BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024935
Article Type:	Research
Date Submitted by the Author:	21-Jun-2018
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Keywords:	Sex difference, diabetes mellitus, major cardiovascular outcomes, all-cause mortality, meta-analysis

Associations of diabetes mellitus with the risk of major cardiovascular outcomes and all-cause mortality in women compared with men: A meta-analysis of data from 1,149,809 individuals in 31 prospective cohort studies

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Running title: Sex difference of DM and major cardiovascular outcomes

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Keywords: sex difference; diabetes mellitus; major cardiovascular outcomes; all-cause mortality; meta-analysis

Abstract

Objective

Previous studies have already demonstrated sex differences of relation between diabetes mellitus (DM) and coronary heart disease (CHD) and stroke, while the sex difference on other major cardiovascular outcomes including cardiac death and all-cause mortality in women compared with men were not illustrated. We conducted this quantitative meta-analysis to provide reliable estimates of sex differences in the effect of DM on major cardiovascular outcomes.

Methods

We systematically searched prospective cohort studies from PubMed, Embase, and the Cochrane Library throughout April 2018. All of included studies reported the relation between DM and major cardiovascular outcomes stratified by sex. The ratio of relative risk (RRR) using random-effects model were employed to calculate the sex differences in the relation between DM and major cardiovascular outcomes.

Results

We included 31 prospective cohort studies reporting data on 1,149,809 individuals. The pooled women-to men RRR suggested DM women were associated with increased risk of CHD (RRR: 1.52; 95% confidence interval [CI]: 1.32-1.76; P<0.001), stroke (RRR: 1.22; 95%CI: 1.09-1.37; P=0.001), cardiac death (RRR: 1.49; 95%CI: 1.11-2.00; P=0.009), and all-cause mortality (RRR: 1.51; 95%CI:

1.23-1.85; P<0.001). In addition, the sex difference of the comparison between DM and non-DM for investigated outcomes were variable after stratified by publication year, country, sample size, assessment of DM, follow-up duration, adjusted important cardiovascular risk factors, and study quality.

Conclusions

The findings of this study suggested DM women with excess risk of CHD, stroke, cardiac death, and all-cause mortality as compared with DM men.

Article Summary:

Strengths and limitations of this study:

(1) the comprehensive inclusion of published studies with large sample size, and the findings of this study was more robust than are those of any individual study.

(2) all of studies included were prospectively designed and population based, which could eliminate uncontrolled biases.

(3) large included studies with broad characteristics of patients could ensure the applicability of the summary results because of worldwide distributed populations were included.

(4) stratified results of the sex difference between DM and major cardiovascular outcomes based on study or patients characteristics were calculated.

(5) the heterogeneity among included studies was resolved in multiple methods and no publication bias was found, which could support the robustness of the pooled results.

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, which accounted for 10.3% of the global burden of disease, and approximately 30% of patients

dying of first CVD events [1,2]. Numerous studies have already illustrated the risk of CVD and its risk factors in various populations [3-7]. It is well established the morbidity and mortality of CVD risk were significantly increased in patients with diabetes mellitus (DM) [8-11]. Further, DM is an independently risk factor for CVD, all-cause mortality, blindness, kidney failure, amputations, fractures, frailty, depression, and cognitive decline [12]. Therefore, emphasizing the need for monitor high CVD risk in DM patients.

Sex differences in the effect of DM on the excess risk of CHD and stroke have been illustrated, while these sex difference varies by several risk factors [13,14]. These two-large-scale quantitative meta-analyses suggested DM women have 44% and 27% greater risk of coronary heart disease (CHD) and stroke, respectively. Although the mechanism of action is unclear, the exposure effects might be affected by non-DM women with persistently healthy lifestyle, and well control other important cardiovascular risk factors [15]. However, the data from included studies were not fully analysis to evaluate these sex differences on CHD and stroke in various populations. Further, other important outcomes included cardiac death, and all-cause mortality were not illustrated in previous studies.

Although previous meta-analyses have illustrated the sex differences of DM and CHD and stroke risk, the current study is the first meta-analysis to quantify any potential sex differences for cardiac death and all-cause mortality. Clarifying the sex difference of DM and major cardiovascular outcomes is particularly important to identify high-risk population for the development of major cardiovascular outcomes, as it has not been definitively determined. We therefore conducted a large-scale examination of the available prospective cohort studies that reported sex-specific effects of DM on subsequent risk of CHD, stroke, cardiac death, and all-cause mortality to determine the sex differences between DM and major cardiovascular outcomes.

Material and methods

Data sources, search strategy, and selection criteria

This study was conducted and reported according to the meta-analysis of observational studies in

epidemiology protocol [16]. Studies with prospective cohort design and studied the associations of DM with CHD, stroke, cardiac death, and all-cause mortality risk published in English language were potential eligible for inclusion in this meta-analysis, and these studies without restricted in publication status. Three electronic databases (PubMed, EmBase, and Cochrane Library) were searched for studies published from the inception to April 2018 and used ("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” as the search terms. The detail of searching strategy in PubMed have presented in Supplemental 1. Additional eligible studies were identified by manual searches of reference lists in relevant original and review articles. The study title, design, exposure, control, and outcome variables effect in men and women separately of these studies were employed to select the relevant studies.

The literature search and study selection were performed by independently two reviewers, and any disagreement between these reviewers were resolved by the corresponding author until a consensus was reached. The inclusion criteria are listed as follows: (1) Design: prospective cohort design; (2) Exposure and control: DM and non-DM; (3) Outcomes: CHD, stroke, cardiac death, and all-cause mortality; and (4) Effect estimate: the relation between DM and CHD, stroke, cardiac death, and all-cause mortality in men and women should be reported separately. The exclusion criteria included study reported single sex populations, studies with retrospective observational design, and study reported standard incidence/mortality ratio.

Data collection and quality assessment

Two independently reviewers performed data collection and quality assessment, and any inconsistencies was adjudicated by referring to the original studies. The collected data items included the first author or study group’s name, publication year, country, sample size, age range, percentage of women, number of DM, assessment of DM, follow-up duration, adjusted factors, and investigated outcomes. We selected the effect estimate with maximally adjusted for confounders if the study reported several multivariable adjusted effect estimates. The study quality assessment was conducted using the Newcastle-Ottawa Scale (NOS), which based on selection (4 items),

comparability (1 item), and outcome (3 items) [17]. A "star system" (range, 0-9) was used to evaluate the study quality.

Statistical analysis

The sex differences of the relation between DM and CHD, stroke, cardiac death, or all-cause mortality risk were based on the sex-specific effect estimate and corresponding 95% confidence interval (CI) in each individual study. Given the low prevalence of CHD, stroke, cardiac death, or all-cause mortality, odds ratio could be assumed to be accurate estimates of RR. Further, hazard ratio was regarded to equivalent to RR in study with cohort design. The summary RRs and 95% for DM versus non-DM and the risk of CHD, stroke, cardiac death, and all-cause mortality in men and women were calculated separately by using random-effects model [18,19]. After this, the female-to-male ratio of RRs (RRR) and 95%CIs in each study for CHD, stroke, cardiac death, or all-cause mortality were calculated based on sex-specific RRs and 95%CIs [20]. Finally, the summary RRR and 95%CIs for the sex differences of DM versus non-DM and CHD, stroke, cardiac death, or all-cause mortality risk were calculated using random-effects model.

I-square and Q statistic were employed to evaluate the heterogeneity among included studies, and if P values less than 0.10 were regarded as significant heterogeneity [21,22]. Then a sensitivity analysis was conducted to evaluate the impact of individual study on the overall estimates by excluding one by one sequentially [23]. After this, subgroup analyses for the sex differences of DM on CHD, stroke, cardiac death, or all-cause mortality risk were calculated based on publication year (2010 or after, before 2010), country (Eastern, Western), sample size (≥10000, <10000), assessment of DM (self-reported, measured, both), follow-up duration (≥10, <10), adjusted other cardiovascular risk factors (yes, no), and study quality (high, low). Finally, publication biases for investigated outcomes were assessed using funnel plots, Egger, and Begg tests [24,25]. P values were two sided with a significant level of 0.05 for pooled analyses. Statistical analyses were performed using STATA software (version 10.0; Stata Corporation, College Station, TX, USA).

Results

Literature search

The study selection process was shown in Supplemental 2. Thirteen thousand four hundred and seventy-one records were identified from the initial electronic search, of which 12,745 articles were excluded due to duplicates and irrelevant topics. Abstracts assessment for 726 articles, and 633 studies were excluded due to the study with other design and reported cardiovascular risk factors as outcomes. Full test were retrieved for the remaining 93 studies to identify potential included studies, and 31 prospective cohort studies satisfied the inclusion criteria, which ultimately were included in the meta-analysis [26-56]. There was no additional eligible studies after manual search of the reference lists within these studies.

Study characteristics

Of the 31 studies involving a total of 1,149,809 individuals and 52845 DM patients were included. Table 1 summarized the baseline characteristics of the included studies. The follow-up period for participants was 5.0–32.0 years, while 787–436,832 individuals were included in each study. Twenty-six cohorts were from the Western countries, and the remaining 8 cohorts from Eastern countries. Further, the percentage of women ranged from 33.0 to 63.0%. Nine studies used self-reported methods to assess of DM, 17 studies used medical measured to assess of DM, and the remaining 5 studies used both self-reported and medical measured to assess of DM. Overall, 9 studies had a score of 8, 12 studies had a score of 7, and the remaining 10 had a score of 6.

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

Study	Publication year	Country	Sample size	Age range	Percentage of women (%)	Number of DM	Assessment of DM	Follow-up duration (years)	Adjusted factors	Study quality
EPESE [26]	1993	US	2812	>65	58.0	386	Self-reported	6.0	Age, AHT use, smoking, BMI, diabetes, angina, chest pain on exertion	6
Hisayama [27]	2010	Japan	2421	40-79	57.0	291	Measured	14.0	Age, SBP, smoking, BMI, TC, HDL, alcohol intake, PA,ECG abnormalities	7
Hisayama [28]	2000	Japan	1621	>40	56.0	130	Measured	32.0	Age	6
APCSC-Asia [29]	2003	27 cohorts in Asia	436832	>20	33.0	17763	Self-reported or measured	7.0	Age, SBP, smoking, BMI, TC	7
APCSC-Australia and New Zealand [29]	2003	9 cohorts in Australia and New Zealand	99624	>20	45.0	4784	Self-reported or measured	7.0	Age, SBP, smoking, BMI, TC	7
Advantist Health Study [30]	1992	US	27658	>25	63.0	656	Measured	6.0	Age, hypertension, smoking, BMI, PA	6
DECODE [31]	2009	7 cohorts in Finland and Sweden	9278	40-69	55.0	826	Measured	5-21	Age, hypertension, smoking, BMI, TC, HDL	6

Renfrew and Paisley Survey [32]	2005	Scotland	15426	45-64	54.0	228	Self-reported or measured	25.0	Age, SBP, smoking, BMI, TC, SES	8
Collins-Indians [33]	1996	Fiji	1220	>20.0	55.0	166	Measured	11.0	Age, SBP, smoking, BMI, TC, survey area	6
Collins-Melanesians [33]	1996	Fiji	1324	>20.0	53.0	65	Measured	11.0	Age, SBP, smoking, BMI, TC, survey area	6
Kuopio and North Karelia [34]	2005	Finland	51735	25-74	51.0	1108	Self-reported	17.0	Age, SBP, smoking, BMI, TC, study year	8
San Antonio Heart Study [35]	2007	US	4996	25-64	57.0	524	Measured	16.0	Age, ethnicity	7
Hawaii-Los Angeles-Hiroshima study [36]	2002	Japan	927	40-79	56.0	169	Measured	10-18	Age, hypertension, smoking, BMI, TC, triacylglycerols, uric acid, ECG abnormalities	6
Reykjavik study [37]	2002	Iceland	18519	32-60	52.0	295	Self-reported or measured	17.0	Age, hypertension, smoking, BMI, TC, triacylglycerols, diabetes, glucose, prior CHD, LVH	8

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Charleston Heart Study-White [38]	1993	US	1394	>35	53.0	38	Measured	30.0	Age	6
Charleston Heart Study-Black [38]	1993	US	787	>35	58.0	37	Measured	30.0	Age	6
Strong Heart Study [39]	2006	US	4372	45-74	61.0	724	Measured	12.0	Age, SBP, DBP, smoking, HDL, LDL, albuminuria	7
HUNT 1 [40]	2012	Norway	47951	>20	52.0	1992	Self-reported	17.0	Age, hypertension, smoking, BMI, CVD, PA	8
Framingham study [41]	2003	2 cohorts in US	5243	35-75	52.0	229	Measured	20.0	Age, hypertension, smoking, BMI, TC	7
SALLS [42]	1998	Sweden	39055	25-74	51.0	174	Self-reported	16.0	Age	6
Dubbo study [43]	1995	Australia	2805	>60	56.0	206	Measured	5.0	Age, AHT use, BMI, TC, HDL, triacylglycerols, ApoB, LPa, diabetes, self-rated health, prior CH	6
SHHEC [44]	2007	Scotland	13343	30-74	51.0	184	Measured	16.0	Age, SBP, smoking, BMI, TC	7
NHANES I [45]	1988	US	7381	40-77	55.0	407	Self-reported	9.0	Age, SBP, smoking, BMI, TC	7

Iso [46]	2004	Japan	10582	40-69	60.0	267	Measured	17.0	Age, hypertension, smoking, BMI, TC, HDL, skinfold, alcohol, community, menopause	8
Framingham Offspring [47]	2006	US	2097	50-81	50.0	99	Measured	14.0	Age, SBP, AHT, CVD, atrial fibrillation, LVH, smoking	7
JPHC [48]	2011	2 cohorts in Japan	35657	40-69	63.0	2034	Measured	12.0	Age, SBP, AHT, smoking, BMI, TC, HDL, triglycerides, alcohol, fasting status, residential areas	8
NHANES III [49]	1994	US	18603	18-90	46.0	1290	Self-reported or measured	13.0	Age, SBP, smoking, BMI, TC	7
ARIC [50]	1989	US	15732	45-64	55.0	1610	Measured	18.0	Age, SBP, smoking, BMI, TC	7
EPIC-Norfolk [51]	2008	UK	22516	40-79	55.0	441	Self-reported	10.0	Age, SBP, smoking, BMI, TC, triglycerides	8
Sievers [52]	1992	US	5131	15-84	52.0	1266	Measured	10.0	Age	7
Rancho Bernado [53]	1988	US	3778	50-79	54.0	320	Self-reported	12.0	Age, SBP, TC, smoking, obesity, family history, oestrogen use	6
Takayama [54]	2008	Japan	29079	>35	54.0	1217	Self-reported	7.0	Age, hypertension, smoking, BMI, PA, education, energy, vegetables, fat, alcohol	8

ESPro [55]	2017	Germany	105000	>18	51.0	7190	Self-reported or measured	14.0	Calendar year, age	7
JACC [56]	2017	Japan	104910	40-79	58.0	5729	Self-reported	19.0	Age, education, smoking, alcohol, PA, BMI, history of hypertension, or history of DM	8

*AHT, anti-hypertensive; ApoB, apolipoprotein B; CVD, cardiovascular disease; DBP, diastolic BP; LPa, lipoprotein a; LVH, left ventricle hypertrophy; NA, notavailable; PA, physical activity; SALLS, Swedish Annual Level-of-Living Survey; SBP, systolic BP; SES, socioeconomic status

Coronary heart disease

Data for the study reported sex difference of an association between DM and subsequent CHD risk were available from 23 cohorts. The summary results in men and women separately are shown in Supplemental 3, and the results indicated DM were associated with increased risk of CHD risk in men and women. Further, The pooled RRR (female to male) of DM versus non-DM and the risk of CHD was 1.52 (95%CI: 1.32-1.76; P<0.001; Figure 1A); this was associated with statistically significant and there was significant heterogeneity among study (I^2=36.1%; P=0.044). The results of sensitivity analysis was not altered after the sequential exclusion of each study from all the pooled analyses (Supplemental 4). The results of subgroup analyses were consistent with overall analysis in mostly subsets except for the duration of follow-up less than 10.0 years (Table 2).

Table 2. Subgroup analyses for investigated outcomes

Outcomes	Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square	P value for heterogeneity
CHD	Publication year	Before 2010	20	1.53 (1.28-1.82)	<0.001	39.6	0.036
		2010 or after	3	1.42 (1.20-1.68)	<0.001	0.0	0.421
	Country	Western	18	1.50 (1.27-1.77)	<0.001	43.6	0.025
		Eastern	5	1.58 (1.17-2.13)	0.003	6.7	0.368
	Sample size	≥10000	9	1.62 (1.31-2.00)	<0.001	65.4	0.003
		<10000	14	1.34 (1.09-1.63)	0.004	0.0	0.780
	Assessment of DM	Self-reported	6	1.75 (1.29-2.37)	<0.001	74.6	0.001

		Measured	13	1.32 (1.09-1.61)	0.005	0.0	0.764
		Both	4	1.39 (1.11-1.75)	0.005	0.0	0.730
	Follow-up duration (years)	≥10	16	1.69 (1.41-2.04)	<0.001	43.1	0.034
		<10	6	1.22 (0.98-1.52)	0.078	0.0	0.948
	Adjusted other CVD risk factors	Yes	19	1.45 (1.29-1.62)	<0.001	6.6	0.375
		No	4	2.56 (1.89-3.46)	<0.001	0.0	0.423
	Study quality	High	13	1.46 (1.29-1.66)	<0.001	10.6	0.339
		Low	10	1.64 (1.14-2.36)	0.007	47.8	0.045
Stroke	Publication year	Before 2010	19	1.28 (1.10-1.48)	0.001	0.0	0.676
		2010 or after	4	1.11 (0.89-1.40)	0.353	18.1	0.300
	Country	Western	15	1.23 (1.05-1.44)	0.011	0.0	0.587
		Eastern	8	1.21 (1.01-1.45)	0.042	3.6	0.402
	Sample size	≥10000	14	1.25 (1.10-1.42)	<0.001	0.0	0.531
		<10000	9	1.04 (0.76-1.43)	0.792	0.0	0.602
	Assessment of DM	Self-reported	6	1.28 (1.04-1.58)	0.022	0.0	0.668
		Measured	12	1.29 (1.06-1.56)	0.010	0.0	0.555
		Both	5	1.09 (0.85-1.41)	0.484	21.3	0.279
	Follow-up duration (years)	≥10	19	1.27 (1.10-1.45)	0.001	0.0	0.760
		<10	4	1.09 (0.76-1.57)	0.627	36.0	0.196
	Adjusted other CVD risk factors	Yes	19	1.27 (1.11-1.44)	<0.001	0.0	0.695
		No	4	1.06 (0.79-1.43)	0.694	10.6	0.340
	Study quality	High	16	1.24 (1.09-1.41)	0.001	0.0	0.533
		Low	7	1.11 (0.82-1.50)	0.488	0.0	0.524
Cardiac	Publication year	Before 2010	10	1.49 (1.11-2.00)	0.009	31.9	0.153

death		2010 or after	0	-	-	-	-
	Country	Western	7	1.84 (1.45-2.32)	<0.001	3.6	0.399
		Eastern	3	0.97 (0.62-1.51)	0.891	0.0	0.870
	Sample size	≥10000	2	1.96 (1.54-2.49)	<0.001	0.0	0.591
		<10000	8	1.18 (0.85-1.64)	0.322	0.0	0.433
	Assessment of DM	Self-reported	2	2.05 (1.59-2.64)	<0.001	0.0	0.568
		Measured	7	1.10 (0.78-1.54)	0.588	0.0	0.586
		Both	1	1.68 (0.93-3.06)	0.087	-	-
	Follow-up duration (years)	≥10	8	1.57 (1.18-2.09)	0.002	21.8	0.256
		<10	2	1.41 (0.42-4.68)	0.576	66.5	0.084
	Adjusted other CVD risk factors	Yes	8	1.42 (1.02-1.98)	0.040	44.0	0.085
		No	2	2.18 (0.79-6.03)	0.132	0.0	0.524
	Study quality	High	4	1.97 (1.56-2.48)	<0.001	0.0	0.864
		Low	6	1.10 (0.78-1.55)	0.593	0.0	0.417
All-cause mortality	Publication year	Before 2010	7	1.51 (1.23-1.85)	<0.001	38.2	0.138
		2010 or after	0	-	-	-	-
	Country	Western	6	1.63 (1.41-1.88)	<0.001	8.2	0.364
		Eastern	1	0.71 (0.33-1.55)	0.394	-	-
	Sample size	≥10000	3	1.66 (1.46-1.90)	<0.001	0.0	0.772
		<10000	4	1.06 (0.59-1.90)	0.844	43.7	0.149
	Assessment of DM	Self-reported	2	1.69 (1.46-1.95)	<0.001	0.0	0.669
		Measured	4	1.06 (0.59-1.90)	0.844	43.7	0.149
		Both	1	1.50 (1.03-2.19)	0.035	-	-
	Follow-up duration	≥10	7	1.51 (1.23-1.85)	<0.001	38.2	0.138

(years)	<10	0	-	-	-	-
Adjusted other CVD risk factors	Yes	4	1.50 (1.12-2.01)	0.006	39.4	0.176
	No	3	1.33 (0.75-2.36)	0.321	57.6	0.095
Study quality	High	2	1.69 (1.41-2.02)	<0.001	0.0	0.490
	Low	5	1.25 (0.80-1.94)	0.329	53.3	0.073

Stroke

Data for the study reported sex difference of an association between DM and subsequent stroke risk were available from 23 cohorts. The pooled results in DM men and women were associated with statistically significant increased (Supplemental 3). The pooled RRR (female to male) suggested that DM women was associated with an increased risk of stroke as compared with DM men (RRR: 1.22; 95%CI: 1.09-1.37; P=0.001; Figure 1B), and no evidence of heterogeneity was observed (I^2=0.0%; P=0.614). Sensitivity analysis indicated the conclusion was not affected after sequential exclusion of each study from the pooled analyses (Supplemental 4). Subgroup analysis indicated no sex difference for the relation of DM with stroke risk if pooled studies published in 2010 or after, sample size<10000, study use both self-reported and measured, duration of follow-up less than 10.0 years, the study not adjusted other cardiovascular risk factors, and the study with low quality (Table 2).

Cardiac death

Data for the study reported sex difference of an association between DM and subsequent cardiac death risk were available from 10 cohorts. We noted DM were associated with greater risk of cardiac death in men and women separately (Supplemental 3). The pooled RRR (female to male) of DM versus non-DM on cardiac death risk was 1.49 (95%CI: 1.11-2.00; P=0.009; Figure 2A), which associated with statistically significant. Further unimportant heterogeneity was detected (I^2=31.9%; P=0.153). The result of sensitivity analysis was changed after excluding the Kuopio and North Karelia study (Supplemental 4). Subgroup analysis indicated significant sex difference of DM on cardiac death if the study published before 2010, the study conducted in Western countries, sample

size ≥ 10000, the study used medical measure assess DM, follow-up duration ≥ 10.0 years, the study adjusted other cardiovascular risk factors, and the study with high quality (Table 2).

All-cause mortality

Data for the study reported sex difference of an association between DM and subsequent all-cause mortality risk were available from 7 cohorts. The summary results indicated DM were correlated with higher risk of all-caused mortality in men and women separately (Supplemental 3). The pooled female-to-male RRR indicated significant sex difference for all-cause mortality risk between participants with DM and those without DM (RRR: 1.51; 95%CI: 1.23-1.85; P<0.001; Figure 2B), and with moderate heterogeneity among included studies (I^2=38.2%; P=0.138). A sensitivity analysis indicated was conducted and the conclusion was not affected by the exclusion of any specific study (Supplemental 4). Subgroup analyses indicated no sex difference if the study conducted in Eastern countries, sample size<10000, the study used medical measure assess DM, the study not adjusted other cardiovascular risk factors, and the study with low quality (Table 2).

