death or all-cause mortality, ORs could be assumed to be accurate estimates of RR. Furthermore, HR was regarded to be equivalent to Relative Risk (RR) in studies with a cohort design. The summary RRs and 95% CIs for DM versus non-DM and the risk for CHD, stroke, cardiac death and all-cause mortality in men and women were calculated separately using a random-effects model, and the STATA commands were metan lnrr lnrrl lnrru, eform random xlab (0.3, 0.5, 1.0, 2.0) effect (RR) label (namevar=study).[18 19] The female-to-male ratio of RRs (ie, relative risk ratio (RRR)) and 95% CI in each study for CHD, stroke, cardiac death or all-cause mortality were then calculated based on sex-specific RRs and 95% CIs.[14 15 20] Finally, the summary RRR and 95% CIs for sex differences in DM versus non-DM and CHD, stroke, cardiac death or all-cause mortality risk were calculated using a random-effects model.[18 19]

The I^2 and Q statistics were used to evaluate heterogeneity among the included studies; those with p<0.10 were considered to demonstrate significant heterogeneity.[21 22] A sensitivity analysis was then conducted to evaluate the impact of individual studies on the overall estimates by excluding each study sequentially.[23] Subsequently, subgroup analyses for sex differences in DM on CHD, stroke, cardiac death or all-cause mortality risk were

calculated based on the following: publication year (2010 or after, and before 2010); country (Eastern or Western countries); sample size (≥10 000 and <10 000); assessment of DM (self-reported, measured or both); follow-up duration (≥10 and <10 years); adjustment for other cardiovascular risk factors (yes or no); and study quality (high vs low). Finally, publication biases for investigated outcomes were assessed using funnel plots, the Egger test and the Begg test.[24 25] Two-sided p values with a significance level of 0.05 were used in the pooled analyses. Statistical analyses were performed using STATA software V.10.0.

Patient and public involvement

No patients were involved in the development of the research question, outcome measures, design, study implementation, dissemination of the results of the research to the study participants or interpretation of the results.

RESULTS

Literature search

The study selection process is shown in online supplementary file 2. A total of 13 471 articles were identified in the initial electronic search, of which 12 745 were excluded due to duplicates and irrelevant topics. The abstracts of the remaining 726 articles were assessed, and 633 were excluded due to having a design other than prospective cohort and reported cardiovascular risk factors as outcomes. The full text was retrieved for the remaining 93 articles to identify potential studies that may be included. Thirty prospective cohort studies fulfilled the inclusion criteria and were ultimately included in the meta-analysis.[26–55] There was no additional eligible studies after a manual search of the reference lists of these studies.

Study characteristics

A total of 30 studies, which included 75 cohorts, 1 148 188 individuals and 52 715 DM patients were included. Table 1 summarises the baseline characteristics of the included studies. The follow-up period was 5.0–30.0 years, while 787–436 832 individuals were included in each study. Forty-one cohorts were from countries in the Western countries, and the remaining 34 from the Eastern countries. The percentage of women ranged from 33.0% to 63.0%. Nine studies used self-reported methods to assess DM, 16 studies used medical methods and the remaining 5 used both self-reported and medical methods. Overall, 9 studies had a Newcastle-Ottawa Scale score of 8, 12 studies had a score of 7 and the remaining 9 studies had a score of 6 (online supplementary file 3).

Coronary heart disease

Twenty studies reported sex differences in the association between DM and subsequent CHD risk. Summaries of the results in men and women are shown separately in online supplementary file 4. The results indicated that DM was associated with an increased risk for CHD risk in both men and women. Furthermore, the pooled RRR (female to male) of DM versus non-DM and the risk for CHD was 1.52 (95% CI 1.32 to 1.76; p<0.001) (figure 1A). Although the difference was statistically significant, there was significant heterogeneity among the studies (I^2=36.1%; p=0.044). Results of the sensitivity analysis were not affected after sequential exclusion of each study from the pooled analyses (online supplementary file 5). The results of subgroup analyses were consistent with the overall analysis in most subsets, except for follow-up duration <10.0 years (table 2).

