

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

# 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

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-024935
Article Type:	Research
Date Submitted by the Author:	21-Jun-2018
Complete List of Authors:	wang, hao; the first affiliated hospital of Dalian Medical University, Ba, Ying Cai, Run-Ce Xing, Qian
Keywords:	Sex difference, diabetes mellitus, major cardiovascular outcomes, all- cause mortality, meta-analysis
	·



Hao Wang<sup>1\*</sup>, Ying Ba<sup>1</sup>, Run-Ce Cai<sup>1</sup>, Qian Xing<sup>1</sup>

<sup>1</sup>Department of endocrinology, the first affiliated hospital of Dalian Medical University, Dalian, Liaoning province, China, 116000

\*Corresponding author: Hao Wang, Department of endocrinology, the first affiliated hospital of Dalian Medical University, Dalian, Liaoning province, China, 116000. E-mail: wanghaodl@126.com;

KELEZ ONL

Running title: Sex difference of DM and major cardiovascular outcomes

Email:

Hao Wang: wanghaodl@126.com;

Ying Ba: baying126@126.com;

Run-Ce Cai: clearance@sina.com

Qian Xing: xingqiandl@163.com;

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

ıdy s., y as compareo 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

for occurrence with

### **BMJ** Open

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

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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),

### **BMJ** Open

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 ( $\geq$ 10000, <10000), assessment of DM (self-reported, measured, both), follow-up duration ( $\geq$ 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

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

### 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.

1 2	
1 2 3 4 5 6 7 8 9 10	
6	
7 8 0	
11 12	
13 14	
15 16	
17 18	
19 20	
21 22	
23 24	
25 26	
27 28	
29 30	
31 32	
33 34	
35 36	
37 38	
39 40	
41 42	
43 44	
45	
46 47	
48 49	
50 51	
52 53	
54 55 56	
56	

58 59 60

						BMJ Open		136/bmjopen-2018-024935 1 by copyright, including f 	Page	je 10 of 45
1 2								n-20 jht, i		ŗ
3								including		ŗ
4 5 Tab		<b>.</b> .	- 1.		·	· ·	<b>1</b>	idin		ŗ
6	le 1. Baseline	e characteristic c	of studies i	included	in the systema	tic review ar	nd meta-analys	sis gasta sis		ŗ
- <del>7</del> 8 Study	Publication	Country	Sample	Age	Percentage of	Number of	Assessment	Follow-ugg 17	Adjusted factors	Study
9 10	year	-	size	range	women (%)	DM	of DM	duration (years) a Frage to a Fra	-	quality
<sup>11</sup> EPESE [26]	1993	US	2812	>65	58.0	386	Self-reported	t a N		6
13								Dowi ) text	angina, chest pain on exertion	Į
<u>14</u> 1∄isayama [27]	2010	Japan	2421	40-79	57.0	291	Measured	6.0 6.0 6.0 6.0 6.0 6.0 6.0 6.0 6.0 6.0	Age, SBP, smoking, BMI, TC, HDL,	7
16 17								₃d froi ata m	alcohol intake, PA,ECG abnormalities	Ţ
18 19fisayama [28]	2000	Japan	1621	>40	56.0	130	Measured	32.0 g	Age	6
$\frac{20}{21_{\text{APCSC}}}$	2003	27 acharta in	476027	<u></u>	22.0	17762	9-1f raported	<u> </u>	A SDD ampling DMI TC	
<sup>21</sup> APCSC-Asia 22 23 [29]	2003	27 cohorts in Asia	436832	>20	33.0	17763	Self-reported or measured	7.0 training,	Age, SBP, smoking, BMI, TC	7
23 [ <sup>2</sup> <sup>7</sup> ] _24		1 1010				-	of moustres.			
ABCSC-Australia	2003	9 cohorts in	99624	>20	45.0	4784	Self-reported	7.0 and .	Age, SBP, smoking, BMI, TC	7
and New Zealand		Australia and					or measured	7.0 nd similar		,
28 <sup>[29]</sup>		New Zealand						ar t		ŗ
<u>29</u> <b>Ag</b> lvantist Health	1992	US	27658	>25	63.0	656	Measured	<b>2</b>	Age, hypertension, smoking, BMI, PA	6
31 Study [30]								olo 22,		I
32 3BECODE [31] 34	2009	7 cohorts in	9278	40-69	55.0	826	Measured	<b>gie 2025</b> 5-21 8	Acc hypertension smaking BMI TC	6
51	2009	Finland	9210	40-02	33.0	820	Witasuitu	J-21 a	Age, hypertension, smoking, BMI, TC, HDL	U
35 36		1 IIIuita						Departm	HDL .	I
37		and Sweden						rtme		I
<u>38</u> 39								n		
40								GEZ-LTA		
41								LTA		
42 43			_							
43 44			For	peer revie	ew only - http://b	mjopen.bmj.c	com/site/about/gu	uidelines.xhtml		
45										