Publication bias

Review of the funnel plots could not rule out the potential for publication bias for CHD, stroke, cardiac death, and all-cause mortality (Supplemental 5). The Egger and Begg test results showed no evidence of publication bias for CHD (P value for Egger: 0.959; P value for Begg: 0.245), stroke (P value for Egger: 0.378; P value for Begg: 0.398), cardiac death (P value for Egger: 0.418; P value for Begg: 0.721), and all-cause mortality (P value for Egger: 0.118; P value for Begg: 0.230).

Discussion

Our current study was based on prospective cohort studies and explored all possible sex differences between DM and the outcomes of CHD, stroke, cardiac death, all-cause mortality. This large quantitative study included 1,149,809 individuals and 52845 DM patients from 31 prospective cohort studies with a broad range of populations. The findings from our current meta-analysis suggest that significant sex differences for DM versus non-DM on the incidence of CHD, stroke, cardiac death, all-cause mortality, and women with excess risk than those in men. Furthermore, the

findings of subgroup analyses could be biases by publication year, country, sample size, assessment of DM, follow-up duration, adjusted important cardiovascular risk factors, and study quality.

A previous study suggested that DM women is associated with increased risk of CHD or stroke than in DM men [13,14]. However, the sex differences on other important outcomes (cardiac death, all-cause mortality) was not illustrated. Further, the sex differences of relation of DM with CHD and stroke risk in study or participant with specific characteristics were not illustrated. Finally, several data from included studies were not containing to pool this sex difference. We therefore conducted this comprehensive quantitative meta-analysis of available prospective cohort studies to evaluate the sex differences of DM and the risk of major cardiovascular outcomes.

There was significant sex differences between DM and the risk of major cardiovascular outcomes. Although numerous included inconsistent results, while several studies included in our study reported consistent results. The results from the Hawaii-Los Angeles-Hiroshima study found the risk of CHD was increased by 229% in DM women, while this risk in DM men was increased by 54%. However, they point no significant sex difference for the risk of cardiac death [36]. Further, the study conducted by Kuopio and North Karelia indicated significant sex differences for the outcomes of CHD, cardiac death, and mortality, while this difference was not observed for stroke risk [34]. The Hisayama study indicated sex difference on CHD was observed, while this difference was not detected for stroke [27]. Nilsson et al indicated the risk of CHD (703% versus 189%) and all-cause mortality (267% versus 124%) was significantly higher in DM women as compared with DM men [42]. The ARIC study found the risk of stroke in DM women was increased by 216%, while this increased in DM men was 100% [50]. The results of Renfrew and Paisley Survey did not observed sex differences for CHD, stroke, and cardiac death, while the risk on all-cause mortality was associated with statistically significant [32]. The possible reasons for these sex differences could be as follows: (1) High absolute cardiovascular risk in men than in women, then the relative effect of DM was more extreme in women than in men, which could overestimate the sex differences of cardiovascular risk. (2) High cardiovascular event rates and numerous cohorts were included, and power was stronger to detect little sex difference of DM and major cardiovascular outcomes. (3) Corresponding control group in women without DM was associated with persistently more favorable survival rate, which could favorable lipoprotein levels [15].

The findings of subgroups suggested the sex differences of the relation between DM and major cardiovascular outcomes might be variable according to pre-defined factors. First, publication years affected the sex difference on the risk of stroke might due to more advanced diagnosis approach. Second, country could affect the sex differences of the DM and the risk of cardiac death and all-cause mortality, and the reason for this could be that the prevalence of cardiac death and all-caused mortality was differ in Eastern countries and Western countries. Third, sample size affected the sex differences on the risk of stroke, cardiac death and all-cause mortality due to sample size was correlated with statistical power and affected the ability to detect small differences. Fourth, the methods of assessment of DM could affect the sex differences on stroke, cardiac death and all-cause mortality, and the reason for this could be the methods of assessment of DM could affect the prevalence of event rates. Sixth, the follow-up duration could affect the sex difference on the risk of CHD, stroke, and cardiac death. The reason for this could be studies with longer follow-up and higher proportion of CHD than studies with shorter follow-up contributed higher weight to pooled results and more easily detected small sex differences. Finally, the other major cardiovascular risk factors, whether adjusted or not, and study quality were affected the sex difference on stroke, cardiac death and all-cause mortality, and pooled the study with high quality or adjusted other cardiovascular risk factors could acquire more reliable results.

Several strengths should be highlighted in this meta-analysis. First, the comprehensive inclusion of published studies with large sample size, and the findings of this study was more robust than are those of any individual study. Second, all of studies included were prospectively designed and population based, which could eliminate uncontrolled biases. Third, large included studies with broad characteristics of patients could ensure the applicability of the summary results because of worldwide distributed populations were included. Fourth, stratified results of the sex difference between DM and major cardiovascular outcomes based on study or patients characteristics were calculated. Finally, the heterogeneity among included studies was resolved in multiple methods and no publication bias was found, which could support the robustness of the pooled results.

Several limitations regarding this meta-analysis should be acknowledged: (1) various adjusted factors across included studies could affect the development of major cardiovascular outcomes; (2) various DM types, DM assessment method, and the duration of DM among included studies; (3)

publication bias is inevitable due to searching databases, publication language, and unpublished studies with negative results; and (4) data on background drug uses were available in few studies, which could affect the absolute risk of major cardiovascular outcomes.

In conclusion, the summary results of this study indicated DM women were associated with greater risk of CHD, stroke, cardiac death, and all-cause mortality when compared with DM men. Further, the true sex differences for the relation between DM and major cardiovascular outcomes was variable based on several characteristics of study or patients. The sex differences in specific characteristics of patients should be verify and clarify other biological, behavioural, or social factors in future large-scale prospective studies.

Author Contributions

Hao Wang contributed to conception and design; Hao Wang, Ying Ba, Run-Ce Cai, and Qian Xing contributed to acquisition, analysis and interpretation of data; Hao Wang and Qian Xing were involved in drafting or critical revision of the manuscript. All the authors approved the final version.

Conflict of interests: All authors declare no conflict of interest.

Funding statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing statement: No additional data available.

Reference

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Figure legends:

Figure 1. The sex differences of the associations of DM with CHD (A) and stroke (B) risk.

Figure 2. The sex differences of the associations of DM with cardiac death (A) and all-cause mortality (B) risk

Supporting Information Legends:

Supplemental 1: Searching strategy in PubMed

Supplemental 2: Flowchart of the study selection process

Supplemental 3: The summary results of DM and CHD, stroke, cardiac death, and all-cause mortality in men and women separately.

Supplemental 4: Sensitivity analyses for CHD, stroke, cardiac death, and all-cause mortality

Supplemental 5: Funnel plots for CHD, stroke, cardiac death, and all-cause mortality.

Checklist S1: MOOSE Checklist

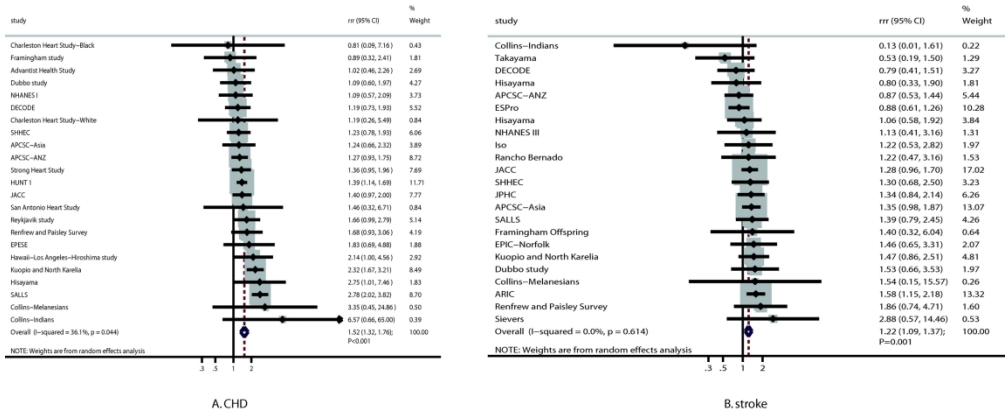

Figure 1. The sex differences of the associations of DM with CHD (A) and stroke (B) risk.

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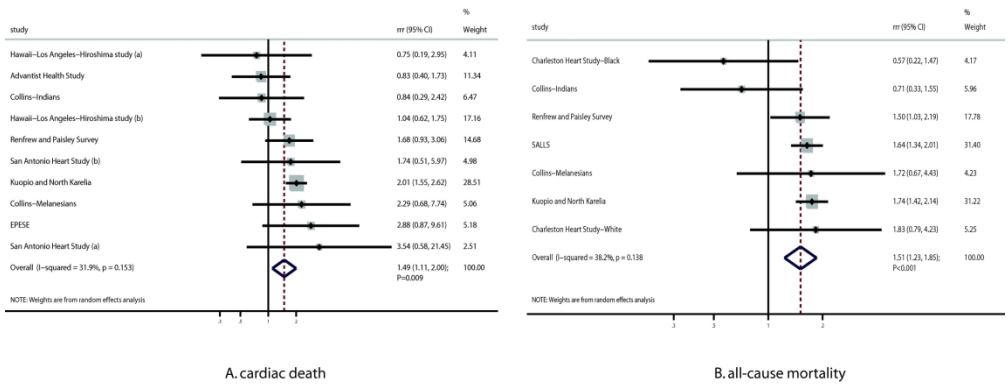


A. cardiac death

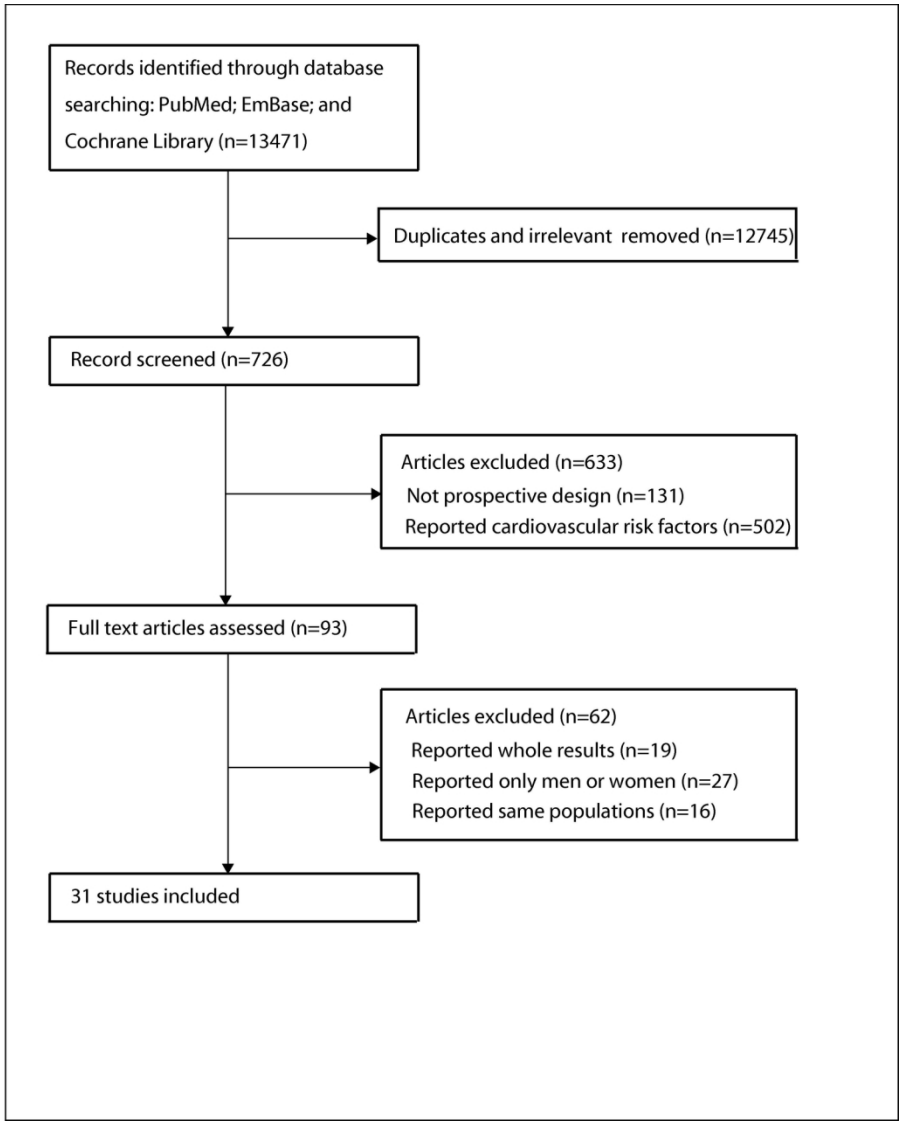
B. all-cause mortality

Figure 2. The sex differences of the associations of DM with cardiac death (A) and all-cause mortality (B) risk

229x92mm (300 x 300 DPI)

Searching strategy in PubMed:

("Coronary Disease"[Mesh] OR "Coronary Disease"[All Fields] OR "Coronary Artery Disease"[Mesh] OR "Coronary Artery Disease"[All Fields] OR "Myocardial Ischemia"[Mesh] OR "Myocardial Ischemia"[All Fields] OR "stroke"[Mesh] OR "stroke"[All Fields] OR "death" [Mesh] OR "death"[All Fields] OR "mortality"[Mesh] OR "mortality"[All Fields]) AND ("Diabetes mellitus"[Mesh] OR "Diabetes"[All Fields]) AND ("men"[Mesh] OR "male"[Mesh]) AND ("women"[Mesh] OR "female"[Mesh]) AND ("Cohort Studies"[Mesh] OR "Prospective Studies"[Mesh])



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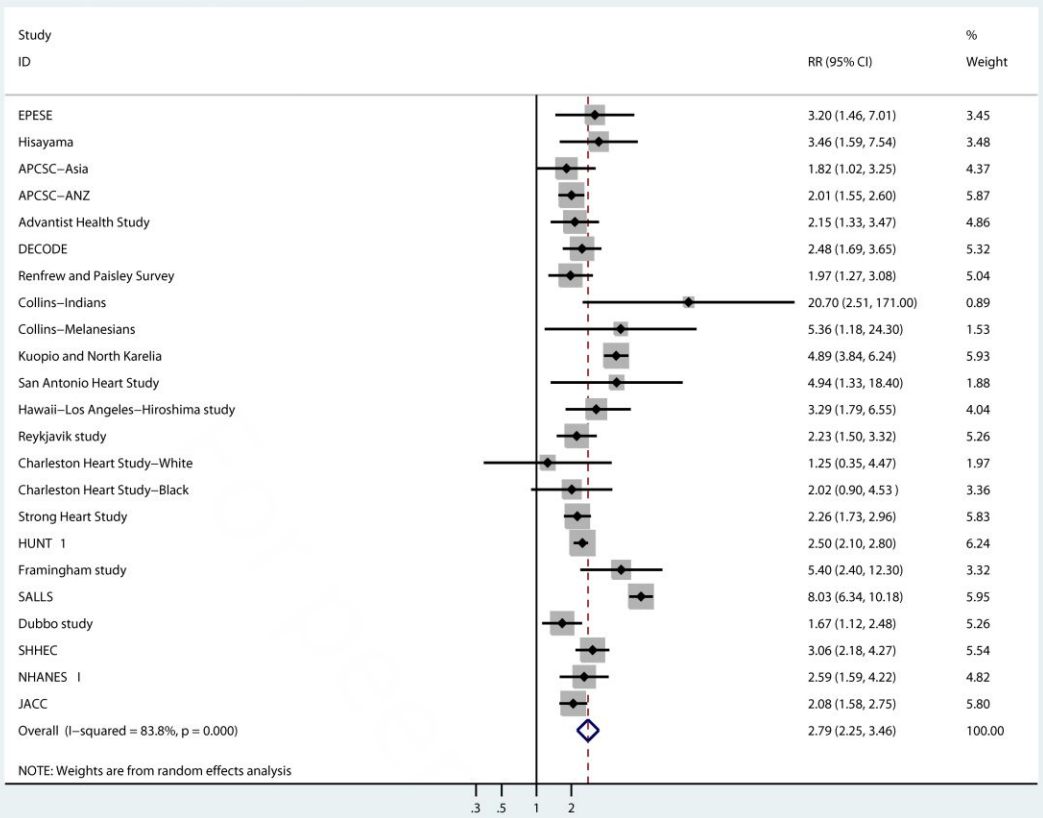