Stroke

Twenty studies reported sex differences in the association between DM and subsequent risk for stroke. The pooled results in men and women with DM were statistically significant (online supplementary file 4). The pooled RRR (female to male) suggested that women with DM had an increased risk for stroke compared with men with DM (RRR 1.23 (95% CI 1.09 to 1.39); p=0.001) (figure 1B), and no evidence of heterogeneity was observed (I^2=0.0%; p=0.568). Sensitivity analysis indicated that the conclusion was not affected by sequential exclusion of each study from the pooled analyses (online supplementary file 5). Subgroup analysis indicated no sex differences in the relationship between DM and stroke risk for pooled studies published in 2010 or after, conducted in the Eastern hemisphere, sample sizes <10 000, those that used both self-reported and measured parameters, duration of follow-up <10.0 years, no adjustments for other cardiovascular risk factors and those of low quality (table 3).

Cardiac death

Ten cohort studies reported sex differences in the association between DM and subsequent risk for cardiac death. DM was associated with a greater risk for cardiac death in men and women independently (online supplementary file 4). The pooled RRR (female to male) of DM versus non-DM for risk for cardiac death was 1.49 (95% CI 1.11 to 2.00; p=0.009) (figure 2A), which was a statistically significant difference; furthermore, non-significant heterogeneity was detected (I^2=31.9%; p=0.153). Results of the sensitivity analysis were altered after excluding the Kuopio and North Karelia studies (online supplementary file 5). Subgroup analysis indicated significant sex differences in DM in cardiac death if the study was published before 2010, was conducted in the Western hemisphere, had a sample size ≥10 000, used medical measures to assess DM, had a follow-up duration ≥10.0 years, was adjusted for other cardiovascular risk factors and was of high quality (table 4).

All-cause mortality

Seven cohort studies reported sex differences in the association between DM and subsequent all-cause mortality risk. Results indicated that DM was associated with a higher risk for all-cause mortality in men and women independently (online supplementary file 4). The pooled

Table 1 Baseline characteristic of studies included in the systematic review and meta-analysis

Study	Publication year	Country	Sample size	Number of DM	Age range	Percentage of women (%)	Assessment of DM	Follow-up duration (years)	Adjusted factors	Study quality
NHANES I[26]	1988	USA	7381	407	40–77	55.0	Self-reported	9.0	Age, SBP, smoking, BMI and TC.	7
Rancho Bernado[27]	1988	USA	3778	320	50–79	54.0	Self-reported	12.0	Age, SBP, TC, smoking, obesity, family history and oestrogen use.	6
ARIC[28]	1989	USA	15 732	1610	45–64	55.0	Measured	18.0	Age, SBP, smoking, BMI and TC.	7
Adventist Health Study[29]	1992	USA	27 658	656	>25	63.0	Measured	6.0	Age, hypertension, smoking, BMI and PA.	6
Sievers[30]	1992	USA	5131	1266	15–84	52.0	Measured	10.0	Age	7
EPESE[31]	1993	USA	2812	386	>65	58.0	Self-reported	6.0	Age, AHT use, smoking, BMI, diabetes, angina and chest pain on exertion.	6
Charleston Heart Study-White[32]	1993	USA	1394	38	>35	53.0	Measured	30.0	Age.	6
Charleston Heart Study-Black[32]	1993	USA	787	37	>35	58.0	Measured	30.0	Age.	6
NHANES III[33]	1994	USA	18 603	1290	18–90	46.0	Self-reported or measured	13.0	Age, SBP, smoking, BMI and TC.	7
Dubbo study[34]	1995	Australia	2805	206	>60	56.0	Measured	5.0	Age, AHT use, BMI, TC, HDL, triacylglycerols, ApoB, LPa, diabetes, self-rated health and prior CH.	6
Collins-Indians[35]	1996	Fiji	1220	166	>20.0	55.0	Measured	11.0	Age, SBP, smoking, BMI, TC and survey area.	6
Collins-Melanesians[35]	1996	Fiji	1324	65	>20.0	53.0	Measured	11.0	Age, SBP, smoking, BMI, TC and survey area.	6
SALLS[36]	1998	Sweden	39 055	174	25–74	51.0	Self-reported	16.0	Age.	6
Hawaii-Los Angeles-Hiroshima study[37]	2002	Japan	927	169	40–79	56.0	Measured	10–18	Age, hypertension, smoking, BMI, TC, triacylglycerols, uric acid and ECG abnormalities.	6
Reykjavik study[38]	2002	Iceland	18 519	295	32–60	52.0	Self-reported or measured	17.0	Age, hypertension, smoking, BMI, TC, triacylglycerols, diabetes, glucose, prior CHD and LVH.	8
APCSC-Asia[39]	2003	27 cohorts in Asia	436 832	17 763	>20	33.0	Self-reported or measured	7.0	Age, SBP, smoking, BMI and TC.	7