Page 11 of 45						BMJ Open	n	136/bmjopen-2 1 by copyright,		
1 2 3 4								n-2018-02 Jht, includ		
5 Renfrew and <sup>6</sup> Paisley Survey 7 8 [32] 9	2005	Scotland	15426	45-64	54.0	228	Self-reported or measured	25.0 for uses	) 5 5 7	8
1Gollins-Indians 11 [33] 12	1996	Fiji	1220	>20.0	55.0	166	Measured	11.0 11.0 11.0	Age, SBP, smoking, BMI, TC, survey area	6
13 Collins- 14 Melanesians [33]	1996	Fiji	1324	>20.0	53.0	65	Measured	11.0 Erasmushogeschool 11.0 11.0 11.0 11.0 11.0 11.0 11.0 11.0	Age, SBP, smoking, BMI, TC, survey area	6
17Kuopio and 18North Karelia 19 20 [34]	2005	Finland	51735	25-74	51.0	1108	Self-reported	ed from http://t ool . 17.0 mining, Al	Age, SBP, smoking, BMI, TC, study year	8
21 22San Antonio PBeart Study [35] 24	2007	US	4996	25-64	57.0	524	Measured	16.0 training, a	Age, ethnicity	7
<ul> <li><sup>25</sup>Hawaii-Los</li> <li><sup>26</sup> 27 Angeles-</li> <li><sup>26</sup> <sup>27</sup> Angeles-</li> <li><sup>26</sup> <sup>27</sup> (36)</li> <li><sup>29</sup> [36]</li> <li><sup>30</sup></li> </ul>	2002	Japan	927	40-79	56.0	169	Measured	10-18 similar technol	triacylglycerols, uric acid, ECG abnormalities	6
31 Reykjavik study 32 [37] 34 35 36 37	2002	Iceland	18519	32-60	52.0	295	Self-reported or measured	ologies.	triacylglycerols, diabetes, glucose, prior	8
38 39 40 41 42 43 44 45			For	r peer revie\	w only - http://bn	njopen.bmj	j.com/site/about/guide	ht GEZ-LTA delines.xhtml	!	

						BMJ Ope	n	1 soromjopen-z 1 by copyright,	Page	12 of 45
1 2 3								right, includ		
©harleston Heart §tudy-White [38] 7	1993	US	1394	>35	53.0	38	Measured	30.0 g for us	Age	6
Sharleston Heart Study-Black [38]	1993	US	787	>35	58.0	37	Measured	30.0 Erasr Erasr	Age	6
12Strong Heart 13 Study [39] 14 15	2006	US	4372	45-74	61.0	724	Measured	12.0 to text and data - 17.0 17.0 17.0	Age, SBP, DBP, smoking, HDL, LDL, albuminuria	7
16 HUNT 1 [40] 17 18 19	2012	Norway	47951	>20	52.0	1992	Self-reported	17.0 data minin	PA	8
20Framingham 21 study [41] 22	2003	2 cohorts in US	5243	35-75	52.0	229	Measured	20.0 Al train	Age, hypertension, smoking, BMI, TC	7
<sup>23</sup> SALLS [42] 24	1998	Sweden	39055	25-74	51.0	174	Self-reported	16.0 <b>g</b>	Age	6
- 25 Dubbo study [43] 27 28 29 30	1995	Australia	2805	>60	56.0	206	Measured	5.0 5.0 5.0	triacylglycerols, ApoB, LPa, diabetes, self-	6
<sup>31</sup> SHHEC [44] 32	2007	Scotland	13343	30-74	51.0	184	Measured	16.0 <b>logie</b>	Age, SBP, smoking, BMI, TC	7
33 34HANES I [45] -35 36 27	1988	US	7381	40-77	55.0	407	Self-reported	9.0 at post		7
37 38 39 40 41 42 43 44 45 46			Foi	r peer review	only - http://bm	jopen.bm	j.com/site/about/gu	ent GEZ-ETA		