Figure S1. The summary results for DM and the risk of CHD in women

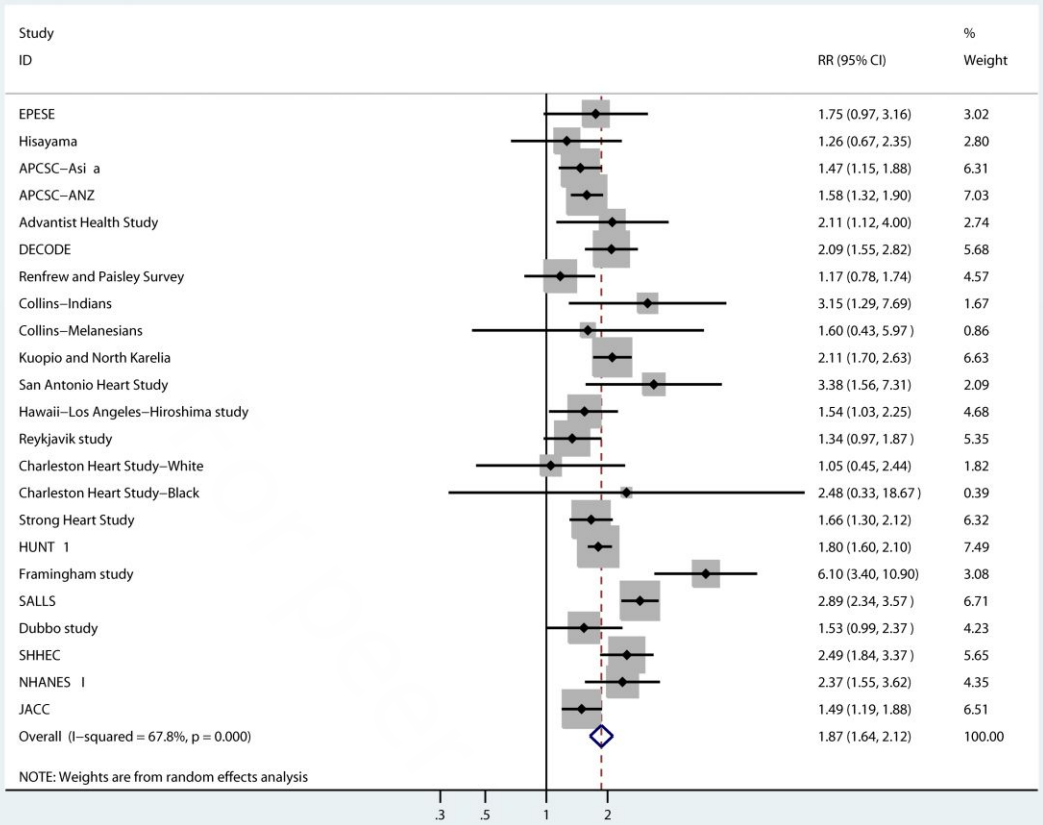


Figure S2. The summary results for DM and the risk of CHD in men

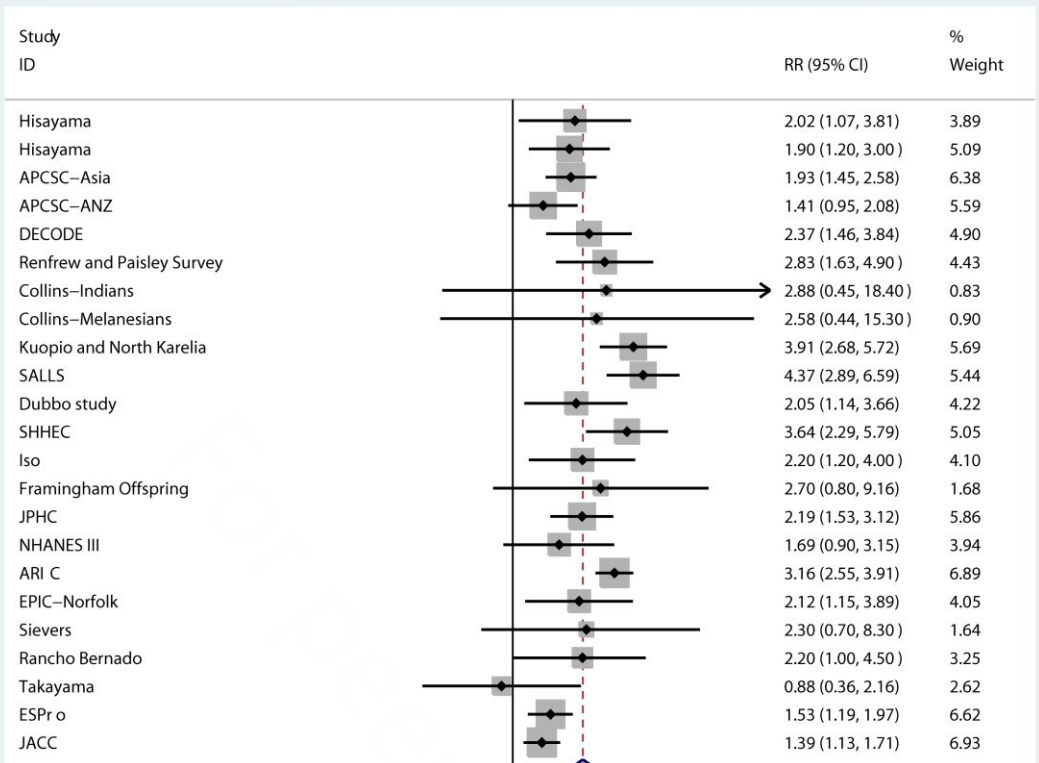


Figure S3. The summary results for DM and the risk of stroke in women

Figure S4. The summary results for DM and the risk of stroke in men

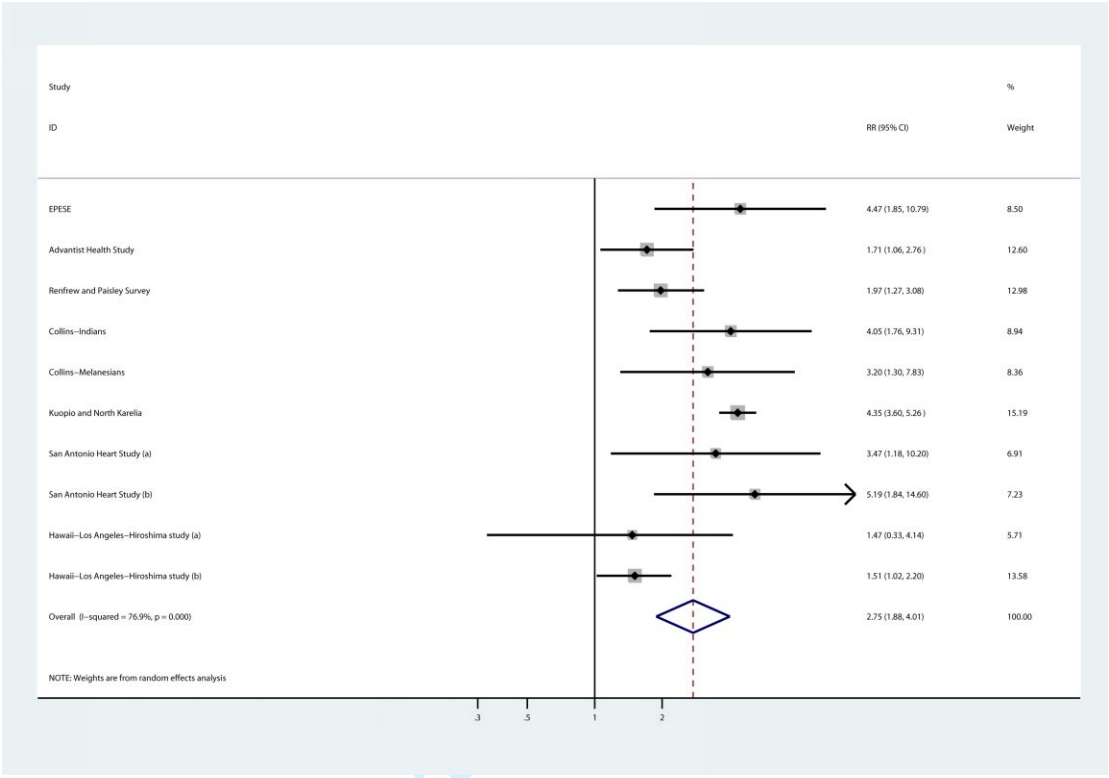


Figure S5. The summary results for DM and the risk of cardiac death in women

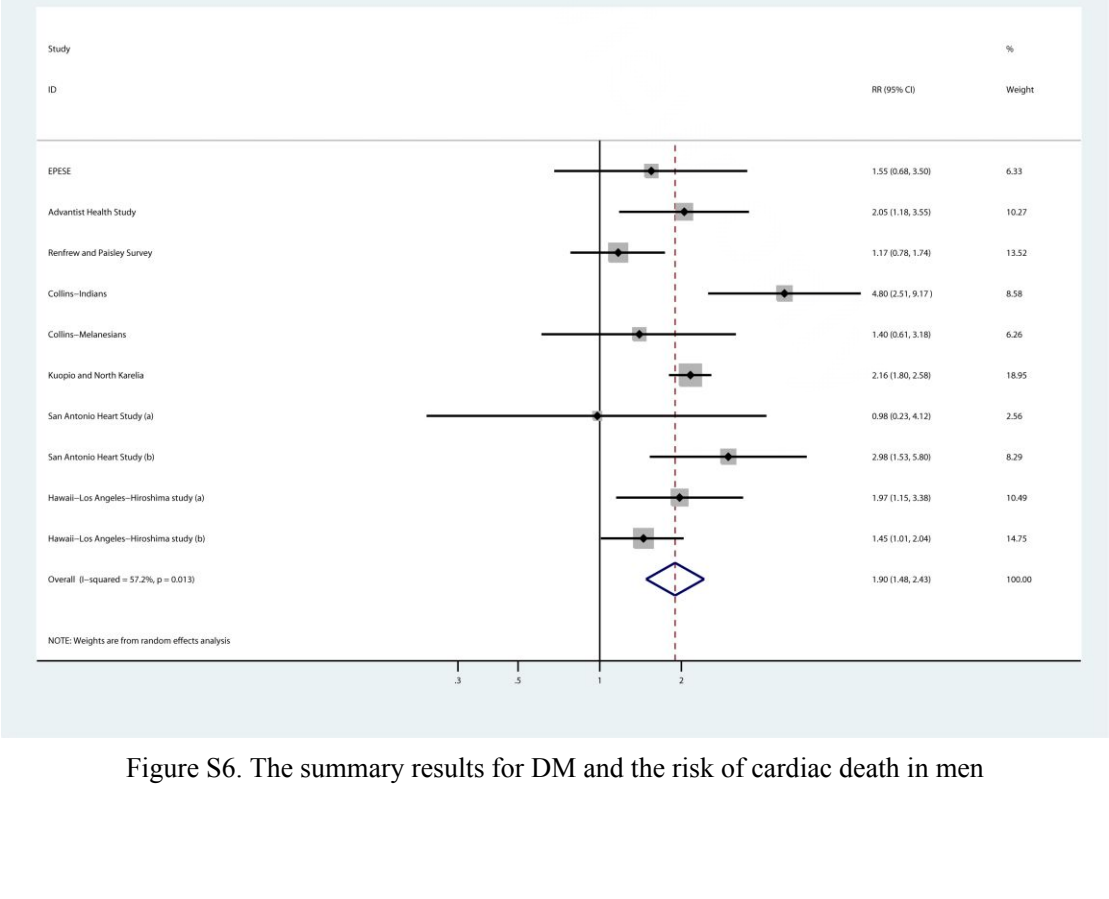


Figure S6. The summary results for DM and the risk of cardiac death in men

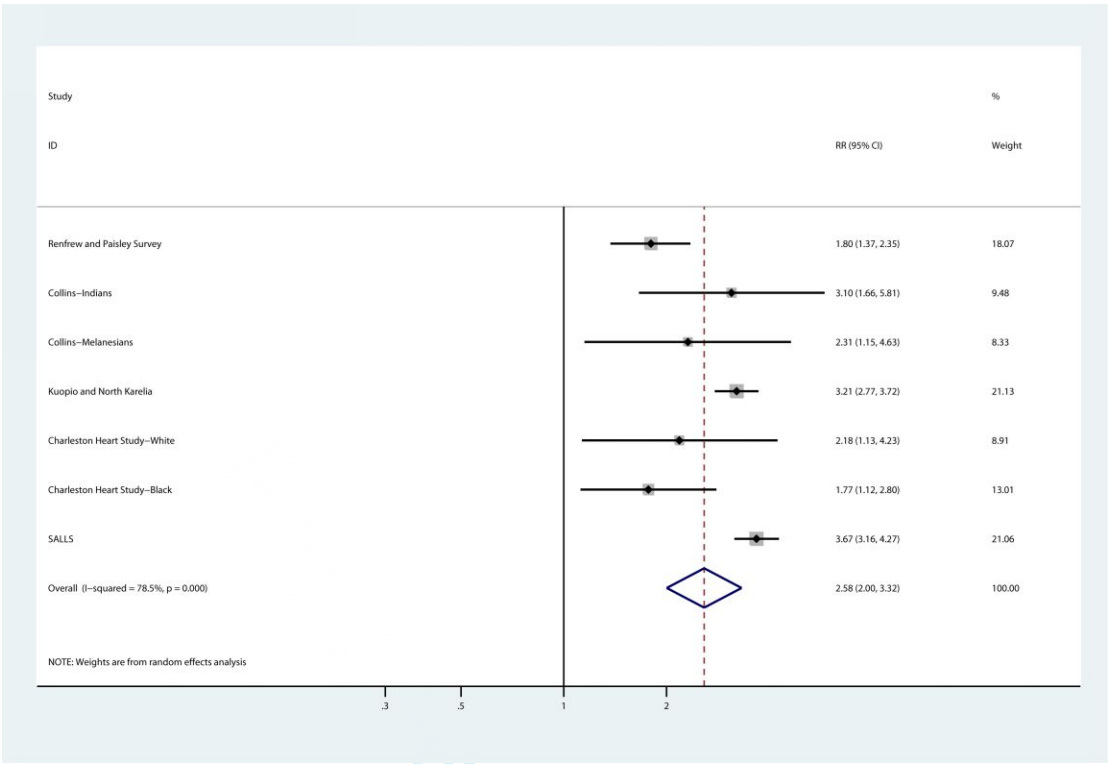


Figure S7. The summary results for DM and the risk of all-cause mortality in women

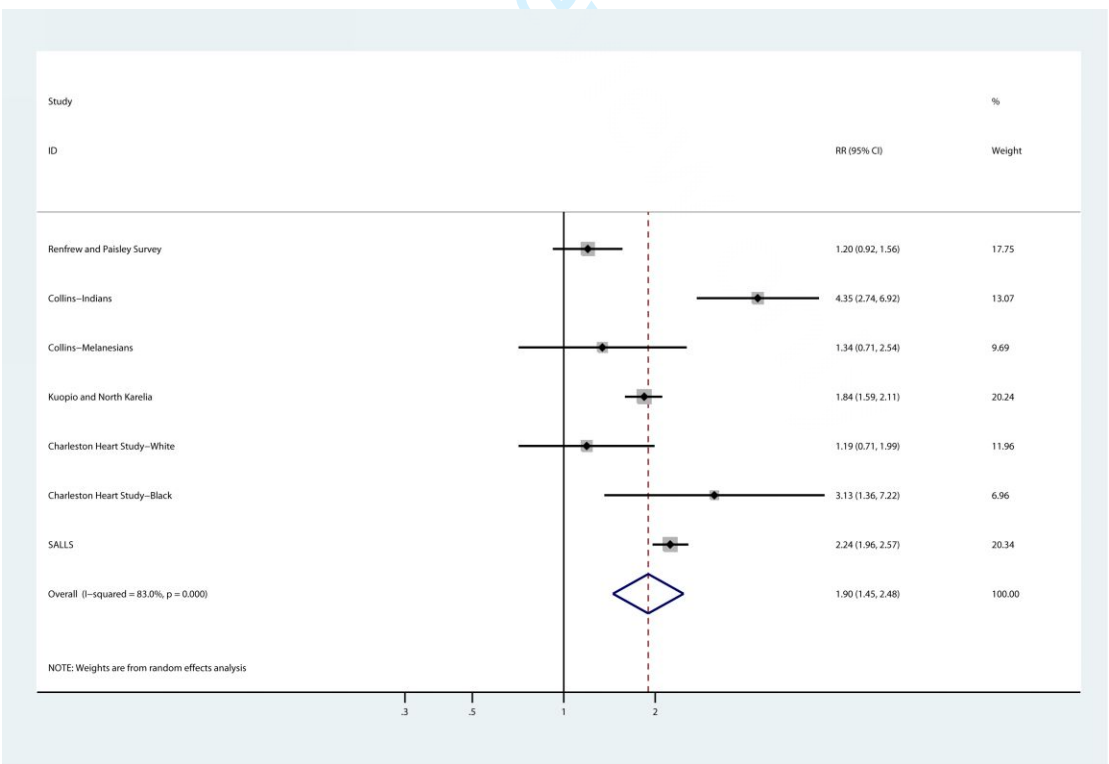


Figure S8. The summary results for DM and the risk of all-cause mortality in men

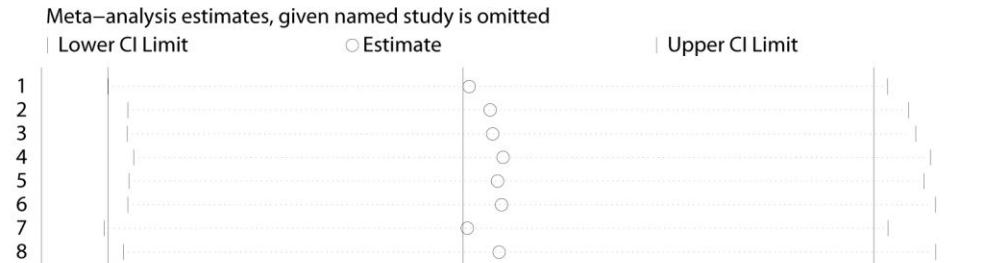


Figure S1. sensitivity analysis for CHD in women compared with men

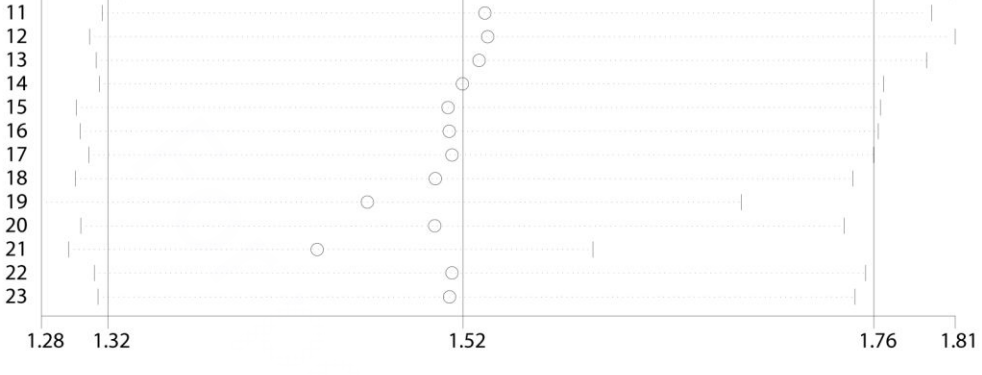


Figure S2. sensitivity analysis for stroke in women compared with men

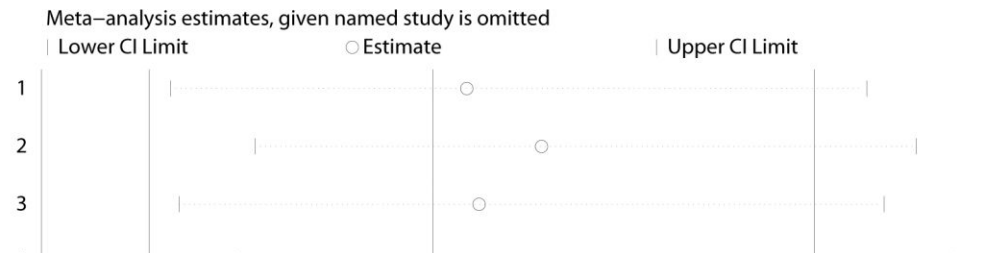


Figure S3. sensitivity analysis for cardiac death in women compared with men

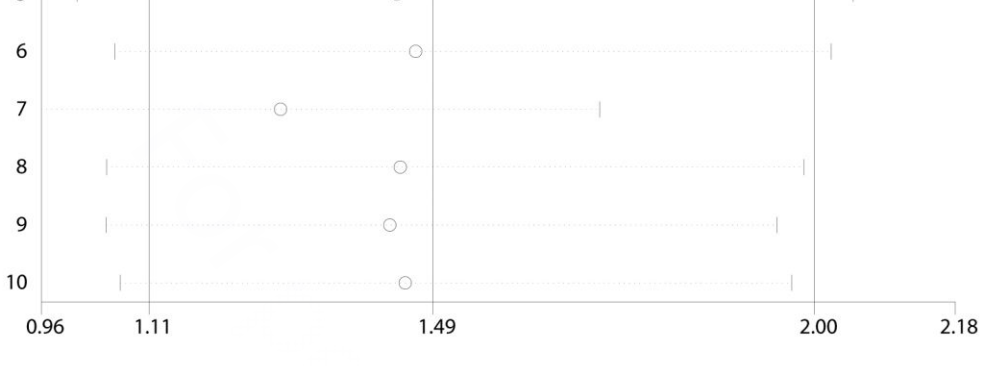
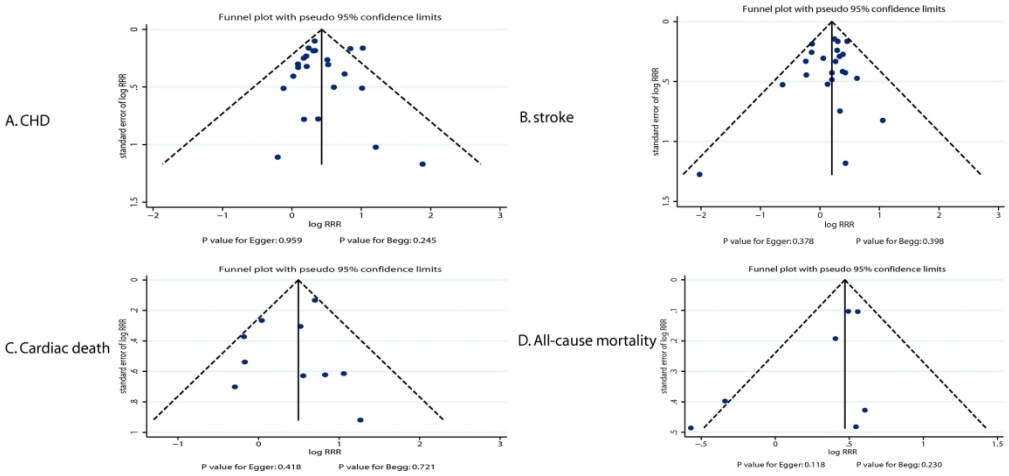


Figure S4. sensitivity analysis for all-cause mortality in women compared with men



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MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of background should include		
Problem definition	Yes	3
Hypothesis statement	Yes	3
Description of study outcomes	Yes	3
Type of exposure or intervention used	Yes	3
Type of study designs used	Yes	3
Study population	Yes	3
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	Yes	4
Search strategy, including time period used in the synthesis and key words	Yes	4
Effort to include all available studies, including contact with authors	Yes	4
Databases and registries searched	Yes	4
Search software used, name and version, including special features used (eg explosion)	Yes	4
Use of hand searching (eg reference lists of obtained articles)	Yes	4
List of citations located and those excluded, including justification	Yes	4
Method of addressing articles published in languages other than English	Yes	4
Method of handling abstracts and unpublished studies	Yes	4
Description of any contact with authors	No	NA
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	No	NA
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	Yes	4
Documentation of how data were classified and coded (eg multiple raters, blinding and interrater reliability)	Yes	4
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	Yes	5
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Yes	5

Assessment of heterogeneity	Yes	5
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	5
Provision of appropriate tables and graphics	Yes	5
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Yes	6-7
Table giving descriptive information for each study included	Yes	17-20
Results of sensitivity testing (eg subgroup analysis)	Yes	21-22
Indication of statistical uncertainty of findings	Yes	6-8
Reporting of discussion should include		
Quantitative assessment of bias (eg publication bias)	Yes	8-
Justification for exclusion (eg exclusion of non-English language citations)	No	8-10
Assessment of quality of included studies	Yes	17-20
Strengths and weaknesses	Yes	10
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Yes	8-9
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	Yes	10
Guidelines for future research	Yes	10
Disclosure of funding source	Yes	11

NA: Not Applicable

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024935.R1
Article Type:	Research
Date Submitted by the Author:	02-Mar-2019
Complete List of Authors:	wang, hao; First Affiliated Hospital of Dalian Medical University Ba, Ying; First Affiliated Hospital of Dalian Medical University Cai, Run-Ce; First Affiliated Hospital of Dalian Medical University Xing, Qian; First Affiliated Hospital of Dalian Medical University
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Sex difference, diabetes mellitus, major cardiovascular outcomes, all-cause mortality, meta-analysis

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

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Running title: Sex difference of DM and major cardiovascular outcomes

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Keywords: sex difference; diabetes mellitus; major cardiovascular outcomes; all-cause mortality; meta-analysis

ABSTRACT

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

Design: Meta-analysis

Data Sources: We systematically searched PubMed, Embase, and the Cochrane Library during April 2018.

Eligibility Criteria: Studies that were designed as prospective cohort studies, which reported the association between DM and major cardiovascular outcomes and all-cause mortality stratified by sex, were included.

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

Results

We included 30 prospective cohort studies that reported data on 1,148,188 individuals. The pooled women-to men RRR suggested that women were associated with increased risk of CHD (RRR: 1.52; 95% confidence interval [CI]: 1.32–1.76; P<0.001), stroke (RRR: 1.23; 95% CI: 1.09–1.39; P=0.001), cardiac death (RRR: 1.49; 95% CI: 1.11–2.00; P=0.009), and all-cause mortality (RRR: 1.51; 95% CI: 1.23–1.85; P<0.001). In addition, the sex differences for the investigated outcomes in the comparison between DM and non-DM patients were variable after stratification of studies by publication year, country, sample size, assessment of DM, follow-up duration, adjusted important cardiovascular risk factors, and study quality.

Conclusions

The findings of this study suggested that women with DM had an extremely high risk of CHD, stroke, cardiac death, and all-cause mortality compared to men with DM.

ARTICLE SUMMARY:

Strengths and limitations of this study:

- Published studies with large sample size were comprehensively included, and the findings of this study were more robust than those of any individual study.
- All studies included were prospectively designed and population-based, which eliminated the possibility of uncontrolled biases.
- Large studies with a diverse range of patients' characteristics could ensure the applicability of the summary results because populations distributed worldwide were included.
- Stratified results of the sex difference between DM and major cardiovascular outcomes and all-cause mortality were calculated based on the study or patient characteristics.
- The heterogeneity in the included studies was resolved by multiple methods, and no publication bias was found, thus, suggesting the robustness of the pooled results.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, and accounted for 10.3% of the global disease burden, with approximately 30% mortality at the first CVD events.[1,2] Numerous studies have already illustrated the risk of CVD and its factors in various populations.[3-7] It is well established that the morbidity and mortality of CVD risk were significantly increased in patients with diabetes mellitus (DM).[8-11] Further, DM is an independent risk factor for CVD, all-cause mortality, blindness, kidney failure, amputations, fractures, frailty, depression, and cognitive decline.[12] Therefore, emphasising the need for us to monitor high CVD risk in DM patients.

Sex differences in the effect of DM on the excess risk of CHD and stroke have been illustrated, and these vary based on several risk factors.[13,14] These two-large-scale quantitative meta-analyses suggested that women with DM have a 44% and 27% greater risk of coronary heart disease (CHD) and stroke, respectively. Although the mechanism of action is unclear, the exposure effects might be affected by non-DM women with persistently healthy lifestyle and be well controlled by other important cardiovascular risk factors.[15] However, several other important outcomes including cardiac death, and all-cause mortality were not illustrated in previous studies.

Although previous meta-analyses have illustrated the sex differences of DM and CHD and stroke risk, the current study is the first meta-analysis to quantify any potential sex differences for cardiac death and all-cause mortality. Clarifying the sex difference of 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, as it has not been definitively determined. We therefore conducted a large-scale examination of the available prospective cohort studies that reported sex-specific effects of DM on subsequent risk of CHD, stroke, cardiac death, and all-cause mortality to determine the sex differences of DM concerning major cardiovascular outcomes and all-cause mortality.

MATERIAL AND METHODS

Data sources, search strategy, and selection criteria

This study was conducted and reported according to the meta-analysis of observational studies in epidemiology protocol.[16] Studies with a prospective cohort design that analysed the associations of DM with CHD, stroke, cardiac death, and all-cause mortality risk, and were published in English language were potentially eligible for inclusion in this meta-analysis, and these studies were without restriction in publication status. Three electronic databases (PubMed, EmBase, and Cochrane Library) were searched for studies published from the time of inception of the databases to April 2018 using ("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" as the search terms. The details of the strategy used to search PubMed are presented in Supplemental 1. Additional eligible studies were identified by manual searches of reference lists in 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 to select the relevant studies.

The literature search and study selection were performed independently by two reviewers, and any disagreement between these reviewers were resolved by the corresponding author until a consensus was reached. The inclusion criteria are as follows: (1) Design: prospective cohort design; (2) Exposure and control: DM (irrespective of DM types) and non-DM; (3) Outcomes: CHD, stroke, cardiac death, and all-cause mortality; and (4) Effect estimate: the relation between DM and CHD, stroke, cardiac death, and all-cause mortality in men and women should be reported separately. The exclusion criteria included study reported with single sex populations, studies with retrospective observational design, and study reported with standard incidence/mortality ratio.

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, assessment of DM, follow-up duration, adjusted factors, and investigated outcomes. We selected the effect estimate and maximally adjusted for confounders if the study

reported several multivariable adjusted effect estimates. Quality assessment of the study was conducted using the Newcastle-Ottawa Scale (NOS), which is based on selection (4 items), comparability (1 item), and outcome (3 items).[17] A "star system" (range, 0–9) was used to evaluate the study quality.

Statistical analysis

The sex differences in the relation between DM and CHD, stroke, cardiac death, or all-cause mortality risk were based on the sex-specific effect estimate and corresponding 95% confidence interval (CI) in each individual study. Given the low prevalence of CHD, stroke, cardiac death, or all-cause mortality, odds ratio could be assumed to be accurate estimates of RR. Further, hazard ratio was regarded to be equivalent to RR in studies with cohort design. The summary RRs and 95% CIs for DM versus non-DM and the risk of CHD, stroke, cardiac death, and all-cause mortality in men and women were calculated separately by using the random-effects model, and the command of STATA was metan7 lnrr lnrrl lnrru, eform random xlab(0.3, 0.5, 1.0, 2.0) effect(RR) label(namevar=study).[18,19] After this, the female-to-male ratio of RRs (RRR) and 95% CIs in each study for CHD, stroke, cardiac death, or all-cause mortality were calculated based on sex-specific RRs and 95% Cis.[20] Finally, the summary RRR and 95% CIs for the sex differences of DM versus non-DM and CHD, stroke, cardiac death, or all-cause mortality risk were calculated using random-effects model.