Continued

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Table 1 Continued

Study	Publication year	Country	Sample size	Number of DM	Age range	Percentage of women (%)	Assessment of DM	Follow-up duration (years)	Adjusted factors	Study quality
APCSC-Australia and New Zealand[39]	2003	Nine cohorts in Australia and New Zealand	99 624	4784	>20	45.0	Self-reported or measured	7.0	Age, SBP, smoking, BMI and TC.	7
Framingham study[40]	2003	Two cohorts in USA	5243	229	35–75	52.0	Measured	20.0	Age, hypertension, smoking, BMI and TC.	7
Iso[41]	2004	Japan	10 582	267	40–69	60.0	Measured	17.0	Age, hypertension, smoking, BMI, TC, HDL, skinfold, alcohol, community and menopause.	8
Renfrew and Paisley Survey[42]	2005	Scotland	15 426	228	45–64	54.0	Self-reported or measured	25.0	Age, SBP, smoking, BMI, TC and SES.	8
Kuopio and North Karelia[43]	2005	Finland	51 735	1108	25–74	51.0	Self-reported	17.0	Age, SBP, smoking, BMI, TC and study year.	8
Strong Heart Study[44]	2006	USA	4372	724	45–74	61.0	Measured	12.0	Age, SBP, DBP, smoking, HDL, LDL and albuminuria.	7
Framingham Offspring[45]	2006	USA	2097	99	50–81	50.0	Measured	14.0	Age, SBP, AHT, CVD, atrial fibrillation, LVH and smoking.	7
San Antonio Heart Study[46]	2007	USA	4996	524	25–64	57.0	Measured	16.0	Age and ethnicity.	7
SHHEC[47]	2007	Scotland	13 343	184	30–74	51.0	Measured	16.0	Age, SBP, smoking, BMI and TC.	7
EPIC-Norfolk[48]	2008	UK	22 516	441	40–79	55.0	Self-reported	10.0	Age, SBP, smoking, BMI, TC and triglycerides.	8
Takayama[49]	2008	Japan	29 079	1217	>35	54.0	Self-reported	7.0	Age, hypertension, smoking, BMI, PA, education, energy, vegetables, fat and alcohol.	8
DECODE[50]	2009	Seven cohorts in Finland and Sweden	9278	826	40–69	55.0	Measured	5–21	Age, hypertension, smoking, BMI, TC and HDL.	6
Hisayama[51]	2010	Japan	2421	291	40–79	57.0	Measured	14.0	Age, SBP, smoking, BMI, TC, HDL, alcohol intake, PA and ECG abnormalities.	7