Page 13 of 45						BMJ Open		136/bmjopen-2 d by copyright,		
1 2 3 4								n-2018-02 ht, includ		
5 Iso [46] 6 7 8 9	2004	Japan	10582	40-69	60.0	267	Measured	17.0 for uses r	Age, hypertension, smoking, BMI, TC, HDL, skinfold, alcohol, community, menopause	8
10 <sup>F</sup> ramingham 10ffspring [47] 12 13	2006	US	2097	50-81	50.0	99	Measured	Lift 14.0 14.0 14.0		7
14 JPHC [48] 15 16 17 18	2011	2 cohorts in Japan	35657	40-69	63.0	2034	Measured	of 9. Dowinloaded from id to text and data mir 12.0	<ul> <li>Age, SBP, AHT, smoking, BMI, TC, HDL,</li> <li>triglycerides, alcohol, fasting status,</li> <li>residential areas</li> </ul>	8
NPANES III [49] 20 21	1994	US	18603	18-90	46.0	1290	Self-reported or measured	13.0 g, Al tra	Age, SBP, smoking, BMI, TC	7
<sup>-22</sup> 23 ARIC [50]	1989	US	15732	45-64	55.0	1610	Measured	18.0 aining,	Age, SBP, smoking, BMI, TC	7
24 25 EPIC-Norfolk 26 [51] 27	2008	UK	22516	40-79	55.0	441	Self-reported	10.0 and simil	Age, SBP, smoking, BMI, TC, triglycerides	8
<sup>28</sup> Sievers [52] 29	1992	US	5131	15-84	52.0	1266	Measured	<u> </u>	Age	7
30 Rancho Bernado 32 [53] 33	1988	US	3778	50-79	54.0	320	Self-reported	10.0 r technologies.	Age, SBP, TC, smoking, obesity, family	6
3 <b>#</b> akayama [54] 35 36	2008	Japan	29079	>35	54.0	1217	Self-reported	7.0 tt Departe	Age, hypertension, smoking, BMI, PA,	8
37 38 39 40 41 42 43 44 45			For	peer revie	w only - http://br	njopen.bmj.	.com/site/about/guid	nent GEZ-LTA idelines.xhtml		

						BMJ Oper	n		136/bmjo	Page <sup>-</sup>	14 of 45
1 2 3 4								ру соругідні, піста	136/bmjopen-2018-024935		
5 ESPro [55] 6 7	2017	Germany	105000	>18	51.0	7190	Self-reported or measured	14.0 g	c S	Calendar year, age	7
8 JACC [56] 9 10 11 12	2017	Japan	104910	40-79	58.0	5729	Self-reported	19.0 g	Tuly 2019. I Erasmus	Age, education, smoking, alcohol, PA, BMI, history of hypertension, or history of DM	8
12         13         14         15         16         17         18         19         20         21         22         23         24         25         26         27         28         29         30         31         32         33         34         35         36         37         38         39         40         41         42					000		ien		7 July 2019. Downloaded from http://bmjopen.bmj.com/ on May 22, 2025 at Department GEZ-LTA Erasmushogeschool .		
43 44 45			For	peer reviev	v only - http://k	omjopen.bmj	.com/site/about/gu	idelines.xhtml			

### **BMJ** Open

\*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<sup>2</sup>=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

able ion year	Group Before 2010 2010 or after	Number of cohorts 20 3	RRR and 95%CI 1.53 (1.28-1.82)	P value <0.001	I-square 39.6	P value for heterogeneity 0.036
ion year 		20	1.53 (1.28-1.82)	<0.001	39.6	heterogeneity
ion year			1.53 (1.28-1.82)	<0.001	39.6	0.036
	2010 or after	2				ų,
		3	1.42 (1.20-1.68)	< 0.001	0.0	0.421
ntry	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
e 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
nt of DM	Self-reported	6	1.75 (1.29-2.37)	< 0.001	74.6	0.001
	nt of DM					