I-square and Q statistic were employed to evaluate the heterogeneity among the included studies, and studies were regarded as showing significant heterogeneity if P values were less than 0.10.[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] After this, subgroup analyses for the sex differences of DM on CHD, stroke, cardiac death, or all-cause mortality risk were calculated based on publication year (2010 or after, before 2010), country (Eastern, Western), sample size (≥10000, <10000), assessment of DM (self-reported, measured, both), follow-up duration (≥10, <10), adjusted other cardiovascular risk factors (yes, no), and study quality (high, low). Finally, publication biases for investigated outcomes were assessed using funnel plots, Egger tests, and Begg tests.[24,25] Two-sided P values with a significance level of 0.05 were in pooled analyses.

Statistical analyses were performed using STATA software (version 10.0; Stata Corporation, College Station, TX, USA).

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 Supplemental 2. Thirteen thousand four hundred and seventy-one records were identified from the initial electronic search, of which 12,745 articles were excluded due to duplicates and irrelevant topics. Abstracts of 726 articles were assessed, and 633 studies were excluded due to the study having a design other than a prospective cohort design and reported cardiovascular risk factors as outcomes. Full test were retrieved for the remaining 93 studies to identify the potential studies that may be included, and 30 prospective cohort studies satisfied the inclusion criteria and were ultimately included in the meta-analysis.[26-55] There was no additional eligible studies after manual search of the reference lists within these studies.

Study characteristics

A total of 30 studies that 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 for participants was 5.0–30.0 years, while 787–436,832 individuals were included in each study. Forty-one cohorts were from the Western countries, and the remaining 34 cohorts from Eastern countries. Further, 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 studies used both self-reported and medical methods to assess the DM. Overall, 9 studies had a score of 8, 12 studies had a score of 7, and the remaining 9 had a score of 6 (Supplemental 3).

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	US	7381	407	40-77	55.0	Self-reported	9.0	Age, SBP, smoking, BMI, TC	7
Rancho Bernado [27]	1988	US	3778	320	50-79	54.0	Self-reported	12.0	Age, SBP, TC, smoking, obesity, family history, oestrogen use	6
ARIC [28]	1989	US	15732	1610	45-64	55.0	Measured	18.0	Age, SBP, smoking, BMI, TC	7
Advantist Health Study [29]	1992	US	27658	656	>25	63.0	Measured	6.0	Age, hypertension, smoking, BMI, PA	6
Sievers [30]	1992	US	5131	1266	15-84	52.0	Measured	10.0	Age	7
EPESE [31]	1993	US	2812	386	>65	58.0	Self-reported	6.0	Age, AHT use, smoking, BMI, diabetes, angina, chest pain on exertion	6
Charleston Heart Study-White [32]	1993	US	1394	38	>35	53.0	Measured	30.0	Age	6
Charleston Heart Study-Black [32]	1993	US	787	37	>35	58.0	Measured	30.0	Age	6
NHANES III [33]	1994	US	18603	1290	18-90	46.0	Self-reported or measured	13.0	Age, SBP, smoking, BMI, 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, prior CH	6
Collins-Indians [35]	1996	Fiji	1220	166	>20.0	55.0	Measured	11.0	Age, SBP, smoking, BMI, TC, survey area	6
Collins-Melanesians [35]	1996	Fiji	1324	65	>20.0	53.0	Measured	11.0	Age, SBP, smoking, BMI, TC, survey area	6
SALLS [36]	1998	Sweden	39055	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, ECG abnormalities	6
Reykjavik study [38]	2002	Iceland	18519	295	32-60	52.0	Self-reported or measured	17.0	Age, hypertension, smoking, BMI, TC, triacylglycerols, diabetes, glucose, prior CHD, LVH	8
APCSC-Asia [39]	2003	27 cohorts in Asia	436832	17763	>20	33.0	Self-reported or measured	7.0	Age, SBP, smoking, BMI, TC	7
APCSC-Australia and New Zealand [39]	2003	9 cohorts in Australia and New Zealand	99624	4784	>20	45.0	Self-reported or measured	7.0	Age, SBP, smoking, BMI, TC	7

Framingham study [40]	2003	2 cohorts in US	5243	229	35-75	52.0	Measured	20.0	Age, hypertension, smoking, BMI, TC	7
Iso [41]	2004	Japan	10582	267	40-69	60.0	Measured	17.0	Age, hypertension, smoking, BMI, TC, HDL, skinfold, alcohol, community, menopause	8
Renfrew and Paisley Survey [42]	2005	Scotland	15426	228	45-64	54.0	Self-reported or measured	25.0	Age, SBP, smoking, BMI, TC, SES	8
Kuopio and North Karelia [43]	2005	Finland	51735	1108	25-74	51.0	Self-reported	17.0	Age, SBP, smoking, BMI, TC, study year	8
Strong Heart Study [44]	2006	US	4372	724	45-74	61.0	Measured	12.0	Age, SBP, DBP, smoking, HDL, LDL, albuminuria	7
Framingham Offspring [45]	2006	US	2097	99	50-81	50.0	Measured	14.0	Age, SBP, AHT, CVD, atrial fibrillation, LVH, smoking	7
San Antonio Heart Study [46]	2007	US	4996	524	25-64	57.0	Measured	16.0	Age, ethnicity	7
SHHEC [47]	2007	Scotland	13343	184	30-74	51.0	Measured	16.0	Age, SBP, smoking, BMI, TC	7
EPIC-Norfolk [48]	2008	UK	22516	441	40-79	55.0	Self-reported	10.0	Age, SBP, smoking, BMI, TC, triglycerides	8

Takayama [49]	2008	Japan	29079	1217	>35	54.0	Self-reported	7.0	Age, hypertension, smoking, BMI, PA, education, energy, vegetables, fat, alcohol	8
DECODE [50]	2009	7 cohorts in Finland and Sweden	9278	826	40-69	55.0	Measured	5-21	Age, hypertension, smoking, BMI, TC, HDL	6
Hisayama [51]	2010	Japan	2421	291	40-79	57.0	Measured	14.0	Age, SBP, smoking, BMI, TC, HDL, alcohol intake, PA,ECG abnormalities	7
JPHC [52]	2011	2 cohorts in Japan	35657	2034	40-69	63.0	Measured	12.0	Age, SBP, AHT, smoking, BMI, TC, HDL, triglycerides, alcohol, fasting status, residential areas	8
HUNT 1 [53]	2012	Norway	47951	1992	>20	52.0	Self-reported	17.0	Age, hypertension, smoking, BMI, CVD, PA	8
ESPro [54]	2017	Germany	105000	7190	>18	51.0	Self-reported or measured	14.0	Calendar year, age	7
JACC [55]	2017	Japan	104910	5729	40-79	58.0	Self-reported	19.0	Age, education, smoking, alcohol, PA, BMI, history of hypertension, or history of DM	8

*AHT, anti-hypertensive; ApoB, apolipoprotein B; CVD, cardiovascular disease; DBP, diastolic BP; LPa, lipoprotein a; LVH, left ventricle hypertrophy; NA, notavailable; PA, physical activity; SALLS, Swedish Annual Level-of-Living Survey; SBP, systolic BP; SES, socioeconomic status

Coronary heart disease

Data for studies that reported sex difference in association between DM and subsequent CHD risk were available from 20 studies. The summary results in men and women are separately shown in Supplemental 4, and the results indicated that DM were associated with increased risk of CHD risk in both men and women. Further, the pooled RRR (female to male) of DM versus non-DM and the risk of CHD was 1.52 (95%CI: 1.32–1.76; P<0.001; Figure 1A); this was associated with statistical significance and there was significant heterogeneity among the study (I^2=36.1%; P=0.044). The results of sensitivity analysis were not altered after the sequential exclusion of each study from all the pooled analyses (Supplemental 5). The results of subgroup analyses were consistent with overall analysis in most subsets except for the duration of follow-up less than 10.0 years (Table 2).

Table 2. Subgroup analyses for CHD

Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square (%)	P value for heterogeneity	P value for Meta-regression
Publication year	Before 2010	20	1.53 (1.28-1.82)	<0.001	39.6	0.036	0.260
	2010 or after	3	1.42 (1.20-1.68)	<0.001	0.0	0.421	
Country	Western	18	1.50 (1.27-1.77)	<0.001	43.6	0.025	0.934
	Eastern	5	1.58 (1.17-2.13)	0.003	6.7	0.368	
Sample size	≥10000	9	1.62 (1.31-2.00)	<0.001	65.4	0.003	0.119
	<10000	14	1.34 (1.09-1.63)	0.004	0.0	0.780	
Assessment of DM	Self-reported	6	1.75 (1.29-2.37)	<0.001	74.6	0.001	0.073
	Measured	13	1.32 (1.09-1.61)	0.005	0.0	0.764	
	Both	4	1.39 (1.11-1.75)	0.005	0.0	0.730	
Follow-up duration (years)	≥10	16	1.69 (1.41-2.04)	<0.001	43.1	0.034	0.032
	<10	6	1.22 (0.98-1.52)	0.078	0.0	0.948	
Adjusted other CVD risk factors	Yes	19	1.45 (1.29-1.62)	<0.001	6.6	0.375	<0.001
	No	4	2.56 (1.89-3.46)	<0.001	0.0	0.423	
Study quality	High	13	1.46 (1.29-1.66)	<0.001	10.6	0.339	0.052

	Low	10	1.64 (1.14-2.36)	0.007	47.8	0.045	

Stroke

Data for the study reported sex difference of an association between DM and subsequent stroke risk were available from 20 studies. The pooled results in men with DM and women who were associated with statistical significance increased (Supplemental 4). The pooled RRR (female to male) suggested that women with DM was associated with an increased risk of stroke compared to men with DM (RRR: 1.23; 95%CI: 1.09–1.39; 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 after sequential exclusion of each study from the pooled analyses (Supplemental 5). Subgroup analysis indicated no sex difference for the relation of DM with stroke risk for pooled studies published in 2010 or after, study conducted in Eastern countries, sample size < 10000, study that used both self-reported and measured, duration of follow-up <10.0 years, the study not adjusted for other cardiovascular risk factors, and the study with low quality (Table 3).

Table 3. Subgroup analyses for stroke

Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square (%)	P value for heterogeneity	P value for Meta-regression
Publication year	Before 2010	18	1.29 (1.11-1.50)	0.001	0.0	0.640	0.269
	2010 or after	4	1.11 (0.89-1.40)	0.353	18.1	0.300	
Country	Western	15	1.23 (1.05-1.44)	0.011	0.0	0.587	0.998
	Eastern	7	1.20 (0.97-1.49)	0.091	14.7	0.318	
Sample size	≥10000	14	1.25 (1.10-1.42)	<0.001	0.0	0.531	0.341
	<10000	8	1.04 (0.72-1.50)	0.840	0.0	0.493	
Assessment of DM	Self-reported	6	1.28 (1.04-1.58)	0.022	0.0	0.668	0.423
	Measured	11	1.32 (1.08-1.61)	0.008	0.0	0.508	
	Both	5	1.09 (0.85-1.41)	0.484	21.3	0.279	

Follow-up duration (years)	≥10	18	1.28 (1.11-1.47)	0.001	0.0	0.726	0.313
	<10	4	1.09 (0.76-1.57)	0.627	36.0	0.196	
Adjusted other CVD risk factors	Yes	19	1.27 (1.11-1.44)	<0.001	0.0	0.695	0.237
	No	3	1.14 (0.71-1.83)	0.586	40.4	0.187	
Study quality	High	16	1.24 (1.09-1.41)	0.001	0.0	0.533	0.617
	Low	6	1.13 (0.79-1.61)	0.498	2.4	0.401	

Cardiac death

Data for the study reported that sex differences in the association between DM and subsequent cardiac death risk were available from 10 cohorts. We noted that DM was associated with greater risk of cardiac death in men and women independently (Supplemental 4). The pooled RRR (female to male) of DM versus non-DM on cardiac death risk was 1.49 (95%CI: 1.11–2.00; P=0.009; Figure 2A), which was associated with statistical significance. Further unimportant heterogeneity was detected (I^2=31.9%; P=0.153). The result of sensitivity analysis was changed after excluding the Kuopio and North Karelia study (Supplemental 5). Subgroup analysis indicated significant sex difference of DM in cardiac death if the study; was published before 2010, was conducted in Western countries, had sample size ≥ 10000, used medical measure to assess DM, had a follow-up duration ≥ 10.0 years, adjusted for other cardiovascular risk factors, and was of high quality (Table 4).

Table 4. Subgroup analyses for cardiac death

Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square (%)	P value for heterogeneity	P value for Meta-regression
Publication year	Before 2010	10	1.49 (1.11-2.00)	0.009	31.9	0.153	-
	2010 or after	0	-	-	-	-	
Country	Western	7	1.84 (1.45-2.32)	<0.001	3.6	0.399	0.010
	Eastern	3	0.97 (0.62-1.51)	0.891	0.0	0.870	

Sample size	≥10000	2	1.96 (1.54-2.49)	<0.001	0.0	0.591	0.015
	<10000	8	1.18 (0.85-1.64)	0.322	0.0	0.433	
Assessment of DM	Self-reported	2	2.05 (1.59-2.64)	<0.001	0.0	0.568	0.016
	Measured	7	1.10 (0.78-1.54)	0.588	0.0	0.586	
	Both	1	1.68 (0.93-3.06)	0.087	-	-	
Follow-up duration (years)	≥10	8	1.57 (1.18-2.09)	0.002	21.8	0.256	0.257
	<10	2	1.41 (0.42-4.68)	0.576	66.5	0.084	
Adjusted other CVD risk factors	Yes	8	1.42 (1.02-1.98)	0.040	44.0	0.085	0.575
	No	2	2.18 (0.79-6.03)	0.132	0.0	0.524	
Study quality	High	4	1.97 (1.56-2.48)	<0.001	0.0	0.864	0.006
	Low	6	1.10 (0.78-1.55)	0.593	0.0	0.417	

All-cause mortality

Data for the study that reported sex difference in an association between DM and subsequent all-cause mortality risk were available from 7 cohorts. The summary results indicated that DM were correlated with higher risk of all-cause mortality in men and women independently (Supplemental 4). The pooled female-to-male RRR indicated significant sex difference for all-cause mortality risk between participants with DM and those without DM (RRR: 1.51; 95% CI: 1.23–1.85; P<0.001; Figure 2B), and with moderate heterogeneity among included studies (I^2=38.2%; P=0.138). A sensitivity analysis was conducted and indicated that the conclusion was not affected by the exclusion of any specific study (Supplemental 5). Subgroup analyses indicated no sex difference if the study was conducted in Eastern countries, with sample size<10000, used medical measure to assess DM, was not adjusted for other cardiovascular risk factors, and was of low quality (Table 5).

Table 5. Subgroup analyses for all-cause mortality

Outcomes	Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square (%)	P value for heterogeneity	P value for Meta-regression

All-cause mortality	Publication year	Before 2010	7	1.51 (1.23-1.85)	<0.001	38.2	0.138	-
		2010 or after	0	-	-	-	-	
	Country	Western	6	1.63 (1.41-1.88)	<0.001	8.2	0.364	0.039
		Eastern	1	0.71 (0.33-1.55)	0.394	-	-	
	Sample size	≥10000	3	1.66 (1.46-1.90)	<0.001	0.0	0.772	0.050
		<10000	4	1.06 (0.59-1.90)	0.844	43.7	0.149	
	Assessment of DM	Self-reported	2	1.69 (1.46-1.95)	<0.001	0.0	0.669	0.123
		Measured	4	1.06 (0.59-1.90)	0.844	43.7	0.149	
		Both	1	1.50 (1.03-2.19)	0.035	-	-	
	Follow-up duration (years)	≥10	7	1.51 (1.23-1.85)	<0.001	38.2	0.138	-
		<10	0	-	-	-	-	
	Adjusted other CVD risk factors	Yes	4	1.50 (1.12-2.01)	0.006	39.4	0.176	0.850
		No	3	1.33 (0.75-2.36)	0.321	57.6	0.095	
	Study quality	High	2	1.69 (1.41-2.02)	<0.001	0.0	0.490	0.414
		Low	5	1.25 (0.80-1.94)	0.329	53.3	0.073	

Publication bias

Review of the funnel plots could not rule out the potential for publication bias for CHD, stroke, cardiac death, and all-cause mortality (Supplemental 6). The Egger and Begg test results showed no evidence of publication bias for CHD (P-value for Egger: 0.959; P-value for Begg: 0.245), stroke (P-value for Egger: 0.407; P-value for Begg: 0.398), cardiac death (P-value for Egger: 0.418; P-value for Begg: 0.721), and all-cause mortality (P-value for Egger: 0.118; P-value for Begg: 0.230).

DISCUSSION

Our current study was based on 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 with a broad range of populations. The findings from our current meta-analysis suggest that there were significant sex differences for DM versus non-DM on the incidence of CHD, stroke, cardiac death, all-cause mortality, and women with excessively higher risk than those in men. Furthermore, the findings of subgroup analyses could be biased by publication year, country, sample size, assessment of DM, follow-up duration, adjusted important cardiovascular risk factors, and study quality.

A previous study suggested that women with DM are associated with increased risk of CHD or stroke than in men with DM.[13,14] They point out that the incidence of CHD was 44% greater in women with DM than in men with DM.[13] Moreover, women with DM were associated with an increased risk of stroke than men with DM.[14] However, the sex differences on other important outcomes (cardiac death, all-cause mortality) was not illustrated. We therefore conducted this comprehensive quantitative meta-analysis of available prospective cohort studies to evaluate the sex differences of DM and major cardiovascular outcomes. As with previous meta-analysis, the significantly increased risk of cardiac death and all-cause mortality in women with DM compared to men with DM, were observed. The excess risk of cardiac death in women with DM could be due to the higher risk of CHD in women with DM, which might be due to the fact that women with DM have a greater adverse cardiovascular risk and are less likely to achieve the recommended levels as compared to men with DM. Finally, the increased risk of all-cause mortality in women with DM might due to higher incidence of CHD, stroke, and cardiac death.

There were significant sex differences between DM and the risk of major cardiovascular outcomes and all-cause mortality. Although numerous studies included inconsistent results, several other studies included in our study reported consistent results. The results from the Hawaii-Los Angeles-Hiroshima study found that the risk of CHD was increased by 229% in women with DM, while this risk, in men with DM, was increased by 54%. However, they point out no significant sex difference for the risk of cardiac death.[37] Further, the study conducted by Kuopio and North Karelia indicated significant sex differences for the outcomes of CHD, cardiac death, and mortality, but not for stroke risk.[43] The Hisayama study indicated that sex difference on CHD was observed, while

this difference was not detected for stroke.[51] Nilsson et al indicated that the risk of CHD (703% versus 189%) and all-cause mortality (267% versus 124%) was significantly higher in women with DM as compared to men with DM.[36] The ARIC study found that the risk of stroke in women with DM was increased by 216%, while in men with DM, it was 100%. [28] The results of the Renfrew and Paisley survey did not observe sex differences for CHD, stroke, and cardiac death, while the risk on all-cause mortality was associated with statistical significance.[42] The possible reasons for these sex differences could be as follows: (1) High absolute cardiovascular risk in men than in women but the relative effect of DM was more extreme in women than in men, which could overestimate the sex differences of cardiovascular risk. (2) High cardiovascular event rates and numerous cohorts were included, and the sensitivity to detect minute sex differences of DM and major cardiovascular outcomes was stronger. (3) Corresponding control group in women without DM was associated with persistently more favourable survival rate, which could favour lipoprotein levels.[15]

The findings of subgroups suggested that the sex differences in the relationship between DM and major cardiovascular outcomes and all-cause mortality might be variable according to pre-defined factors. First, publication years affected the sex difference concerning the risk of stroke, which might be due to a more advanced diagnostic approach. Second, country could affect the sex differences of the DM and the risk of cardiac death and all-cause mortality, and the reason for this could be that the prevalence of cardiac death and all-cause mortality differed in Eastern countries and Western countries. Third, sample size affected the sex differences on the risk of stroke, cardiac death and all-cause mortality due to sample size being correlated with statistical power; and this affected the ability to detect small differences. Fourth, the methods of assessment of DM could affect the sex differences on stroke, cardiac death and all-cause mortality, and the reason for this could be that the methods of assessment of DM could affect the prevalence of event rates. Fifth, the follow-up duration could affect the sex difference on the risk of CHD, stroke, and cardiac death. The reason for this could be that there were studies with longer follow-up and higher proportion of CHD than studies with shorter follow-up which contributed to the higher weight in pooled results and made it easier to detect small sex differences. Finally, the other major cardiovascular risk factors, whether adjusted or not, and study quality affected the sex difference on stroke, cardiac death and

all-cause mortality, and the pooled study with high quality or adjusted other cardiovascular risk factors, could acquire more reliable results.

Several strengths should be highlighted in this meta-analysis. First, the comprehensive inclusion of published studies with large sample size, and the findings of this study was more robust than are those of any individual study. Second, all studies included were prospectively designed and population based, which could eliminate uncontrolled biases. Third, large included studies with broad characteristics of patients could ensure the applicability of the summary results because of worldwide distributed populations were included. Fourth, stratified results of the sex difference between DM and major cardiovascular outcomes based on study or patients' characteristics were calculated. Finally, the heterogeneity among included studies was resolved in multiple methods and no publication bias was found, which could support the robustness of the pooled results.

Several limitations regarding this meta-analysis should be acknowledged: (1) various adjusted cardiovascular risk factors across the included studies could affect the development of major cardiovascular outcomes; (2) various DM types, DM assessment method, and the duration of DM among included studies; (3) publication bias is inevitable due to searching of databases, publication language, and unpublished studies with negative results; and (4) data on background drug uses were available in few studies, which could affect the absolute risk of major cardiovascular outcomes.

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

Author Contributions

Hao Wang contributed to conception and design; Hao Wang, Ying Ba, Run-Ce Cai, and Qian Xing contributed to acquisition, analysis and interpretation of data; Hao Wang and Qian Xing were involved in drafting or critical revision of the manuscript. All the authors approved the final version.

Conflict of interests: All authors declare no conflict of interest.

Funding statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing statement: No additional data available.

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Figure legends:

Figure 1. The sex differences of the associations of DM with CHD (A) and stroke (B) risk.

Figure 2. The sex differences of the associations of DM with cardiac death (A) and all-cause mortality (B) risk

Supporting Information Legends:

Supplemental 1: Searching strategy in PubMed

Supplemental 2: Flowchart of the study selection process

Supplemental 3: NOS scale for included studies

Supplemental 4: The summary results of DM and CHD, stroke, cardiac death, and all-cause mortality in men and women separately.

Supplemental 5: Sensitivity analyses for CHD, stroke, cardiac death, and all-cause mortality

Supplemental 6: Funnel plots for CHD, stroke, cardiac death, and all-cause mortality.