Table 1 Continued

Study	Publication year	Country	Sample size	Number of DM	Age range	Percentage of women (%)	Assessment of DM	Follow-up duration (years)	Adjusted factors	Study quality
JPHC[52]	2011	Two cohorts in Japan	35 657	2034	40–69	63.0	Measured	12.0	Age, SBP, AHT, smoking, BMI, TC, HDL, triglycerides, alcohol, fasting status and residential areas.	8
HUNT 1[53]	2012	Norway	47 951	1992	>20	52.0	Self-reported	17.0	Age, hypertension, smoking, BMI, CVD and PA.	8
ESPro[54]	2017	Germany	105 000	7190	>18	51.0	Self-reported or measured	14.0	Calendar year and age.	7
JACC[55]	2017	Japan	104 910	5729	40–79	58.0	Self-reported	19.0	Age, education, smoking, alcohol, PA, BMI, history of hypertension or history of DM.	8

AHT, antihypertensive; APCSC, Asia Pacific Cohort Studies Collaboration; ApoB, apolipoprotein B; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DECODE, Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe; DM, diabetes mellitus; EPESE, Established Populations for Epidemiology Studies of the Elderly; EPIC, European Prospective Investigation into Cancer; HDL, high-density lipoprotein; JACC, Japan Collaborative Cohort; LDL, low-density lipoprotein; LPa, lipoprotein a; LVH, left ventricle hypertrophy; NA, not available; NHANES, National Health and Nutrition Examination Survey; PA, physical activity; SALLS, Swedish Annual Level-of-Living Survey; SBP, systolic BP; SES, socioeconomic status; SHHEC, Scottish Heart Health Extended Cohort; TC, total cholesterol.

female-to-male RRR indicated significant sex differences for risk for all-cause mortality between participants with DM and those without DM (RRR 1.51 (95% CI 1.23 to 1.85); p<0.001) (figure 2B), with moderate heterogeneity among the included studies (I^2=38.2%; p=0.138). Sensitivity analysis revealed that the conclusion was not affected by the exclusion of any specific study (online supplementary file 5). Subgroup analyses indicated no sex difference if the study was conducted in the Eastern hemisphere, with a sample size <10 000, used medical measure to assess DM, was not adjusted for other cardiovascular risk factors and was of low quality (table 5).

Publication bias

A review of the funnel plots could not rule out the potential for publication bias for CHD, stroke, cardiac death and all-cause mortality (online supplementary file 6). The Egger and Begg test results revealed no evidence of publication bias for CHD (Egger p=0.959; Begg p=0.245), stroke (Egger p=0.407; Begg p=0.398), cardiac death (Egger p=0.418; Begg p=0.721) and all-cause mortality (Egger p=0.118; Begg p=0.230).

DISCUSSION

The current investigation was based on a collection of prospective cohort studies and explored all possible sex differences between DM and the outcomes of CHD, stroke, cardiac death and all-cause mortality. This large quantitative study included 1 148 188 individuals and 52 715 DM patients from 30 prospective cohort studies investigating a broad range of populations. Findings from the current meta-analysis suggest that there are significant sex differences in DM versus non-DM regarding the incidence of CHD, stroke, cardiac death, all-cause mortality, with women demonstrating excessively higher risks than men. Furthermore, the findings of subgroup analyses could have been biased by publication year, country, sample size, assessment of DM, follow-up duration, adjustment for important cardiovascular risk factors and study quality.