		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	≥10	16	1.69 (1.41-2.04)	< 0.001	43.1	0.034	
	(years)	<10	6	1.22 (0.98-1.52)	0.078	0.0	0.948	
	Adjusted other	Yes	19	1.45 (1.29-1.62)	<0.001	6.6	0.375	
	CVD risk factors	No	4	2.56 (1.89-3.46)	< 0.001	0.0	0.423	
		High	13	1.46 (1.29-1.66)	<0.001	10.6	0.339	
	Study quality _	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	
		Self-reported	6	1.28 (1.04-1.58)	0.022	0.0	0.668	
	Assessment of DM	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	≥10	19	1.27 (1.10-1.45)	0.001	0.0	0.760	
	(years)	<10	4	1.09 (0.76-1.57)	0.627	36.0	0.196	_
	Adjusted other	Yes	19	1.27 (1.11-1.44)	< 0.001	0.0	0.695	
	CVD risk factors	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	
Study qu	Study quanty _	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	

# BMJ Open

leath		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
		Self-reported	2	2.05 (1.59-2.64)	<0.001	0.0	0.568
	Assessment of DM	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	≥10	8	1.57 (1.18-2.09)	0.002	21.8	0.256
	(years)	<10	2	1.41 (0.42-4.68)	0.576	66.5	0.084
	Adjusted other	Yes	8	1.42 (1.02-1.98)	0.040	44.0	0.085
	CVD risk factors	No	2	2.18 (0.79-6.03)	0.132	0.0	0.524
		High	4	1.97 (1.56-2.48)	<0.001	0.0	0.864
	Study quality _	Low	6	1.10 (0.78-1.55)	0.593	0.0	0.417
-cause	Publication year	Before 2010	7	1.51 (1.23-1.85)	<0.001	38.2	0.138
ortality	-	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
		Self-reported	2	1.69 (1.46-1.95)	<0.001	0.0	0.669
	Assessment of DM	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	Yes	4	1.50 (1.12-2.01)	0.006	39.4	0.176	
CVD risk factors	No	3	1.33 (0.75-2.36)	0.321	57.6	0.095	
	High	2	1.69 (1.41-2.02)	< 0.001	0.0	0.490	
Study quality	Low	5	1.25 (0.80-1.94)	0.329	53.3	0.073	
							Protec
Stroke							Protected by copyright, including for uses related to text and data i
SHUKE							/ copy
Data for the study	reported sex diffe	erence of an	association between I	OM and subse	quent stroke risk		/right
were available from	m 23 cohorts. Th	e pooled rea	sults in DM men and	women were	e associated with		, incl
statistically signifi	cant increased (S	Supplementa	al 3). The pooled RR	R (female to	male) suggested		uding
that DM women w	vas associated wit	h an increas	ed risk of stroke as co	ompared with	DM men (RRR:		for u
1.22; 95%CI: 1.09	9-1.37; P=0.001;	Figure 1B)	, and no evidence of	f heterogenei	ty was observed		ses r
(I <sup>2</sup> =0.0%; P=0.614	). Sensitivity ana	lysis indica	ted the conclusion wa	as not affected	l after sequential		elated
exclusion of each s	study from the po	oled analyse	es (Supplemental 4). S	Subgroup anal	ysis indicated no		I to te
sex difference for	the relation of D	M with strol	ke risk if pooled stud	ies published	in 2010 or after,		xt and
sample size<10000	), study use both s	self-reported	l and measured, durat	ion of follow-	up less than 10.0		d data
years, the study no	t adjusted other c	ardiovascula	ar risk factors, and the	study with lo	w quality (Table		mir
2).							ng, A
							l train
Cardiac death							ing, AI training, and similar technologies.
Data for the study	reported sex dif	ference of a	n association between	n DM and su	bsequent cardiac		nd sin
death risk were ava	ailable from 10 co	horts. We no	oted DM were associa	ted with great	er risk of cardiac		nilar t
death in men and	women separatel	y (Supplem	ental 3). The pooled	RRR (female	to male) of DM		echnu
versus non-DM or	n cardiac death r	isk was 1.49	9 (95%CI: 1.11-2.00;	; P=0.009; Fi	gure 2A), which		ologie
associated with sta	tistically signific	ont Further	unimportant heteroge	naitu waa dat	$a_{a} = \frac{1}{2} - \frac{1}{2} - \frac{1}{2} = \frac{1}{2} - \frac{1}{2} - \frac{1}{2} = \frac{1}{2} - \frac{1}{2$		ŝ.