Checklist S1: MOOSE Checklist

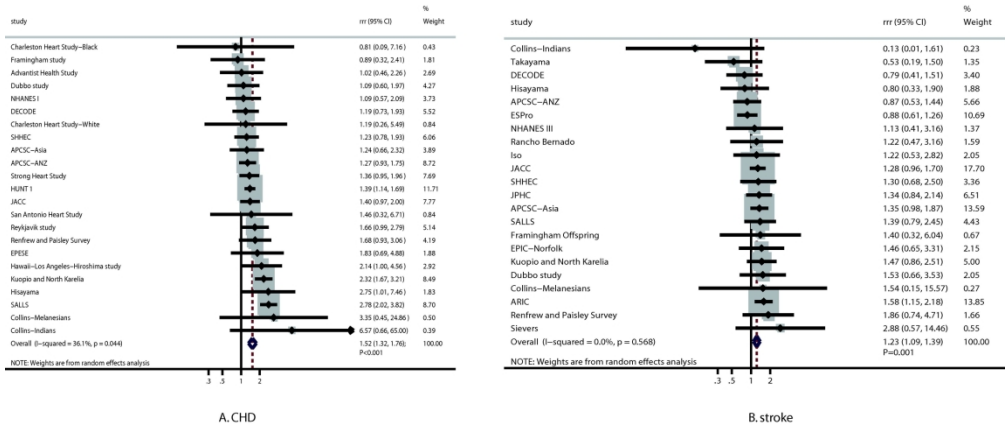

Figure 1. The sex differences of the associations of DM with CHD (A) and stroke (B) risk.

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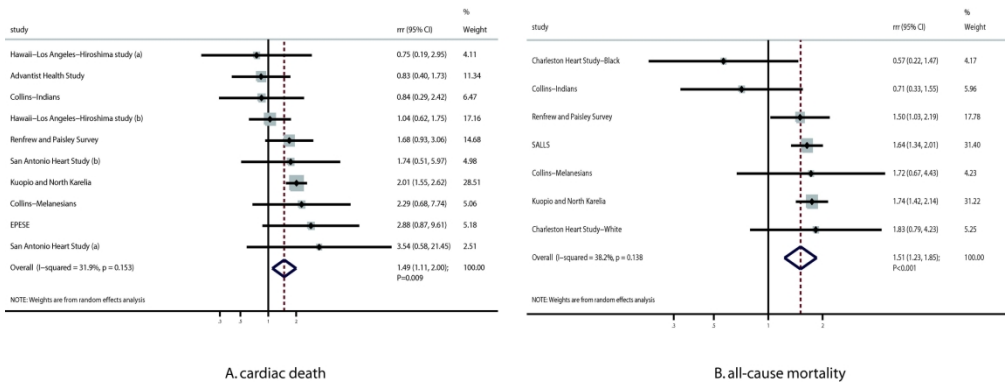


A. cardiac death B. all-cause mortality

Figure 2. The sex differences of the associations of DM with cardiac death (A) and all-cause mortality (B) risk

229x92mm (300 x 300 DPI)

Searching strategy in PubMed:

("Coronary Disease"[Mesh] OR "Coronary Disease"[All Fields] OR "Coronary Artery Disease"[Mesh] OR "Coronary Artery Disease"[All Fields] OR "Myocardial Ischemia"[Mesh] OR "Myocardial Ischemia"[All Fields] OR "stroke"[Mesh] OR "stroke"[All Fields] OR "death" [Mesh] OR "death"[All Fields] OR "mortality"[Mesh] OR "mortality"[All Fields]) AND ("Diabetes mellitus"[Mesh] OR "Diabetes"[All Fields]) AND ("men"[Mesh] OR "male"[Mesh]) AND ("women"[Mesh] OR "female"[Mesh]) AND ("Cohort Studies"[Mesh] OR "Prospective Studies"[Mesh])

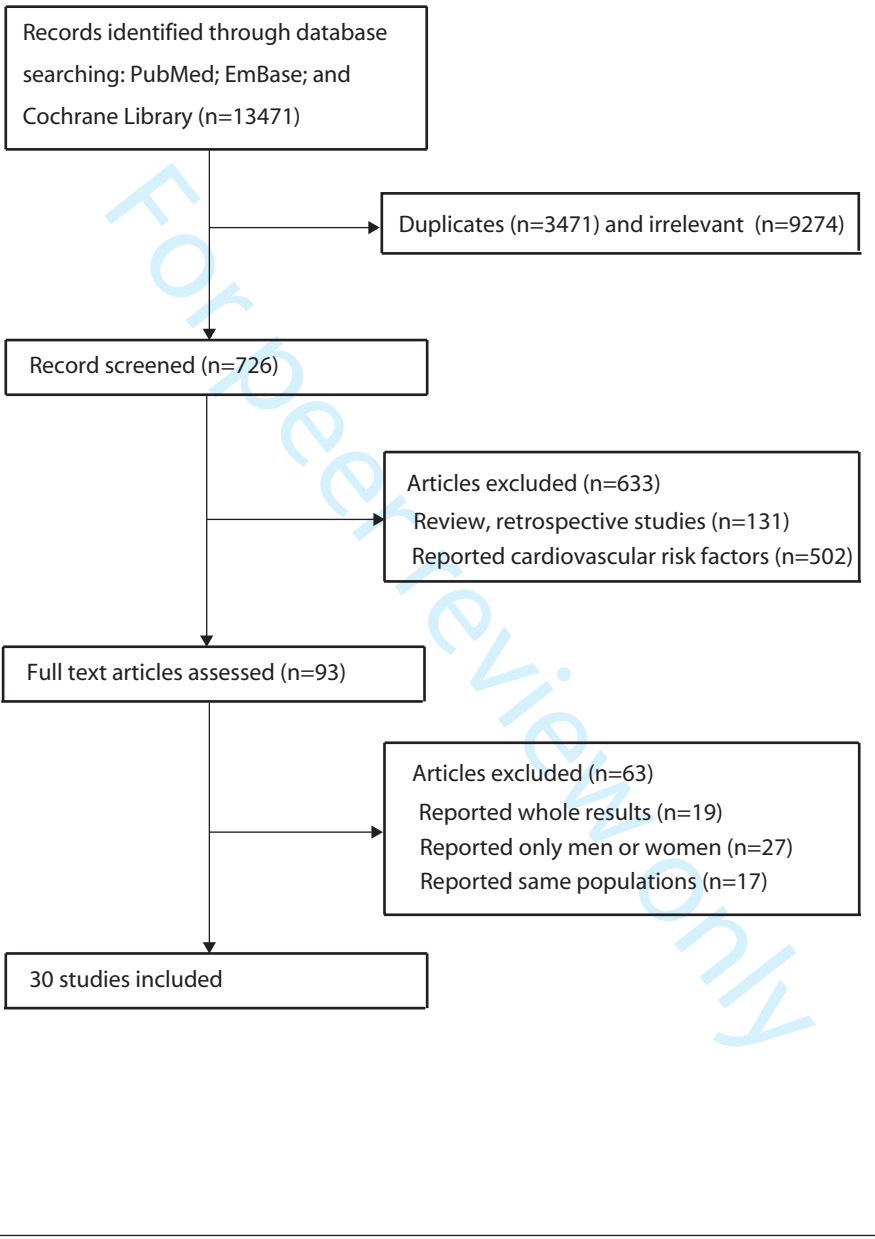


Table S1. Quality scores of prospective cohort studies using Newcastle-Ottawa Scale.

Study	Selection				Comparability	Outcome			NOS
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of DM	Demonstration that outcomes was not present at start of study	Comparability on the basis of the design or analysis	Assessment of outcome	Adequate follow-up duration	Adequate follow-up rate	Overall score
NHANES I [26]	1	1	1	0	1	1	1	1	7
Rancho Bernado [27]	0	1	1	0	1	1	1	1	6
ARIC [28]	1	1	1	0	1	1	1	1	7
Advantist Health Study [29]	1	0	1	1	1	1	0	1	6
Sievers [30]	0	1	1	1	1	1	1	1	7
EPESE [31]	0	1	1	1	1	1	0	1	6
Charleston Heart Study-White [32]	0	1	1	1	1	1	1	0	6
Charleston Heart Study-Black [32]	0	1	1	1	1	1	1	0	6
NHANES III [33]	1	1	1	0	1	1	1	1	7
Dubbo study [34]	0	1	1	1	1	1	0	1	6
Collins-Indians [35]	0	1	1	0	1	1	1	1	6
Collins-Melanesians [35]	0	1	1	0	1	1	1	1	6
SALLS [36]	1	1	1	0	1	1	1	0	6
Hawaii-Los Angeles-Hiroshima study [37]	0	1	1	0	1	1	1	1	6

Reykjavik study [38]	1	1	1	1	1	1	1	1	8
APCSC-Asia [39]	1	1	1	0	1	1	1	1	7
APCSC-Australia and New Zealand [39]	1	1	1	0	1	1	1	1	7
Framingham study [40]	0	1	1	1	1	1	1	1	7
Iso [41]	1	1	1	1	1	1	1	1	8
Renfrew and Paisley Survey [42]	1	1	1	1	1	1	1	1	8
Kuopio and North Karelia [43]	1	1	1	1	1	1	1	1	8
Strong Heart Study [44]	0	1	1	1	1	1	1	1	7
Framingham Offspring [45]	0	1	1	1	1	1	1	1	7
San Antonio Heart Study [46]	0	1	1	1	1	1	1	1	7
SHHEC [47]	1	1	1	0	1	1	1	1	7
EPIC-Norfolk [48]	1	1	1	1	1	1	1	1	8
Takayama [49]	1	1	1	1	2	1	0	1	8
DECODE [50]	0	1	1	1	1	1	0	1	6
Hisayama [51]	0	1	1	1	1	1	1	1	7
JPHC [52]	1	1	1	1	1	1	1	1	8
HUNT 1 [53]	1	1	1	1	1	1	1	1	8