Previous studies have suggested that women with DM have an increased risk for CHD or stroke compared with men with DM.[13 14] One of these investigations reported that the incidence of CHD was 44% greater in women with DM than in men with DM.[13] Moreover, women with DM exhibited an increased risk for stroke compared with men with DM.[14] However, sex differences regarding other important outcomes (cardiac death and all-cause mortality) were not evident. Therefore, we conducted this comprehensive quantitative meta-analysis of available prospective cohort studies to evaluate sex differences in DM and possible associations with major cardiovascular outcomes. Similar to previous meta-analyses, a significantly increased risk for cardiac death and all-cause mortality was observed in women with DM compared with men with DM. The excess risk for cardiac death in women with DM could be due to the higher risk for CHD
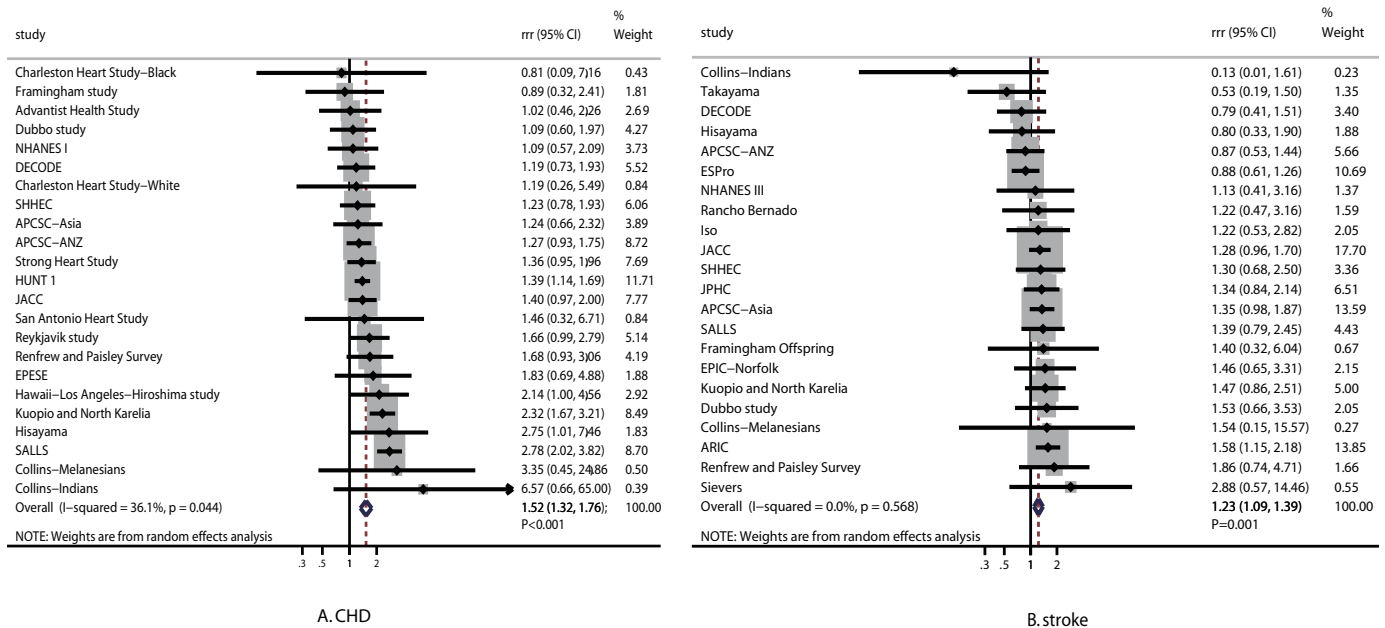
Figure 1 Sex differences in the associations between diabetes mellitus (DM) and the risk for coronary heart disease (CHD) (A) and stroke (B).

in women with DM, which may be due to the fact that women with DM have a greater adverse cardiovascular risk and are less likely to achieve recommended levels compared with men with DM. Cardiac death, as a part of CHD and the sex difference in the relationship between DM and CHD, was addressed in a previous meta-analysis.[13] The death events were mostly caused by CVD in most of the included cohorts and may explain the significant sex differences in the association between DM and

all-cause mortality. Finally, the respective control group in men and women with different cardiovascular risk, which could affect sex differences in the associations between DM and cardiac death and all-cause mortality.