### Stroke

### **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

### **BMJ** Open

### **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<sup>2</sup>=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, allcause 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].

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Page 21 of 45

### **BMJ** Open

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 allcause 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

1. Yusuf S, Reddy S, Ounpuu S, et al. Global burden of cardiovascular diseases, I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001; 104: 2746-2753.

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

2. Chambless L, Keil U, Dobson A, et al. Population versus clinical view of case fatality from acute coronary heart disease: results from the WHO MONICA Project 1985-1990. Multinational MONItoring of Trends and Determinants in CArdiovascular Disease. Circulation 1997; 96: 3849-3859

3. Odutayo A, Wong CX, Hsiao AJ, et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016 Sep 6;354:i4482.

4. Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet 2016;388:465-75.

5. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol 2015;3:514-25.

6. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384:591-598.

7. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, Ezzati M, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet. 2014;383:970-83.

8. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-1847.

 Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care. 1993;16:434-44.

10. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229-34.

 Bartnik M, Norhammar A, Ryden L. Hyperglycaemia and cardiovascular disease. J Intern Med. 2007; 262:145-56.

12. Goff DC Jr, Gerstein HC, Ginsberg HN, et al. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the action to control cardiovascular risk in diabetes (ACCORD) trial. Am J Cardiol 2007; 99: 4i-20i.

13. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease

### **BMJ** Open

in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia 2014;57:1542-51.

14. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. Lancet 2014;383:1973-80.

15. Walden CE, Knopp RH, Wahl PW, et al. Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations. N Engl J Med 1984;311:953-9.

16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group.JAMA. 2000; 283: 2008-12.

17. Wells G, Shea B, O' Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute 2009. Available:http://www.ohri.ca/programs/clinical\_epidemiology /oxford.htm.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177-88.

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

19. Ades AE, Lu G, Higgins JP. The interpretation of random-effects metaanalysis in decision models. Med Decis Making. 2005; 25: 646-54.

20. Woodward M. Epidemiology: study design and data analysis. 2nd edn. Boca Raton, FL, USA: Chapman and Hall/CRC, 2005.

21. Deeks JJ, Higgins JPT, Altman DG. Analyzing data and undertaking meta-analyses. In: Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions 5.0.1. Oxford, UK: The Cochrane Collaboration: 2008; chap 9.

22. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557-60.

23. Tobias A. Assessing the influence of a single study in meta-analysis. Stata Tech Bull. 1999; 47:15-17.

24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315: 629-34.

 **BMJ** Open

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias.
 Biometrics. 1994; 50: 1088-1101.

26. Seeman T, de Mendes LC, Berkman L, et al. Risk factors for coronary heart disease among older men and women: a prospective study of community-dwelling elderly. Am J Epidemiol 1993; 138:1037-1049.

27. Doi Y, Ninomiya T, Hata J, et al. Impact of glucose tolerance status on development of ischemic stroke and coronary heart disease in a general Japanese population: the Hisayama study. Stroke 2010;41:203-209.

28. Tanizaki Y, Kiyohara Y, Kato I, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000; 31:2616-22.

29. Woodward M, Barzi F, Martiniuk A, et al. Cohort profi le: the Asia Pacific Cohort Studies Collaboration. Int J Epidemiol 2006; 35:1412-16.

30. Fraser GE, Strahan TM, Sabate J, et al. Effects of traditional coronary risk factors on rates of incident coronary events in a low-risk population. The Adventist Health Study. Circulation 1992; 86:406-413.

31. Hyvärinen M, Tuomilehto J, Laatikainen T, et al. The impact of diabetes on coronary heart disease differs from that on ischaemic stroke with regard to the gender. Cardiovasc Diabetol 2009; 8:17.