ESPro [54]	1	1	1	1	1	1	1	0	7
JACC [55]	1	1	1	1	1	1	1	1	8

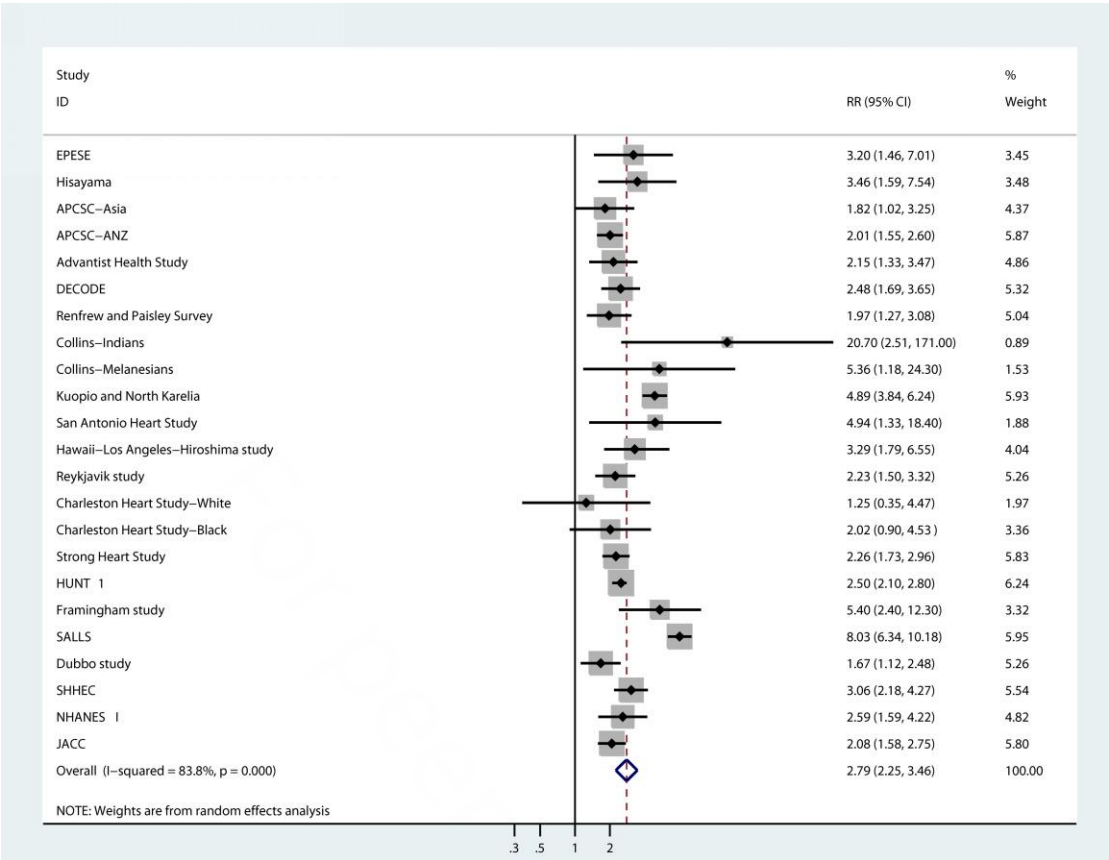


Figure S1. The summary results for DM and the risk of CHD in women

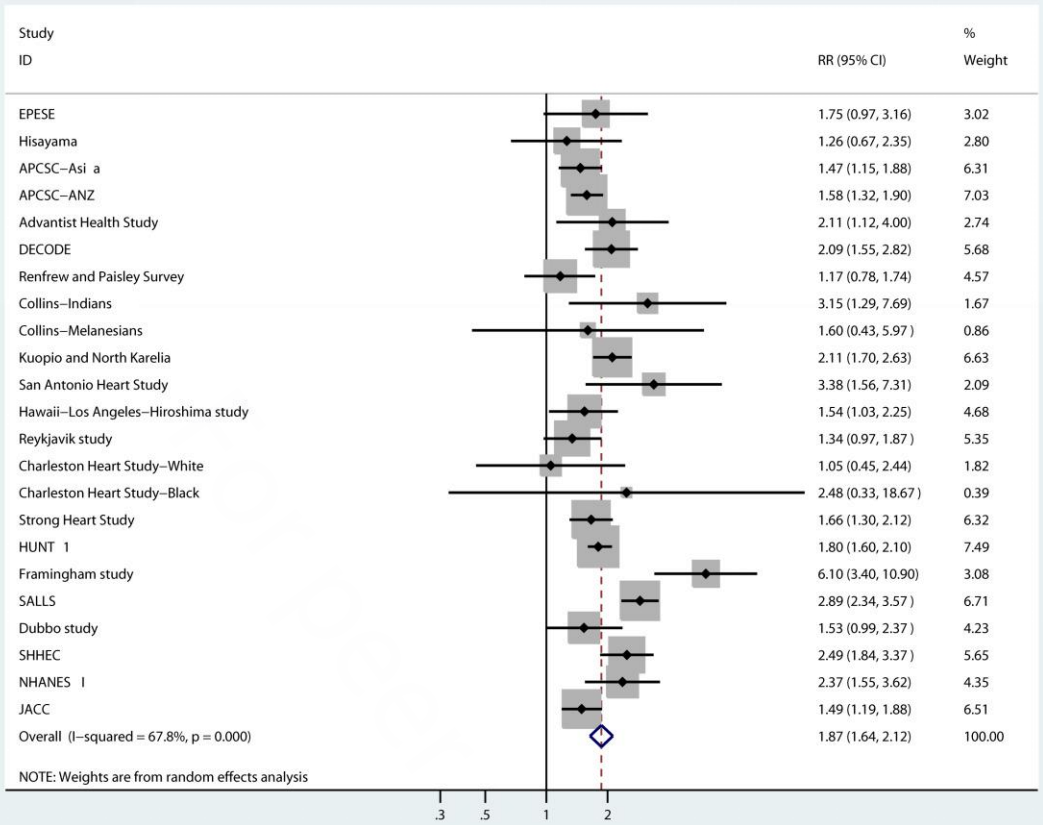


Figure S2. The summary results for DM and the risk of CHD in men

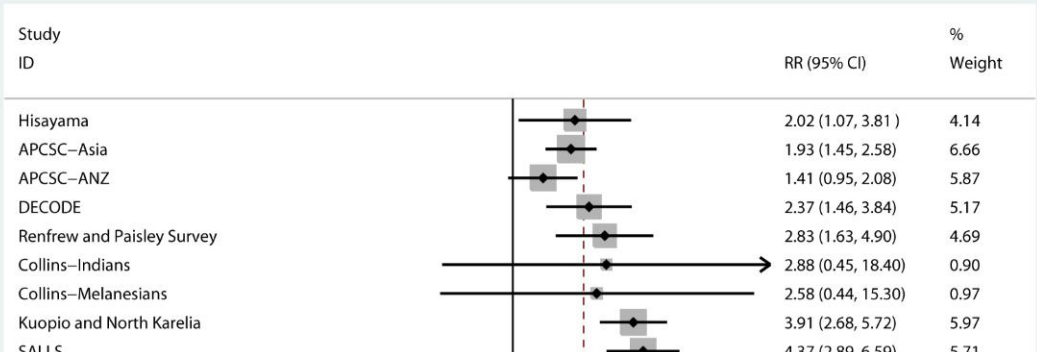


Figure S3. The summary results for DM and the risk of stroke in women

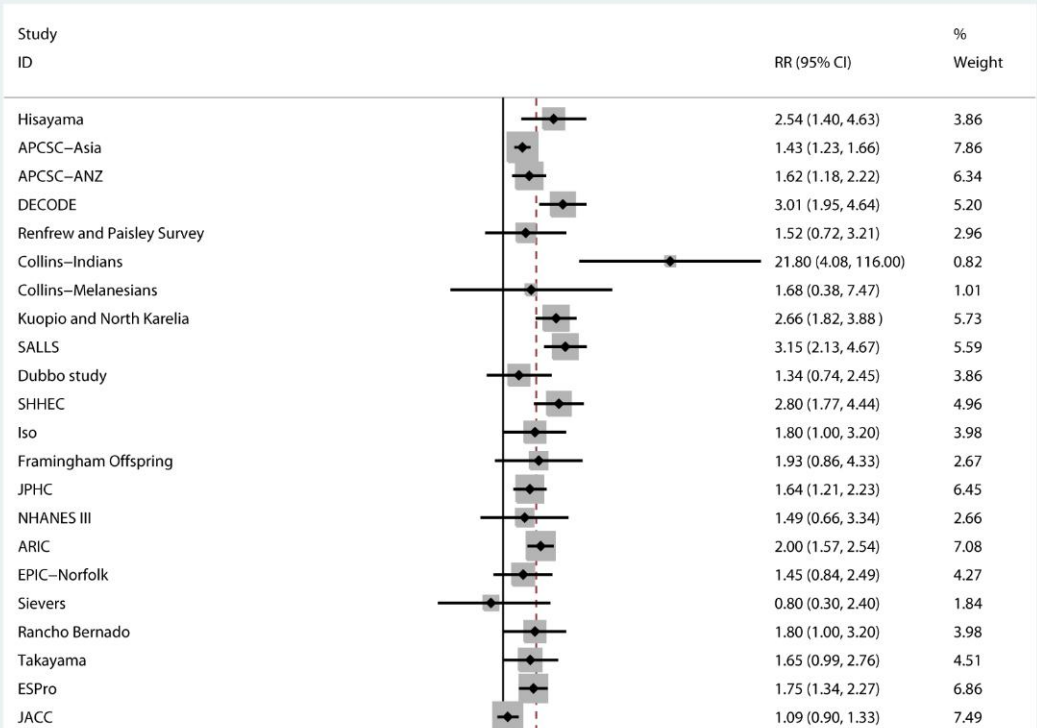


Figure S4. The summary results for DM and the risk of stroke in men

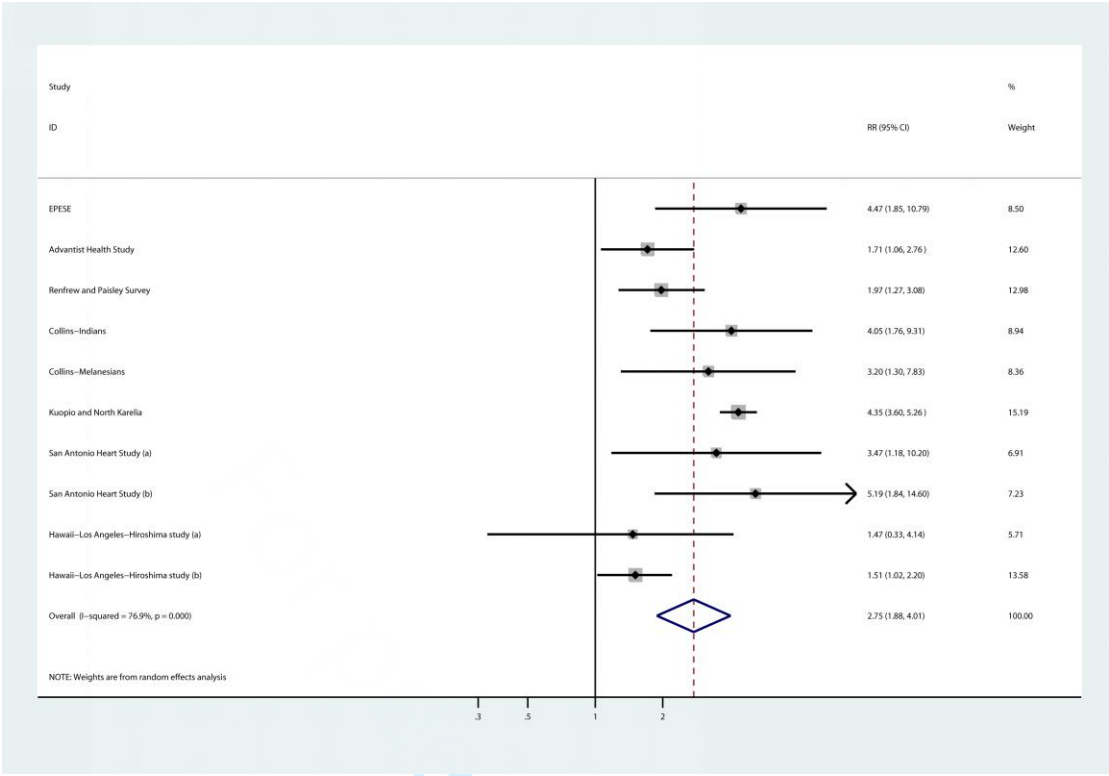


Figure S5. The summary results for DM and the risk of cardiac death in women

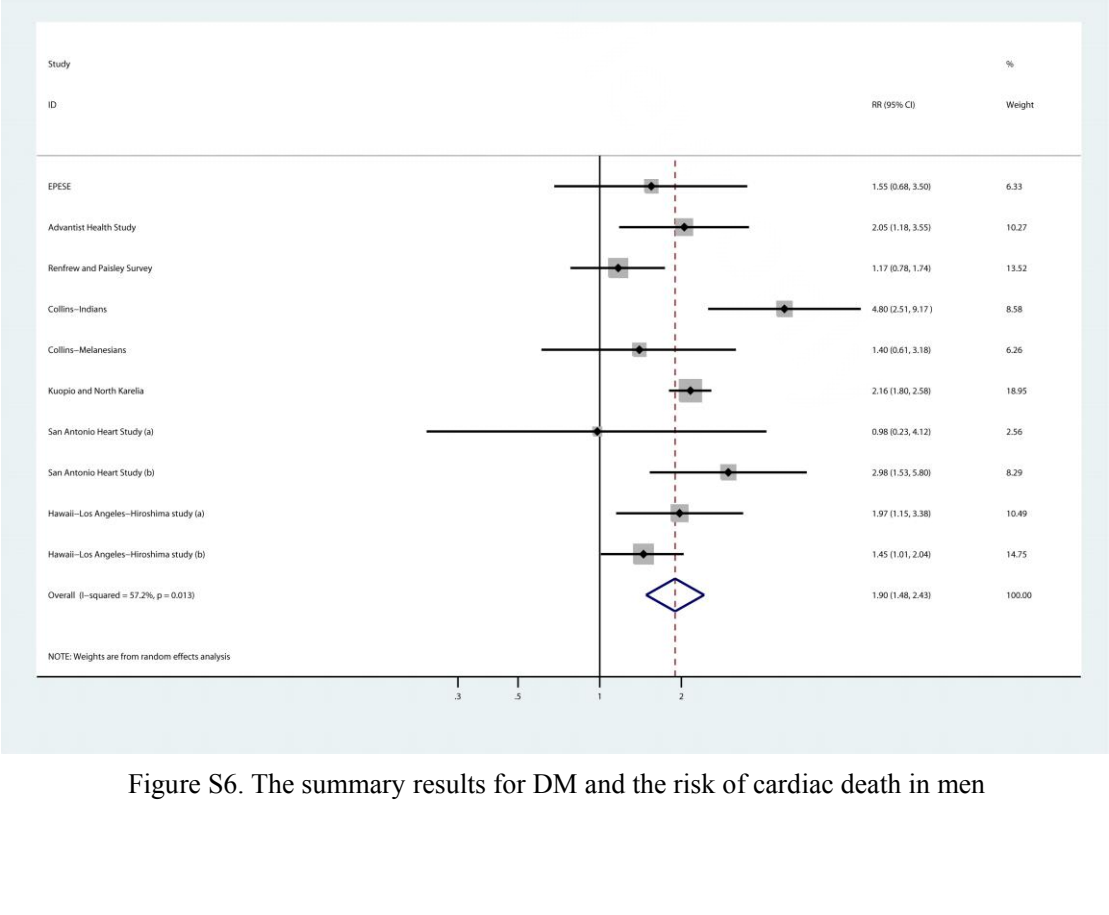


Figure S6. The summary results for DM and the risk of cardiac death in men

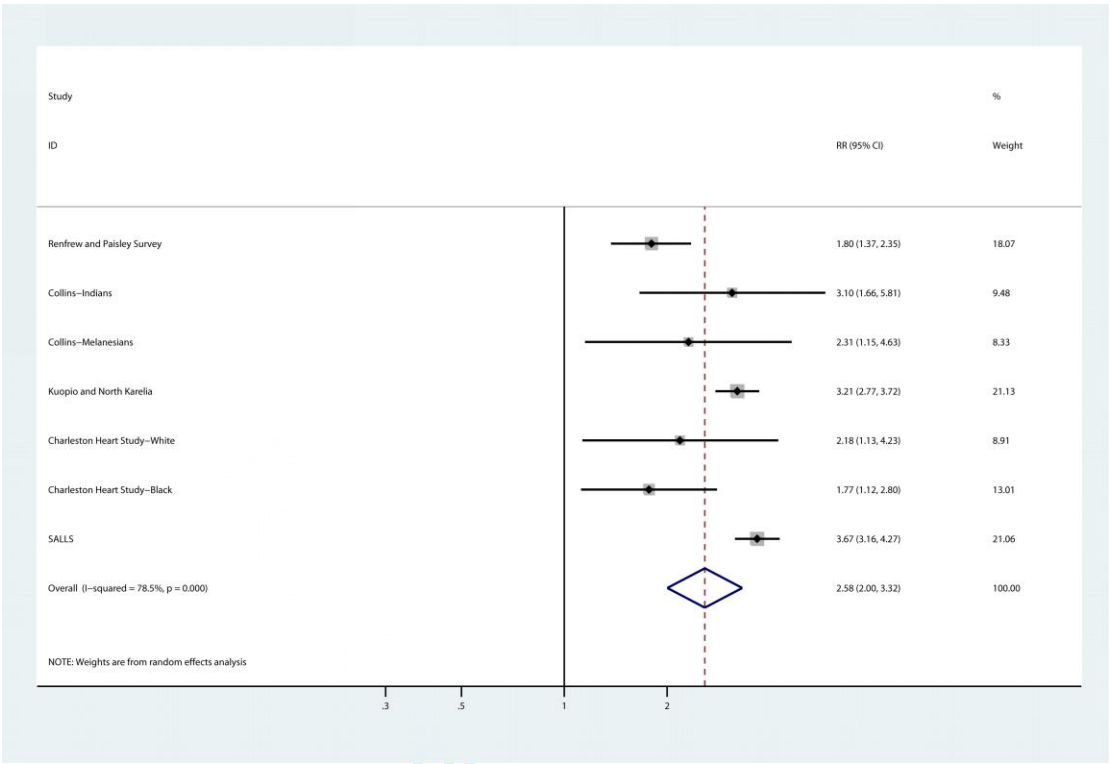


Figure S7. The summary results for DM and the risk of all-cause mortality in women

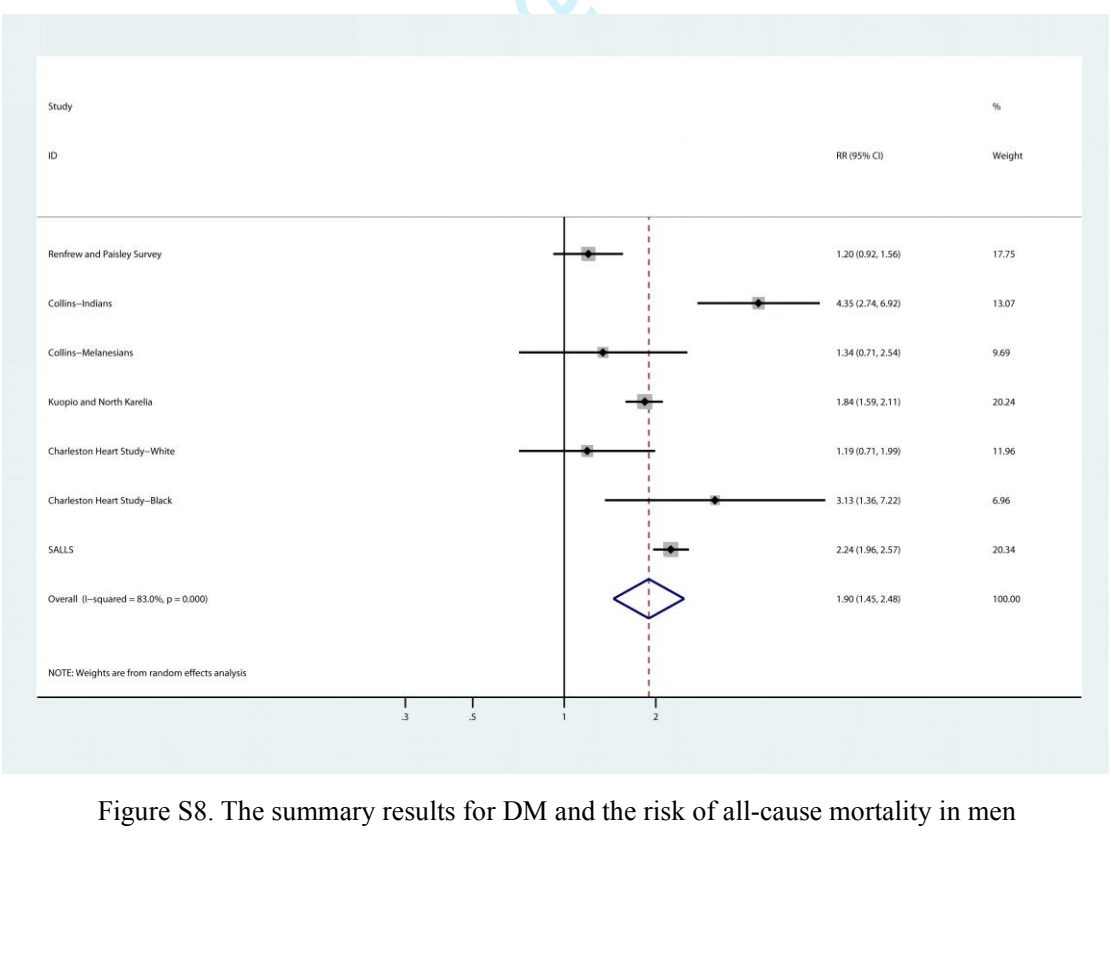


Figure S8. The summary results for DM and the risk of all-cause mortality in men

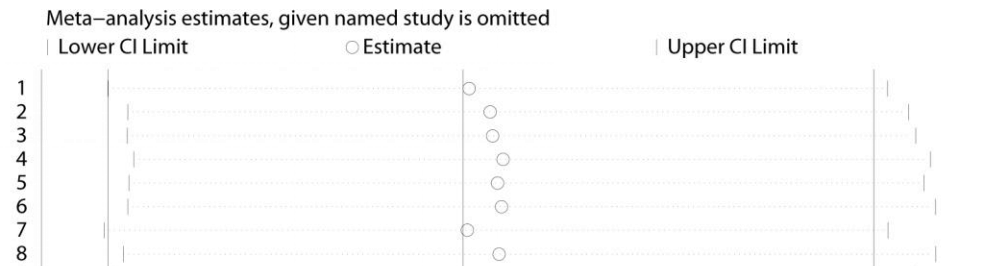


Figure S1. sensitivity analysis for CHD in women compared with men

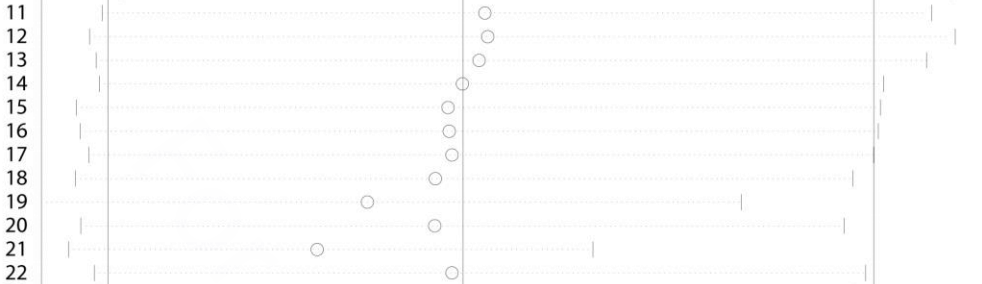


Figure S2. sensitivity analysis for stroke in women compared with men

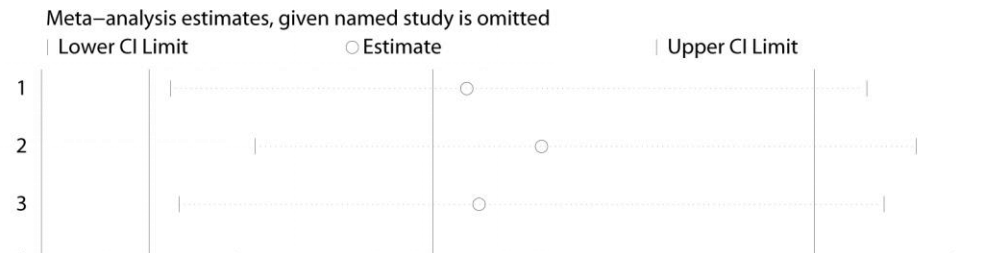


Figure S3. sensitivity analysis for cardiac death in women compared with men

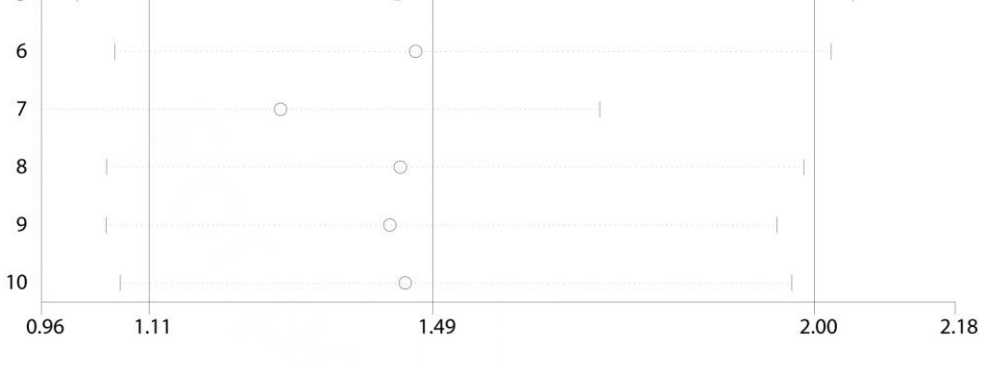
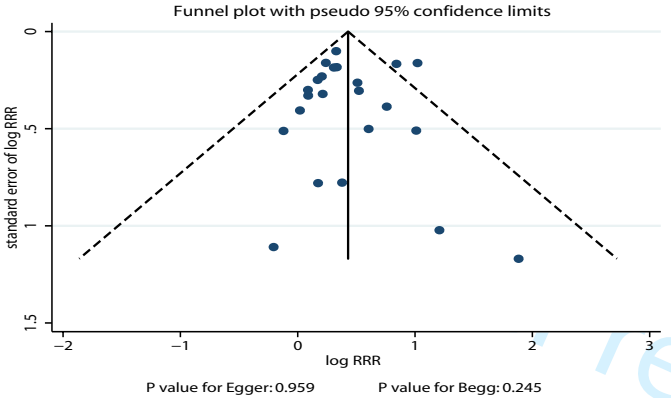
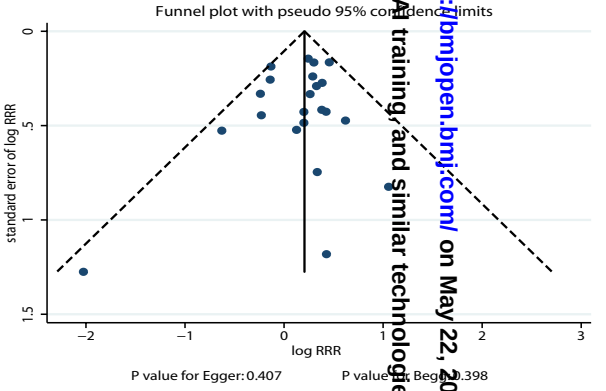


Figure S4. sensitivity analysis for all-cause mortality in women compared with men

A. CHD

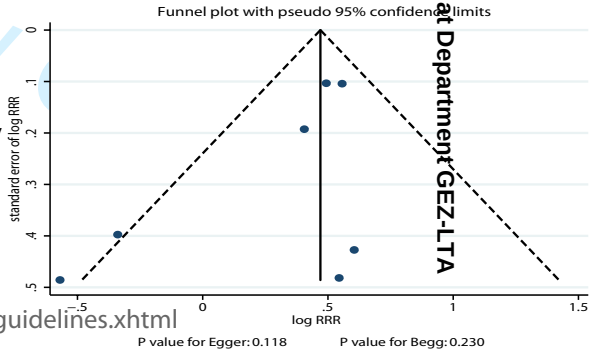


B. stroke



C. Cardiac death

D. All-cause mortality



MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of background should include		
Problem definition	Yes	3
Hypothesis statement	Yes	3
Description of study outcomes	Yes	3
Type of exposure or intervention used	Yes	3
Type of study designs used	Yes	3
Study population	Yes	3
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	Yes	4
Search strategy, including time period used in the synthesis and key words	Yes	4
Effort to include all available studies, including contact with authors	Yes	4
Databases and registries searched	Yes	4
Search software used, name and version, including special features used (eg explosion)	Yes	4
Use of hand searching (eg reference lists of obtained articles)	Yes	4
List of citations located and those excluded, including justification	Yes	4
Method of addressing articles published in languages other than English	Yes	4
Method of handling abstracts and unpublished studies	Yes	4
Description of any contact with authors	No	NA
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	No	NA
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	Yes	4
Documentation of how data were classified and coded (eg multiple raters, blinding and interrater reliability)	Yes	4
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	Yes	5
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Yes	5

Assessment of heterogeneity	Yes	5
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	5
Provision of appropriate tables and graphics	Yes	5
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Yes	6-7
Table giving descriptive information for each study included	Yes	17-20
Results of sensitivity testing (eg subgroup analysis)	Yes	21-22
Indication of statistical uncertainty of findings	Yes	6-8
Reporting of discussion should include		
Quantitative assessment of bias (eg publication bias)	Yes	8-
Justification for exclusion (eg exclusion of non-English language citations)	No	8-10
Assessment of quality of included studies	Yes	17-20
Strengths and weaknesses	Yes	10
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Yes	8-9
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	Yes	10
Guidelines for future research	Yes	10
Disclosure of funding source	Yes	11

NA: Not Applicable

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024935.R2
Article Type:	Research
Date Submitted by the Author:	28-Jun-2019
Complete List of Authors:	wang, hao; First Affiliated Hospital of Dalian Medical University Ba, Ying; First Affiliated Hospital of Dalian Medical University Cai, Run-Ce; First Affiliated Hospital of Dalian Medical University Xing, Qian; First Affiliated Hospital of Dalian Medical University
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Sex difference, diabetes mellitus, major cardiovascular outcomes, all-cause mortality, meta-analysis

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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Running title: Sex difference of DM and major cardiovascular outcomes

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Keywords: sex difference; diabetes mellitus; major cardiovascular outcomes; all-cause mortality; meta-analysis

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% confidence interval (CI) 1.32–1.76]; P<0.001), stroke (RRR 1.23 [95% CI 1.09–1.39]; P=0.001), cardiac death (RRR 1.49 [95% CI 1.11–2.00]; P=0.009), and all-cause mortality (RRR 1.51 [95% CI 1.23–1.85]; 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 to men with DM.

ARTICLE SUMMARY:

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 generalizability 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 Supplemental 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 (4 items), comparability (1 item), and outcome (3 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% confidence interval (CI) of each individual study. Given the low prevalence of CHD, stroke, cardiac death, or all-cause mortality, odds ratios could be assumed to be accurate estimates of RR. Furthermore, hazard ratio was regarded to be equivalent to 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 (i.e., 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, < 10,000); assessment of DM (self-reported, measured, or both); follow-up duration (≥ 10, < 10 years); adjustment for other cardiovascular risk factors (yes, no); and study quality (high versus 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 version 10.0 (StataCorp, College Station, TX, USA).

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 Supplemental 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 to 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 had a score of 7, and the remaining 9 had a score of 6 (Supplemental file 3).

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	US	7381	407	40-77	55.0	Self-reported	9.0	Age, SBP, smoking, BMI, TC	7
Rancho Bernado [27]	1988	US	3778	320	50-79	54.0	Self-reported	12.0	Age, SBP, TC, smoking, obesity, family history, oestrogen use	6
ARIC [28]	1989	US	15732	1610	45-64	55.0	Measured	18.0	Age, SBP, smoking, BMI, TC	7
Advantist Health Study [29]	1992	US	27658	656	>25	63.0	Measured	6.0	Age, hypertension, smoking, BMI, PA	6
Sievers [30]	1992	US	5131	1266	15-84	52.0	Measured	10.0	Age	7
EPESE [31]	1993	US	2812	386	>65	58.0	Self-reported	6.0	Age, AHT use, smoking, BMI, diabetes, angina, chest pain on exertion	6
Charleston Heart Study-White [32]	1993	US	1394	38	>35	53.0	Measured	30.0	Age	6
Charleston Heart Study-Black [32]	1993	US	787	37	>35	58.0	Measured	30.0	Age	6
NHANES III [33]	1994	US	18603	1290	18-90	46.0	Self-reported or measured	13.0	Age, SBP, smoking, BMI, 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, prior CH	6
Collins-Indians [35]	1996	Fiji	1220	166	>20.0	55.0	Measured	11.0	Age, SBP, smoking, BMI, TC, survey area	6
Collins-Melanesians [35]	1996	Fiji	1324	65	>20.0	53.0	Measured	11.0	Age, SBP, smoking, BMI, TC, survey area	6
SALLS [36]	1998	Sweden	39055	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, ECG abnormalities	6
Reykjavik study [38]	2002	Iceland	18519	295	32-60	52.0	Self-reported or measured	17.0	Age, hypertension, smoking, BMI, TC, triacylglycerols, diabetes, glucose, prior CHD, LVH	8
APCSC-Asia [39]	2003	27 cohorts in Asia	436832	17763	>20	33.0	Self-reported or measured	7.0	Age, SBP, smoking, BMI, TC	7
APCSC-Australia and New Zealand [39]	2003	9 cohorts in Australia and New Zealand	99624	4784	>20	45.0	Self-reported or measured	7.0	Age, SBP, smoking, BMI, TC	7

Framingham study [40]	2003	2 cohorts in US	5243	229	35-75	52.0	Measured	20.0	Age, hypertension, smoking, BMI, TC	7
Iso [41]	2004	Japan	10582	267	40-69	60.0	Measured	17.0	Age, hypertension, smoking, BMI, TC, HDL, skinfold, alcohol, community, menopause	8
Renfrew and Paisley Survey [42]	2005	Scotland	15426	228	45-64	54.0	Self-reported or measured	25.0	Age, SBP, smoking, BMI, TC, SES	8
Kuopio and North Karelia [43]	2005	Finland	51735	1108	25-74	51.0	Self-reported	17.0	Age, SBP, smoking, BMI, TC, study year	8
Strong Heart Study [44]	2006	US	4372	724	45-74	61.0	Measured	12.0	Age, SBP, DBP, smoking, HDL, LDL, albuminuria	7
Framingham Offspring [45]	2006	US	2097	99	50-81	50.0	Measured	14.0	Age, SBP, AHT, CVD, atrial fibrillation, LVH, smoking	7
San Antonio Heart Study [46]	2007	US	4996	524	25-64	57.0	Measured	16.0	Age, ethnicity	7
SHHEC [47]	2007	Scotland	13343	184	30-74	51.0	Measured	16.0	Age, SBP, smoking, BMI, TC	7
EPIC-Norfolk [48]	2008	UK	22516	441	40-79	55.0	Self-reported	10.0	Age, SBP, smoking, BMI, TC, triglycerides	8

Takayama [49]	2008	Japan	29079	1217	>35	54.0	Self-reported	7.0	Age, hypertension, smoking, BMI, PA, education, energy, vegetables, fat, alcohol	8
DECODE [50]	2009	7 cohorts in Finland and Sweden	9278	826	40-69	55.0	Measured	5-21	Age, hypertension, smoking, BMI, TC, HDL	6
Hisayama [51]	2010	Japan	2421	291	40-79	57.0	Measured	14.0	Age, SBP, smoking, BMI, TC, HDL, alcohol intake, PA,ECG abnormalities	7
JPHC [52]	2011	2 cohorts in Japan	35657	2034	40-69	63.0	Measured	12.0	Age, SBP, AHT, smoking, BMI, TC, HDL, triglycerides, alcohol, fasting status, residential areas	8
HUNT 1 [53]	2012	Norway	47951	1992	>20	52.0	Self-reported	17.0	Age, hypertension, smoking, BMI, CVD, PA	8
ESPro [54]	2017	Germany	105000	7190	>18	51.0	Self-reported or measured	14.0	Calendar year, age	7
JACC [55]	2017	Japan	104910	5729	40-79	58.0	Self-reported	19.0	Age, education, smoking, alcohol, PA, BMI, history of hypertension, or history of DM	8

*AHT, anti-hypertensive; ApoB, apolipoprotein B; CVD, cardiovascular disease; DBP, diastolic BP; LPa, lipoprotein a; LVH, left ventricle hypertrophy; NA, notavailable; PA, physical activity; SALLS, Swedish Annual Level-of-Living Survey; SBP, systolic BP; SES, socioeconomic status

CHD

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 Supplemental 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 1.32–1.76; 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 (Supplemental 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).