Findings from the subgroup analysis suggested that sex differences in the relationship between DM and major cardiovascular outcomes and all-cause mortality may vary according to predefined factors. First, publication year affected sex differences in the risk for stroke, which may

Table 2 Subgroup analyses for CHD

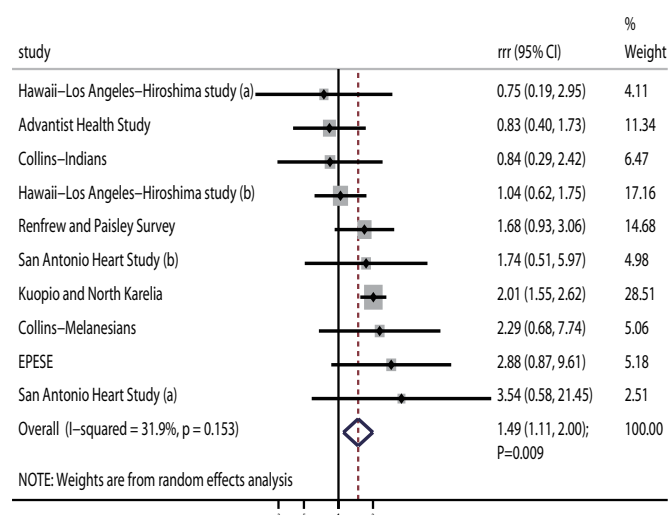| Variable	Group	Number of cohorts	RRR and 95% CI	P value	I^2 (%)	P value for heterogeneity	P value for meta-regression
Publication year	Before 2010	20	1.53 (1.28 to 1.82)	<0.001	39.6	0.036	0.260
	2010 or after	3	1.42 (1.20 to 1.68)	<0.001	0.0	0.421	
Country	Western	18	1.50 (1.27 to 1.77)	<0.001	43.6	0.025	0.934
	Eastern	5	1.58 (1.17 to 2.13)	0.003	6.7	0.368	
Sample size	≥10 000	9	1.62 (1.31 to 2.00)	<0.001	65.4	0.003	0.119
	<10 000	14	1.34 (1.09 to 1.63)	0.004	0.0	0.780	
Assessment of DM	Self-reported	6	1.75 (1.29 to 2.37)	<0.001	74.6	0.001	0.073
	Measured	13	1.32 (1.09 to 1.61)	0.005	0.0	0.764	
	Both	4	1.39 (1.11 to 1.75)	0.005	0.0	0.730	
Follow-up duration (years)	≥10	16	1.69 (1.41 to 2.04)	<0.001	43.1	0.034	0.032
	<10	6	1.22 (0.98 to 1.52)	0.078	0.0	0.948	
Adjusted other CVD risk factors	Yes	19	1.45 (1.29 to 1.62)	<0.001	6.6	0.375	<0.001
	No	4	2.56 (1.89 to 3.46)	<0.001	0.0	0.423	
Study quality	High	13	1.46 (1.29 to 1.66)	<0.001	10.6	0.339	0.052
	Low	10	1.64 (1.14 to 2.36)	0.007	47.8	0.045	

CVD, cardiovascular disease.