Table 2. Subgroup analyses for CHD

Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square (%)	P value for heterogeneity	P value for Meta-regression
Publication year	Before 2010	20	1.53 (1.28-1.82)	<0.001	39.6	0.036	0.260
	2010 or after	3	1.42 (1.20-1.68)	<0.001	0.0	0.421	
Country	Western	18	1.50 (1.27-1.77)	<0.001	43.6	0.025	0.934
	Eastern	5	1.58 (1.17-2.13)	0.003	6.7	0.368	
Sample size	≥10000	9	1.62 (1.31-2.00)	<0.001	65.4	0.003	0.119
	<10000	14	1.34 (1.09-1.63)	0.004	0.0	0.780	
Assessment of DM	Self-reported	6	1.75 (1.29-2.37)	<0.001	74.6	0.001	0.073
	Measured	13	1.32 (1.09-1.61)	0.005	0.0	0.764	
	Both	4	1.39 (1.11-1.75)	0.005	0.0	0.730	
Follow-up duration (years)	≥10	16	1.69 (1.41-2.04)	<0.001	43.1	0.034	0.032
	<10	6	1.22 (0.98-1.52)	0.078	0.0	0.948	
Adjusted other CVD risk factors	Yes	19	1.45 (1.29-1.62)	<0.001	6.6	0.375	<0.001
	No	4	2.56 (1.89-3.46)	<0.001	0.0	0.423	

Study quality	High	13	1.46 (1.29-1.66)	<0.001	10.6	0.339	0.052
	Low	10	1.64 (1.14-2.36)	0.007	47.8	0.045	

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 (Supplemental file 4). The pooled RRR (female to male) suggested that women with DM had an increased risk for stroke compared to men with DM (RRR 1.23 [95% CI 1.09–1.39]; 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 (Supplemental 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).

Table 3. Subgroup analyses for stroke

Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square (%)	P value for heterogeneity	P value for Meta-regression
Publication year	Before 2010	18	1.29 (1.11-1.50)	0.001	0.0	0.640	0.269
	2010 or after	4	1.11 (0.89-1.40)	0.353	18.1	0.300	
Country	Western	15	1.23 (1.05-1.44)	0.011	0.0	0.587	0.998
	Eastern	7	1.20 (0.97-1.49)	0.091	14.7	0.318	
Sample size	≥10000	14	1.25 (1.10-1.42)	<0.001	0.0	0.531	0.341
	<10000	8	1.04 (0.72-1.50)	0.840	0.0	0.493	
Assessment of DM	Self-reported	6	1.28 (1.04-1.58)	0.022	0.0	0.668	0.423
	Measured	11	1.32 (1.08-1.61)	0.008	0.0	0.508	

	Both	5	1.09 (0.85-1.41)	0.484	21.3	0.279	
Follow-up duration (years)	≥10	18	1.28 (1.11-1.47)	0.001	0.0	0.726	0.313
	<10	4	1.09 (0.76-1.57)	0.627	36.0	0.196	
Adjusted other CVD risk factors	Yes	19	1.27 (1.11-1.44)	<0.001	0.0	0.695	0.237
	No	3	1.14 (0.71-1.83)	0.586	40.4	0.187	
Study quality	High	16	1.24 (1.09-1.41)	0.001	0.0	0.533	0.617
	Low	6	1.13 (0.79-1.61)	0.498	2.4	0.401	

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 (Supplemental file 4). The pooled RRR (female to male) of DM versus non-DM for risk for cardiac death was 1.49 (95% CI 1.11–2.00; 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 (Supplemental 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).

Table 4. Subgroup analyses for cardiac death

Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square (%)	P value for heterogeneity	P value for Meta-regression
Publication year	Before 2010	10	1.49 (1.11-2.00)	0.009	31.9	0.153	-
	2010 or after	0	-	-	-	-	
Country	Western	7	1.84 (1.45-2.32)	<0.001	3.6	0.399	0.010
	Eastern	3	0.97 (0.62-1.51)	0.891	0.0	0.870	

Sample size	≥10000	2	1.96 (1.54-2.49)	<0.001	0.0	0.591	0.015
	<10000	8	1.18 (0.85-1.64)	0.322	0.0	0.433	
Assessment of DM	Self-reported	2	2.05 (1.59-2.64)	<0.001	0.0	0.568	0.016
	Measured	7	1.10 (0.78-1.54)	0.588	0.0	0.586	
	Both	1	1.68 (0.93-3.06)	0.087	-	-	
Follow-up duration (years)	≥10	8	1.57 (1.18-2.09)	0.002	21.8	0.256	0.257
	<10	2	1.41 (0.42-4.68)	0.576	66.5	0.084	
Adjusted other CVD risk factors	Yes	8	1.42 (1.02-1.98)	0.040	44.0	0.085	0.575
	No	2	2.18 (0.79-6.03)	0.132	0.0	0.524	
Study quality	High	4	1.97 (1.56-2.48)	<0.001	0.0	0.864	0.006
	Low	6	1.10 (0.78-1.55)	0.593	0.0	0.417	

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 (Supplemental file 4). The pooled 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 1.23–1.85]; 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 (Supplemental 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).

Table 5. Subgroup analyses for all-cause mortality

Outcomes	Variable	Group	Number of cohorts	RRR and 95%CI	P value	I-square (%)	P value for heterogeneity	P value for Meta-regression

All-cause mortality	Publication year	Before 2010	7	1.51 (1.23-1.85)	<0.001	38.2	0.138	-
		2010 or after	0	-	-	-	-	
	Country	Western	6	1.63 (1.41-1.88)	<0.001	8.2	0.364	0.039
		Eastern	1	0.71 (0.33-1.55)	0.394	-	-	
	Sample size	≥10000	3	1.66 (1.46-1.90)	<0.001	0.0	0.772	0.050
		<10000	4	1.06 (0.59-1.90)	0.844	43.7	0.149	
	Assessment of DM	Self-reported	2	1.69 (1.46-1.95)	<0.001	0.0	0.669	0.123
		Measured	4	1.06 (0.59-1.90)	0.844	43.7	0.149	
		Both	1	1.50 (1.03-2.19)	0.035	-	-	
	Follow-up duration (years)	≥10	7	1.51 (1.23-1.85)	<0.001	38.2	0.138	-
		<10	0	-	-	-	-	
	Adjusted other CVD risk factors	Yes	4	1.50 (1.12-2.01)	0.006	39.4	0.176	0.850
		No	3	1.33 (0.75-2.36)	0.321	57.6	0.095	
	Study quality	High	2	1.69 (1.41-2.02)	<0.001	0.0	0.490	0.414
		Low	5	1.25 (0.80-1.94)	0.329	53.3	0.073	

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 (Supplemental 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 females with DM have an increased risk for CHD or stroke compared to 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 to men with DM.[14] However, sex differences regarding other important outcomes (cardiac death, 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 to men with D. The excess risk for cardiac death in women with DM could be due to the higher risk for CHD 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 to 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 cardiovascular disease in most of the included cohorts, and may explain the significant sex differences in the association between DM and all-cause mortality. Finally, the corresponding 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 pre-defined factors. First, publication year affected sex differences in the risk for stroke, which may be due to advances in diagnostic approaches. Second, country (i.e., 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 CHD patients than studies with shorter follow-up, which contributed to the higher weight in pooled results and made it easier to detect small 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 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 generalizability 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 to 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.

Author Contributions

Hao Wang contributed to conception and design; Hao Wang, Ying Ba, Run-Ce Cai, and Qian Xing contributed to acquisition, analysis and interpretation of data; Hao Wang and Qian Xing were involved in drafting or critical revision of the manuscript. All the authors approved the final version.

Conflict of interests: All authors declare no conflict of interest.

Funding statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing statement: No additional data available.

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Figure legends:

Figure 1. Sex differences in the associations between diabetes mellitus (DM) and the risk for coronary heart disease (CHD) (A) and stroke (B).

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

Supporting Information Legends:

Supplemental file 1: Search strategy in PubMed.

Supplemental file 2: Flowchart illustrating the study selection process.

Supplemental file 3: Newcastle-Ottawa scale for included studies.

Supplemental file 4: Summary of results for diabetes mellitus (DM) and coronary heart disease (CHD) stroke, cardiac death, and all-cause mortality in men and women separately.

Supplemental file 5: Sensitivity analyses for coronary heart disease (CHD), stroke, cardiac death, and all-cause mortality

Supplemental file 6: Funnel plots for coronary heart disease (CHD), stroke, cardiac death, and all-cause mortality.

Checklist S1: MOOSE Checklist

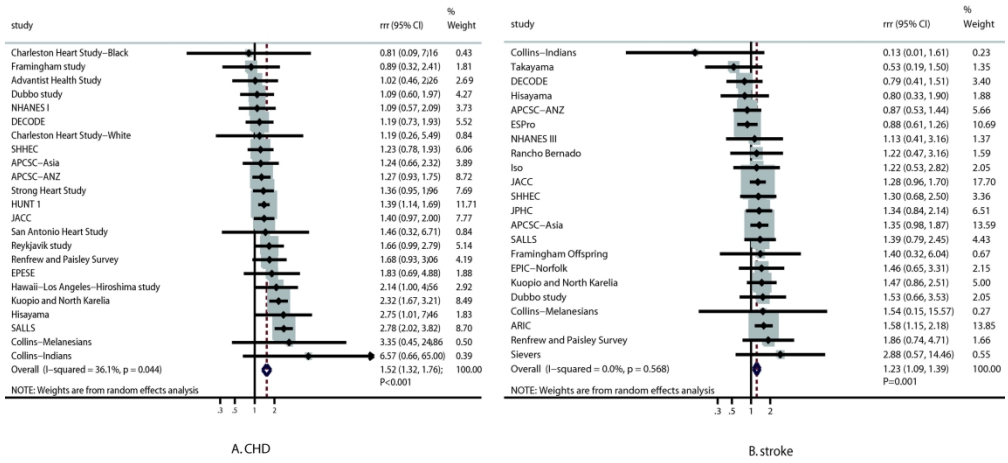

Figure 1. Sex differences in the associations between diabetes mellitus (DM) and the risk for coronary heart disease (CHD) (A) and stroke (B).

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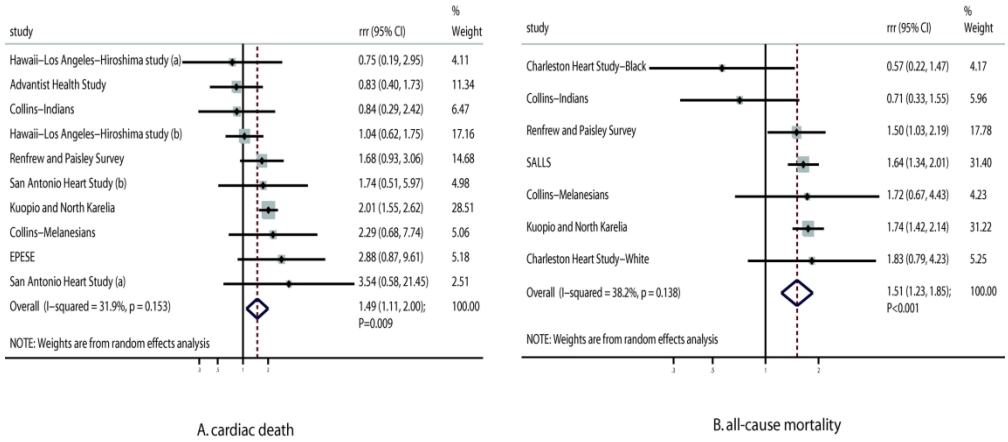

Figure 2. Sex differences in the associations between diabetes mellitus (DM) and the risk for cardiac death (A) and all-cause mortality (B).

227x104mm (300 x 300 DPI)

Searching strategy in PubMed:

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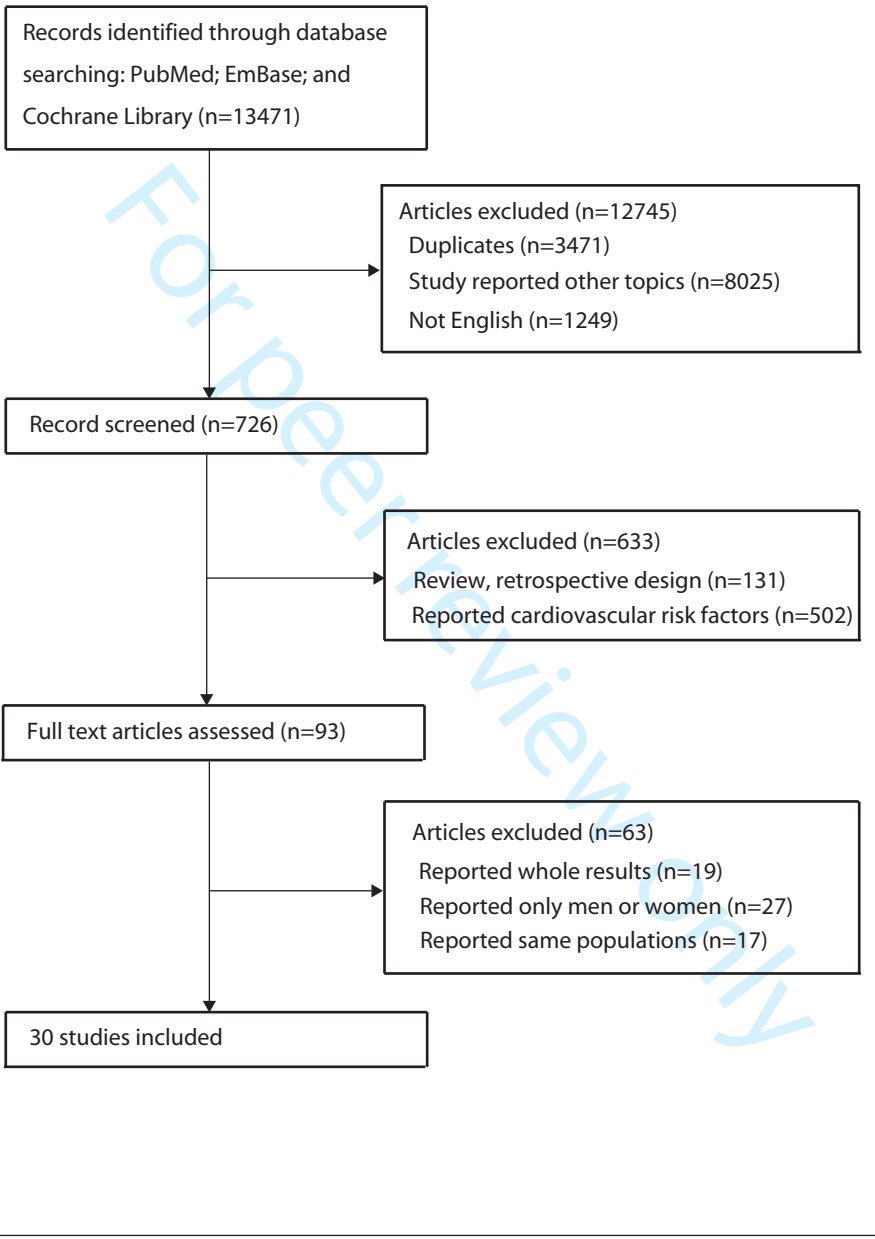


Table S1. Quality scores of prospective cohort studies using Newcastle-Ottawa Scale.

Study	Selection				Comparability	Outcome			NOS
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of DM	Demonstration that outcomes was not present at start of study	Comparability on the basis of the design or analysis	Assessment of outcome	Adequate follow-up duration	Adequate follow-up rate	Overall score
NHANES I [26]	1	1	1	0	1	1	1	1	7
Rancho Bernado [27]	0	1	1	0	1	1	1	1	6
ARIC [28]	1	1	1	0	1	1	1	1	7
Advantist Health Study [29]	1	0	1	1	1	1	0	1	6
Sievers [30]	0	1	1	1	1	1	1	1	7
EPESE [31]	0	1	1	1	1	1	0	1	6
Charleston Heart Study-White [32]	0	1	1	1	1	1	1	0	6
Charleston Heart Study-Black [32]	0	1	1	1	1	1	1	0	6
NHANES III [33]	1	1	1	0	1	1	1	1	7
Dubbo study [34]	0	1	1	1	1	1	0	1	6
Collins-Indians [35]	0	1	1	0	1	1	1	1	6
Collins-Melanesians [35]	0	1	1	0	1	1	1	1	6
SALLS [36]	1	1	1	0	1	1	1	0	6
Hawaii-Los Angeles-Hiroshima study [37]	0	1	1	0	1	1	1	1	6

Reykjavik study [38]	1	1	1	1	1	1	1	1	8
APCSC-Asia [39]	1	1	1	0	1	1	1	1	7
APCSC-Australia and New Zealand [39]	1	1	1	0	1	1	1	1	7
Framingham study [40]	0	1	1	1	1	1	1	1	7
Iso [41]	1	1	1	1	1	1	1	1	8
Renfrew and Paisley Survey [42]	1	1	1	1	1	1	1	1	8
Kuopio and North Karelia [43]	1	1	1	1	1	1	1	1	8
Strong Heart Study [44]	0	1	1	1	1	1	1	1	7
Framingham Offspring [45]	0	1	1	1	1	1	1	1	7
San Antonio Heart Study [46]	0	1	1	1	1	1	1	1	7
SHHEC [47]	1	1	1	0	1	1	1	1	7
EPIC-Norfolk [48]	1	1	1	1	1	1	1	1	8
Takayama [49]	1	1	1	1	2	1	0	1	8
DECODE [50]	0	1	1	1	1	1	0	1	6
Hisayama [51]	0	1	1	1	1	1	1	1	7
JPHC [52]	1	1	1	1	1	1	1	1	8
HUNT 1 [53]	1	1	1	1	1	1	1	1	8

ESPro [54]	1	1	1	1	1	1	1	0	7
JACC [55]	1	1	1	1	1	1	1	1	8

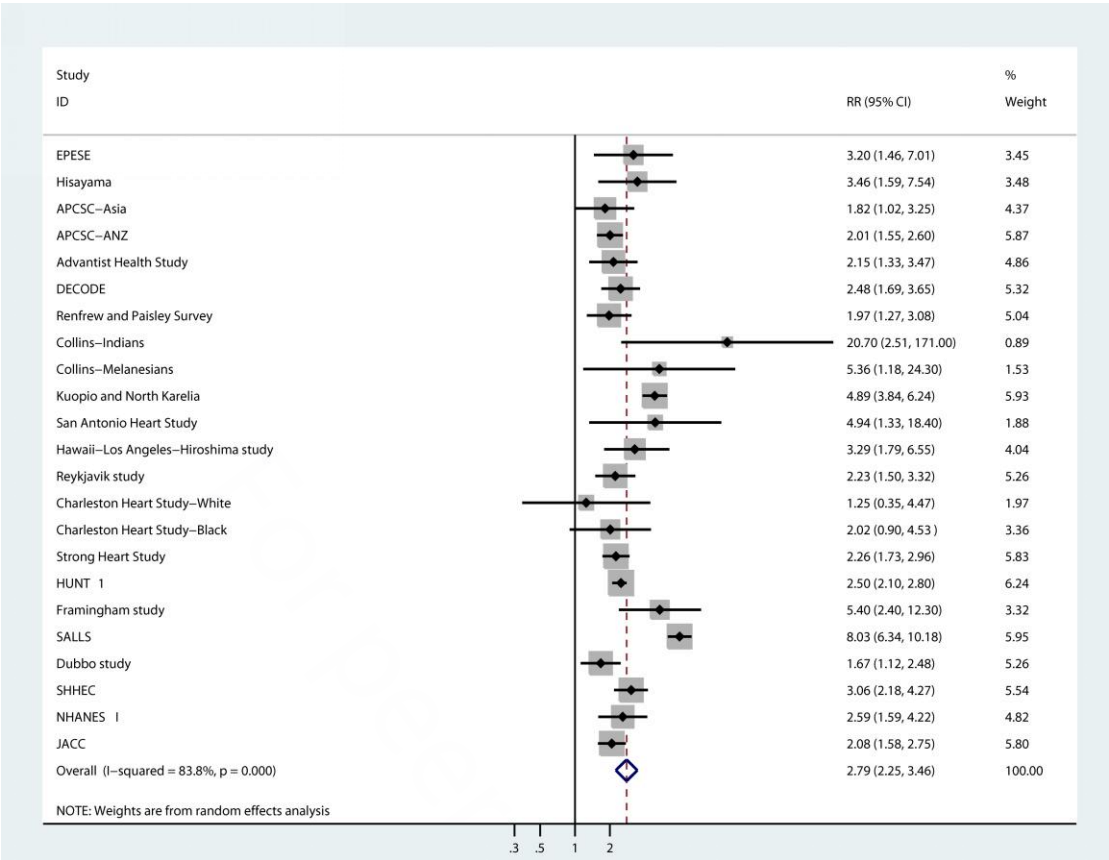


Figure S1. The summary results for DM and the risk of CHD in women

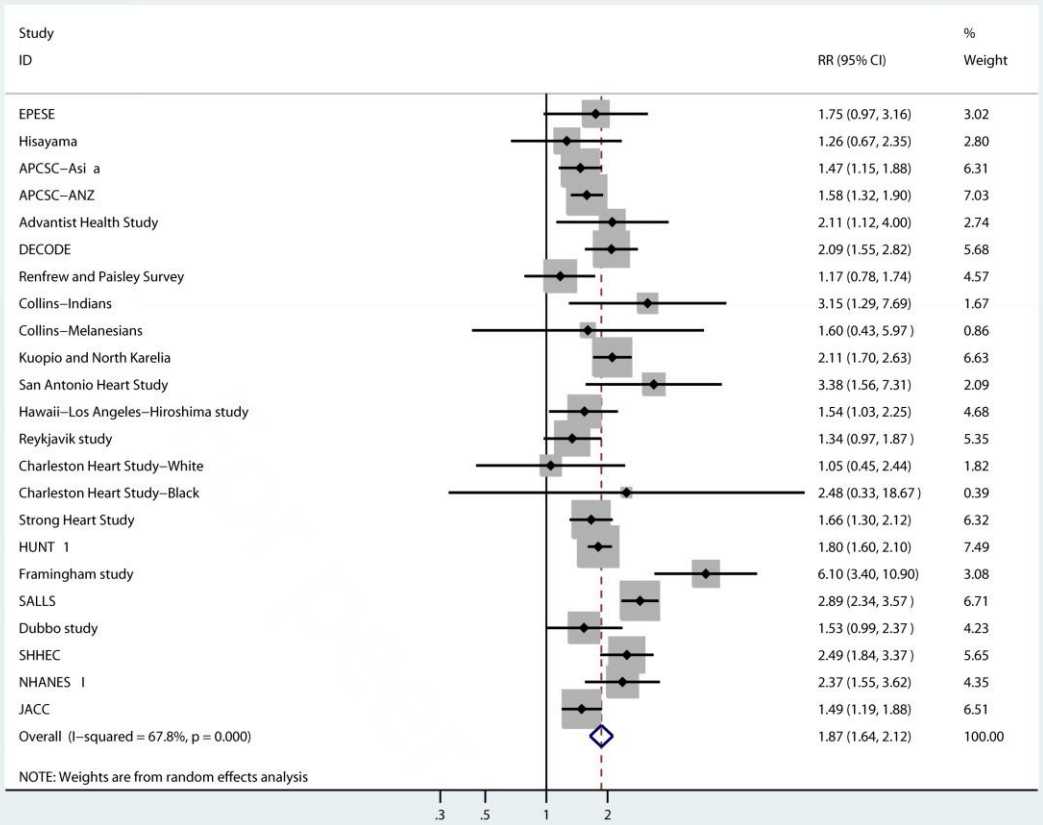


Figure S2. The summary results for DM and the risk of CHD in men

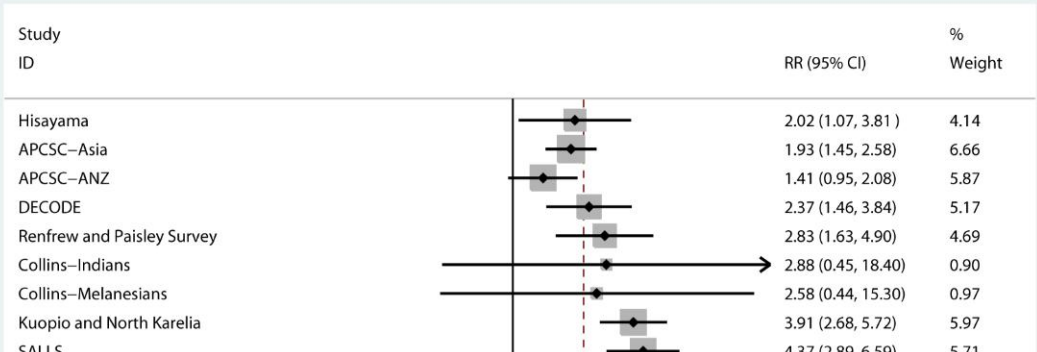


Figure S3. The summary results for DM and the risk of stroke in women

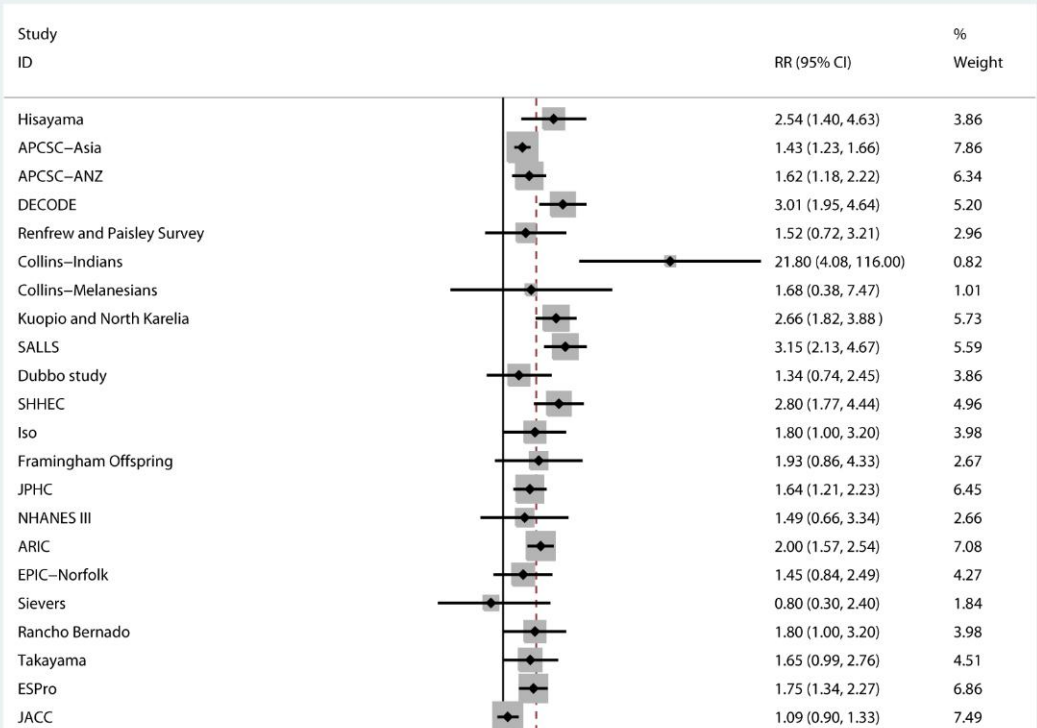


Figure S4. The summary results for DM and the risk of stroke in men

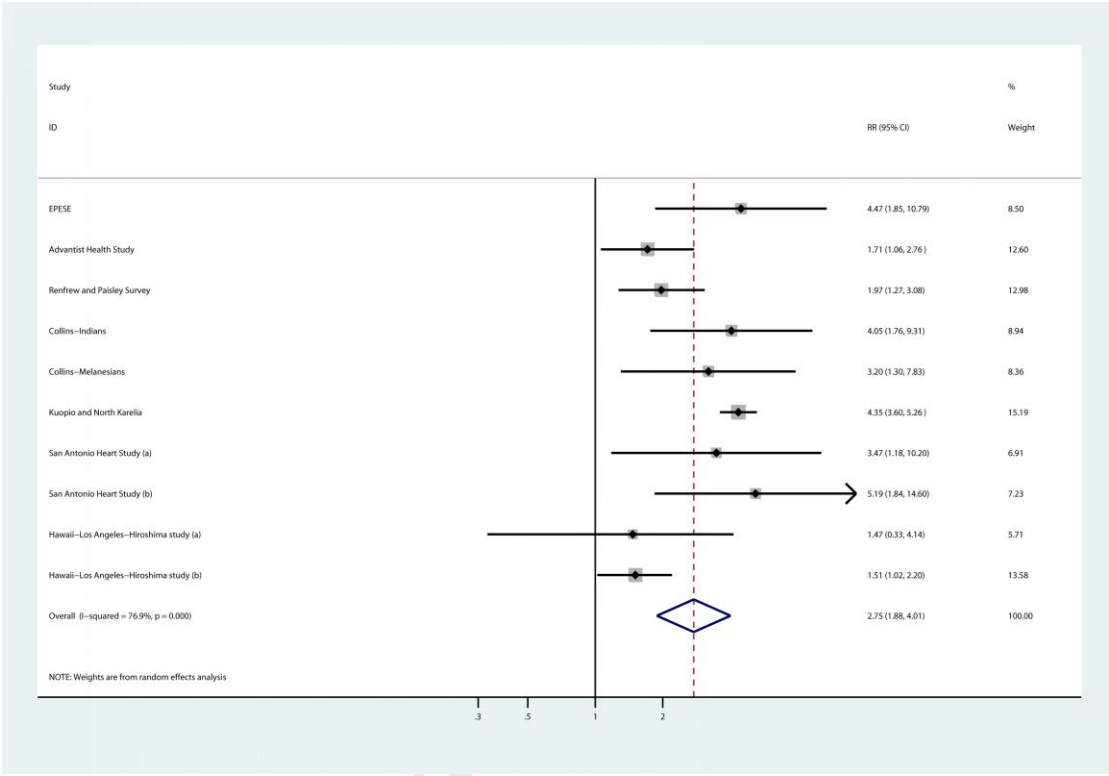


Figure S5. The summary results for DM and the risk of cardiac death in women

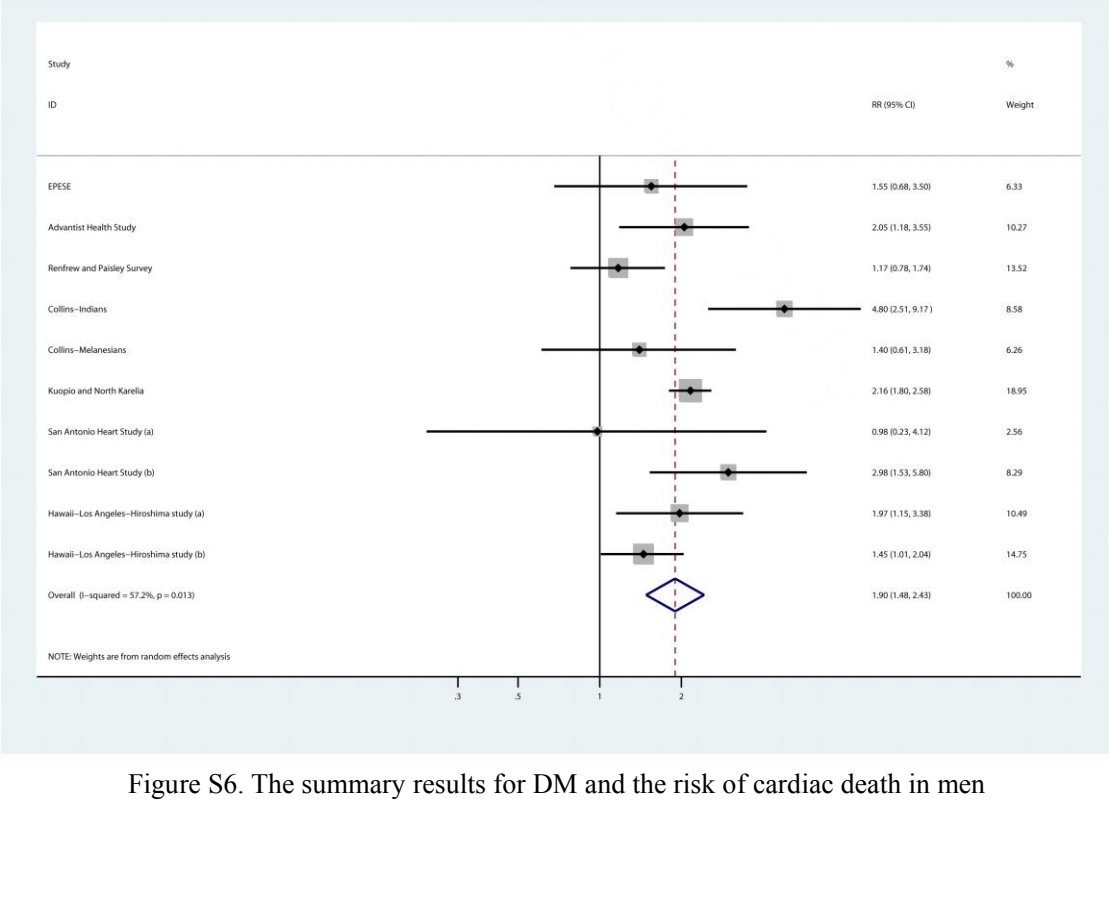


Figure S6. The summary results for DM and the risk of cardiac death in men

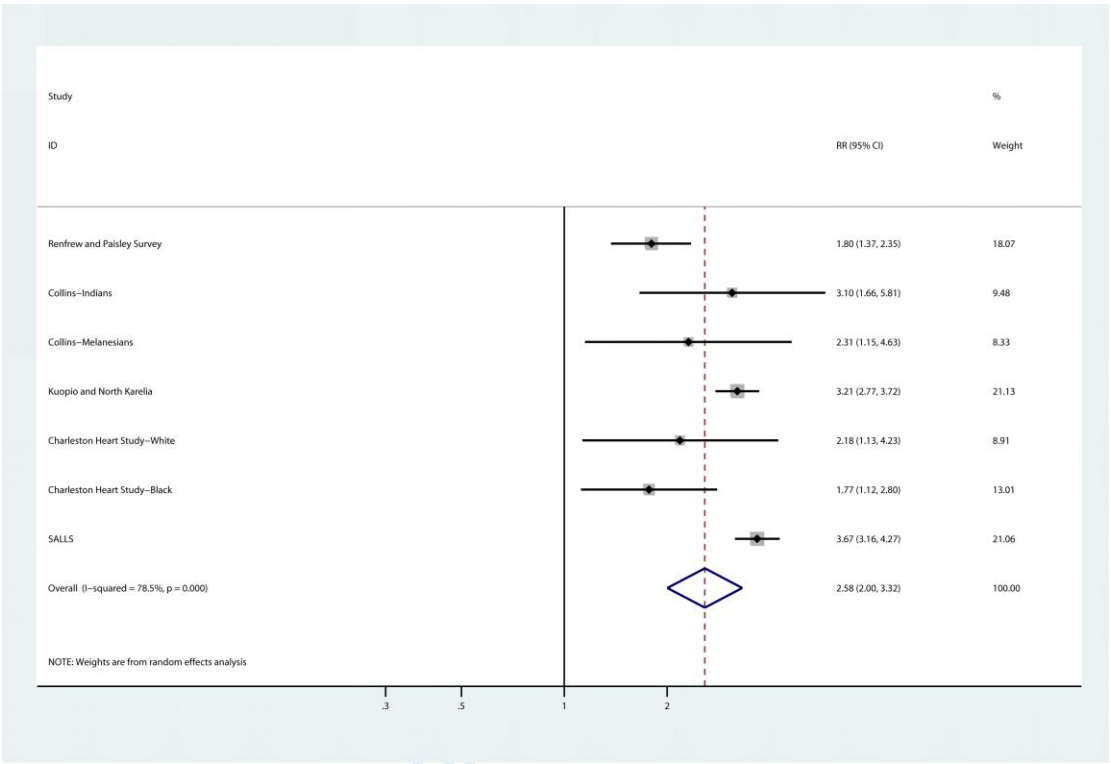


Figure S7. The summary results for DM and the risk of all-cause mortality in women

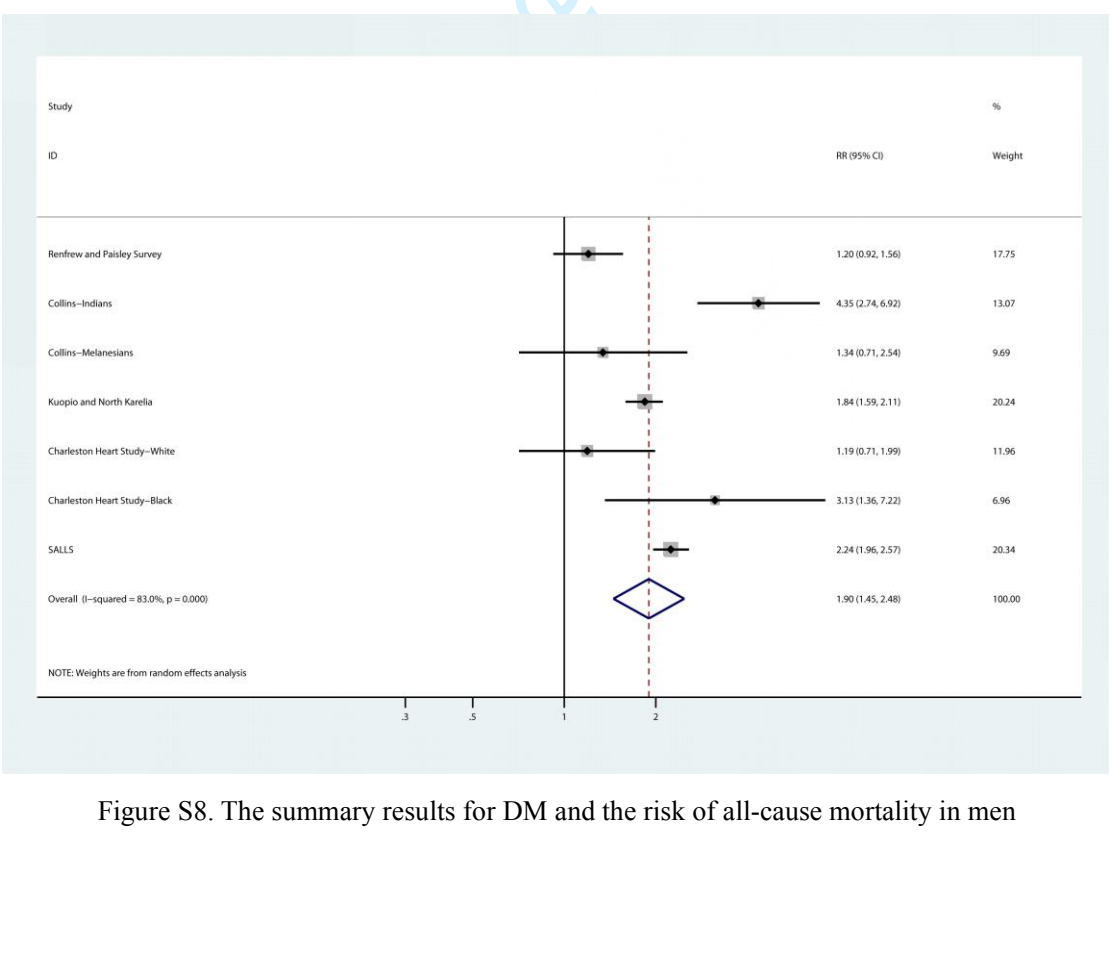


Figure S8. The summary results for DM and the risk of all-cause mortality in men

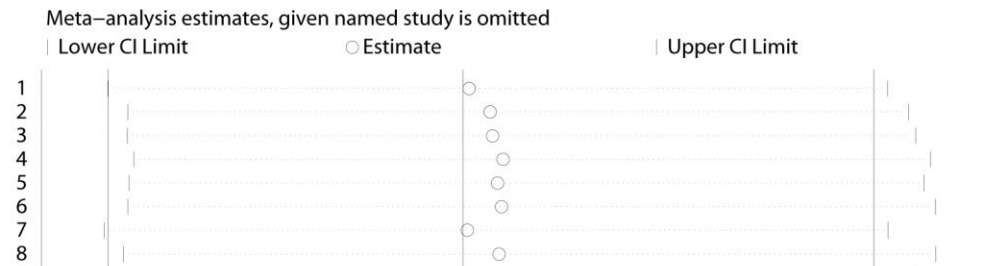


Figure S1. sensitivity analysis for CHD in women compared with men

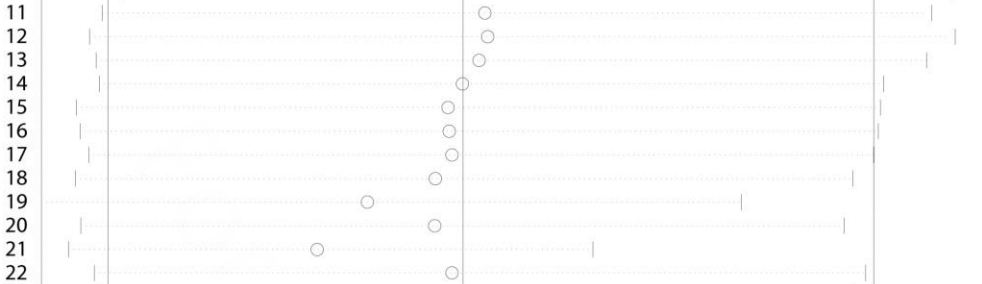


Figure S2. sensitivity analysis for stroke in women compared with men

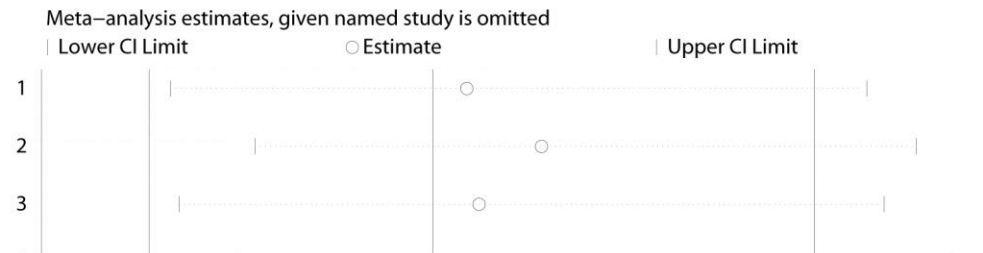


Figure S3. sensitivity analysis for cardiac death in women compared with men

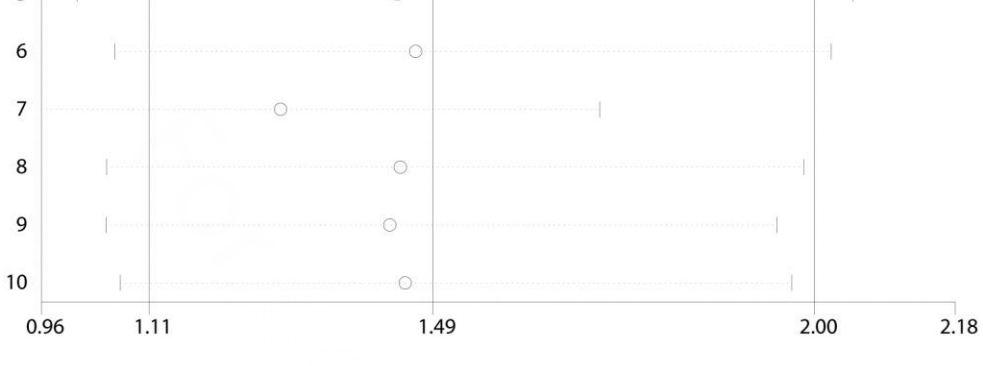
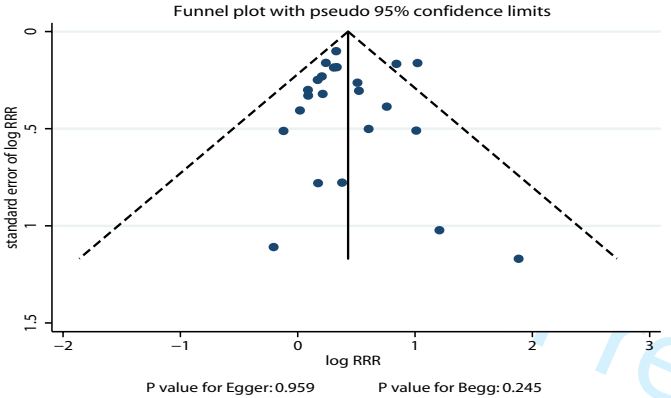
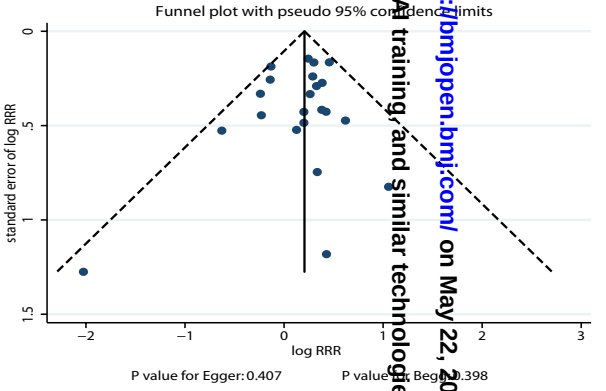


Figure S4. sensitivity analysis for all-cause mortality in women compared with men

A. CHD

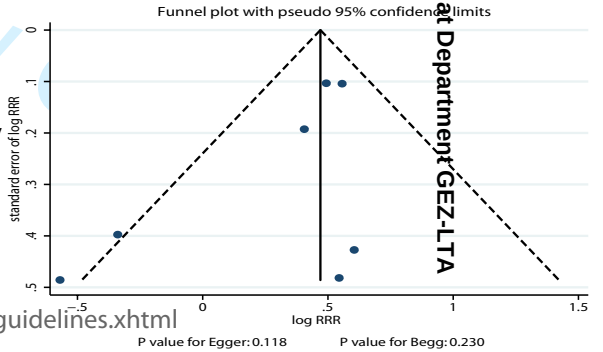


B. stroke



C. Cardiac death

D. All-cause mortality



MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of background should include		
Problem definition	Yes	3
Hypothesis statement	Yes	3
Description of study outcomes	Yes	3
Type of exposure or intervention used	Yes	3
Type of study designs used	Yes	3
Study population	Yes	3
Reporting of search strategy should include		
Qualifications of searchers (eg librarians and investigators)	Yes	4
Search strategy, including time period used in the synthesis and key words	Yes	4
Effort to include all available studies, including contact with authors	Yes	4
Databases and registries searched	Yes	4
Search software used, name and version, including special features used (eg explosion)	Yes	4
Use of hand searching (eg reference lists of obtained articles)	Yes	4
List of citations located and those excluded, including justification	Yes	4
Method of addressing articles published in languages other than English	Yes	4
Method of handling abstracts and unpublished studies	Yes	4
Description of any contact with authors	No	NA
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	No	NA
Rationale for the selection and coding of data (eg sound clinical principles or convenience)	Yes	4
Documentation of how data were classified and coded (eg multiple raters, blinding and interrater reliability)	Yes	4
Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	Yes	5
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Yes	5

Assessment of heterogeneity	Yes	5
Description of statistical methods (eg complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	5
Provision of appropriate tables and graphics	Yes	5
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	Yes	6-7
Table giving descriptive information for each study included	Yes	17-20
Results of sensitivity testing (eg subgroup analysis)	Yes	21-22
Indication of statistical uncertainty of findings	Yes	6-8
Reporting of discussion should include		
Quantitative assessment of bias (eg publication bias)	Yes	8-
Justification for exclusion (eg exclusion of non-English language citations)	No	8-10
Assessment of quality of included studies	Yes	17-20
Strengths and weaknesses	Yes	10
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	Yes	8-9
Generalization of the conclusions (eg appropriate for the data presented and within the domain of the literature review)	Yes	10
Guidelines for future research	Yes	10
Disclosure of funding source	Yes	11

NA: Not Applicable