Table 3 Subgroup analyses for stroke

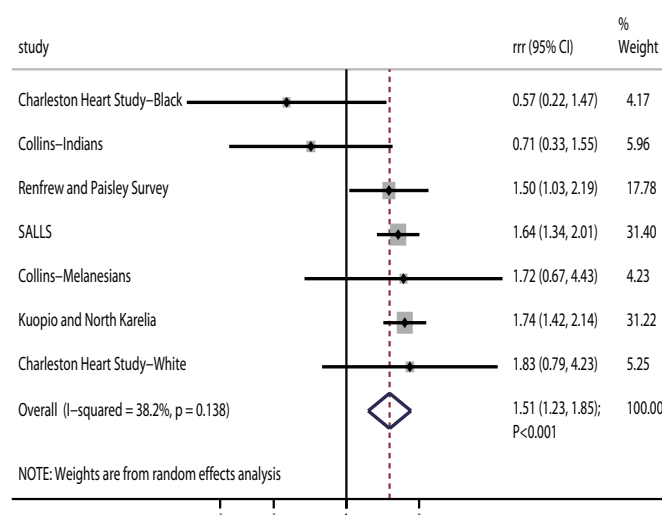| Variable	Group	Number of cohorts	RRR and 95% CI	P value	I^2 (%)	P value for heterogeneity	P value for meta-regression
Publication year	Before 2010	18	1.29 (1.11 to 1.50)	0.001	0.0	0.640	0.269
	2010 or after	4	1.11 (0.89 to 1.40)	0.353	18.1	0.300	
Country	Western	15	1.23 (1.05 to 1.44)	0.011	0.0	0.587	0.998
	Eastern	7	1.20 (0.97 to 1.49)	0.091	14.7	0.318	
Sample size	≥10 000	14	1.25 (1.10 to 1.42)	<0.001	0.0	0.531	0.341
	<10 000	8	1.04 (0.72 to 1.50)	0.840	0.0	0.493	
Assessment of DM	Self-reported	6	1.28 (1.04 to 1.58)	0.022	0.0	0.668	0.423
	Measured	11	1.32 (1.08 to 1.61)	0.008	0.0	0.508	
	Both	5	1.09 (0.85 to 1.41)	0.484	21.3	0.279	
Follow-up duration (years)	≥10	18	1.28 (1.11 to 1.47)	0.001	0.0	0.726	0.313
	<10	4	1.09 (0.76 to 1.57)	0.627	36.0	0.196	
Adjusted other CVD risk factors	Yes	19	1.27 (1.11 to 1.44)	<0.001	0.0	0.695	0.237
	No	3	1.14 (0.71 to 1.83)	0.586	40.4	0.187	
Study quality	High	16	1.24 (1.09 to 1.41)	0.001	0.0	0.533	0.617
	Low	6	1.13 (0.79 to 1.61)	0.498	2.4	0.401	

CVD, cardiovascular disease; RRR, relative risk ratio.

be due to advances in diagnostic approaches. Second, country (ie, hemisphere) could affect sex differences in DM and the risk for cardiac death and all-cause mortality, which could be explained by differences in the prevalence of cardiac death and all-cause mortality Eastern and Western countries. Third, sample size affected sex differences in the risk for stroke, cardiac death and all-cause mortality due to sample sizes being correlated with statistical power, which may have affected the ability to detect

small differences. Fourth, the methods of assessing DM could affect sex differences in stroke, cardiac death and all-cause mortality because they may affect the prevalence of event rates. Fifth, follow-up duration could affect sex differences in the risk for CHD, stroke and cardiac death, because there were studies with longer follow-up and higher proportion of patients with CHD than studies with shorter follow-up, which contributed to the higher weight in pooled results and made it easier to detect small

A. cardiac death

B. all-cause mortality

Figure 2 Sex differences in the associations between diabetes mellitus (DM) and the risk for cardiac death (A) and all-cause mortality (B).

Table 4 Subgroup analyses for cardiac death

Variable	Group	Number of cohorts	RRR and 95% CI	P value	I² (%)	P value for heterogeneity	P value for meta-regression
Publication year	Before 2010	10	1.49 (1.11 to 2.00)	0.009	31.9	0.153	–
	2010 or after	0	–	–	–	–	
Country	Western	7	1.84 (1.45 to 2.32)	<0.001	3.6	0.399	0.010
	Eastern	3	0.97 (0.62 to 1.51)	0.891	0.0	0.870	
Sample size	≥10 000	2	1.96 (1.54 to 2.49)	<0.001	0.0	0.591	0.015
	<10 000	8	1.18 (0.85 to 1.64)	0.322	0.0	0.433	
Assessment of DM	Self-reported	2	2.05 (1.59 to 2.64)	<0.001	0.0	0.568	0.016
	Measured	7	1.10 (0.78 to 1.54)	0.588	0.0	0.586	
	Both	1	1.68 (0.93 to 3.06)	0.087	–	–	
Follow-up duration (years)	≥10	8	1.57 (1.18 to 2.09)	0.002	21.8	0.256	0.257
	<10	2	1.41 (0.42 to 4.68)	0.576	66.5	0.084	
Adjusted other CVD risk factors	Yes	8	1.42 (1.02 to 1.98)	0.040	44.0	0.085	0.575
	No	2	2.18 (0.79 to 6.03)	0.132	0.0	0.524	
Study quality	High	4	1.97 (1.56 to 2.48)	<0.001	0.0	0.864	0.006
	Low	6	1.10 (0.78 to 1.55)	0.593	0.0	0.417	

CVD, cardiovascular disease; DM, diabetes mellitus.

differences. Finally, the other major cardiovascular risk factors, regardless of whether they were adjusted for, and study quality affected sex differences in stroke, cardiac death and all-cause mortality. Pooled studies with high quality or those that adjusted for other cardiovascular risk factors could have obtained more reliable results.

Several strengths of this meta-analysis should be highlighted. First, given the comprehensive inclusion of

Table 5 Subgroup analyses for all-cause mortality

Outcomes	Variable	Group	Number of cohorts	RRR and 95% CI	P value	I² (%)	P value for heterogeneity	P value for meta-regression
All-cause mortality	Publication year	Before 2010	7	1.51 (1.23 to 1.85)	<0.001	38.2	0.138	–
		2010 or after	0	–	–	–	–	
	Country	Western	6	1.63 (1.41 to 1.88)	<0.001	8.2	0.364	0.039
		Eastern	1	0.71 (0.33 to 1.55)	0.394	–	–	
	Sample size	≥10 000	3	1.66 (1.46 to 1.90)	<0.001	0.0	0.772	0.050
		<10 000	4	1.06 (0.59 to 1.90)	0.844	43.7	0.149	
	Assessment of DM	Self-reported	2	1.69 (1.46 to 1.95)	<0.001	0.0	0.669	0.123
		Measured	4	1.06 (0.59 to 1.90)	0.844	43.7	0.149	
		Both	1	1.50 (1.03 to 2.19)	0.035	–	–	
	Follow-up duration (years)	≥10	7	1.51 (1.23 to 1.85)	<0.001	38.2	0.138	–
		<10	0	–	–	–	–	
	Adjusted other CVD risk factors	Yes	4	1.50 (1.12 to 2.01)	0.006	39.4	0.176	0.850
		No	3	1.33 (0.75 to 2.36)	0.321	57.6	0.095	
	Study quality	High	2	1.69 (1.41 to 2.02)	<0.001	0.0	0.490	0.414
		Low	5	1.25 (0.80 to 1.94)	0.329	53.3	0.073	

CVD, cardiovascular disease; DM, diabetes mellitus.

published studies with large sample sizes, the findings of the present study were more robust than any of those individual studies. Second, all studies included were prospectively designed and population based, which could mitigate—if not eliminate—uncontrolled biases. Third, large-scale studies including patients with a broad range of characteristics support the generalisability of the results given the global distribution of the included populations. Fourth, stratified results of sex differences in DM and major cardiovascular outcomes based on study or patient characteristics were calculated. Finally, heterogeneity among the included studies was resolved using multiple methods, and no publication bias was found, which supports the robustness of the pooled results.

However, several limitations of this meta-analysis should also be acknowledged. First, various adjustments for cardiovascular risk factors across the included studies may have affected the development of major cardiovascular outcomes, as would various DM types, DM assessment methods and the duration of DM. Publication bias is inevitable when searching databases given the variation in publication languages, and the number of published studies with negative results. Finally, data regarding background drug use were available in few studies, which may have affected the absolute risk for major cardiovascular outcomes.

In conclusion, the results of this study indicated that women with DM exhibited a greater risk for CHD, stroke, cardiac death and all-cause mortality compared with men with DM. Furthermore, the true sex differences for the association between DM and major cardiovascular outcomes was variable and based on several characteristics of the study or the patients involved. Sex differences in specific patient characteristics should be verified and clarified, along with other biological, behavioural or social factors in future larger-scale prospective studies.

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