32. Whiteley L, Padmanabhan S, Hole D, et al. Should diabetes be considered a coronary heart disease risk equivalent: results from 25 years of follow-up in the Renfrew and Paisley survey. Diabetes Care 2005; 28:1588-1593.

33. Collins VR, Dowse GK, Ram P, et al. Non-insulin-dependent diabetes and 11-year mortality in Asian Indian and Melanesian Fijians. Diabet Med 1996; 13:125-132.

34. Hu G, Jousilahti P, Qiao Q, et al. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. Diabetologia 2005; 48:856-861.

35. Hunt KJ, Williams K, Hazuda HP, et al. The metabolic syndrome and the impact of diabetes on coronary heart disease mortality in women and men: the San Antonio Heart Study. Ann Epidemiol 2007; 17:870-877.

36. Imazu M, Sumii K, Yamamoto H, et al. Influence of type 2 diabetes mellitus on cardiovascular disease mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Diabetes Res Clin Pract 2002; 57:61-69.

37. Jonsdottir LS, Sigfusson N, Gudnason V, et al. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. J Cardiovasc Risk 2002; 9:67-76.

38. Keil JE, Sutherland SE, Knapp RG, et al. Mortality rates and risk factors for coronary disease in black as compared with white men and women. N Engl J Med 1993; 329:73-78.

39. Lee ET, Howard BV, Wang W, et al. Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. Circulation 2006; 113: 2897-2905.

40. Madssen E, Vatten L, Nilsen TI, et al. Abnormal glucose regulation and gender-specific risk of fatal coronary artery disease in the HUNT 1 study. Scand Cardiovasc J 2012; 46:219-225.

41. Natarajan S, Liao Y, Cao G, et al. Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. Arch Intern Med 2003; 163: 1735-1740.

42. Nilsson PM, Johansson SE, Sundquist J. Low educational status is a risk factor for mortality among diabetic people. Diabet Med 1998; 15:213-219.

43. Simons LA, Friedlander Y, McCallum J, et al. Risk factors for coronary heart disease in the prospective Dubbo Study of Australian elderly. Atherosclerosis 1995; 117:107-118.

 44. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2007;93:172-176.

45. Kleinman JC, Donahue RP, Harris MI, et al. Mortality among diabetics in a national sample. Am J Epidemiol 1988; 128:389-401.

46. Iso H, Imano H, Kitamura A, et al. Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. Diabetologia 2004; 47:2137-44.

47. Najarian RM, Sullivan LM, Kannel WB, et al. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring study. Arch Intern Med 2006; 166: 106-11.

48. Cui R, Iso H, Yamagishi K, et al. Diabetes mellitus and risk of stroke and its subtypes among Japanese: the Japan public health center study. Stroke 2011; 42:2611-14.

49. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. Vital Health Stat 11994; 32:1-407.

50. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. Am J Epidemiol 1989;129:687-702.

51. Myint PK, Sinha S, Luben RN, et al. Risk factors for first-ever stroke in the EPIC-Norfolk prospective population-based study. Eur J Cardiovasc Prev Rehabil 2008; 15:663-69.

52. Sievers ML, Nelson RG, Knowler WC, et al. Impact of NIDDM on mortality and causes of death in Pima Indians. Diabetes Care 1992; 15:1541-49.

53. Barrett-Connor E, Khaw KT. Diabetes mellitus: an independent risk factor for stroke? Am J Epidemiol 1988; 128: 116-23.

54. Oba S, Nagata C, Nakamura K, et al. Selfreported diabetes mellitus and risk of mortality from all causes, cardiovascular disease, and cancer in Takayama: a population-based prospective cohort study in Japan. J Epidemiol 2008; 18: 197-203.

### **BMJ** Open

55. IcksA, ClaessenH, KvitkinaT, et al. Incidence and relative risk of stroke in the diabetic and the non-diabetic population between 1998 and 2014: A community-based stroke register. PLoSONE 2017; 12:e0188306.

56. Matsunaga M, Yatsuya H, Iso H, et al. Similarities and differences between coronary heart disease and stroke in the associations with cardiovascular risk factors: The Japan Collaborative ι sclerosis . itations Cohort Study. Atherosclerosis 2017;261:124-130.

### **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

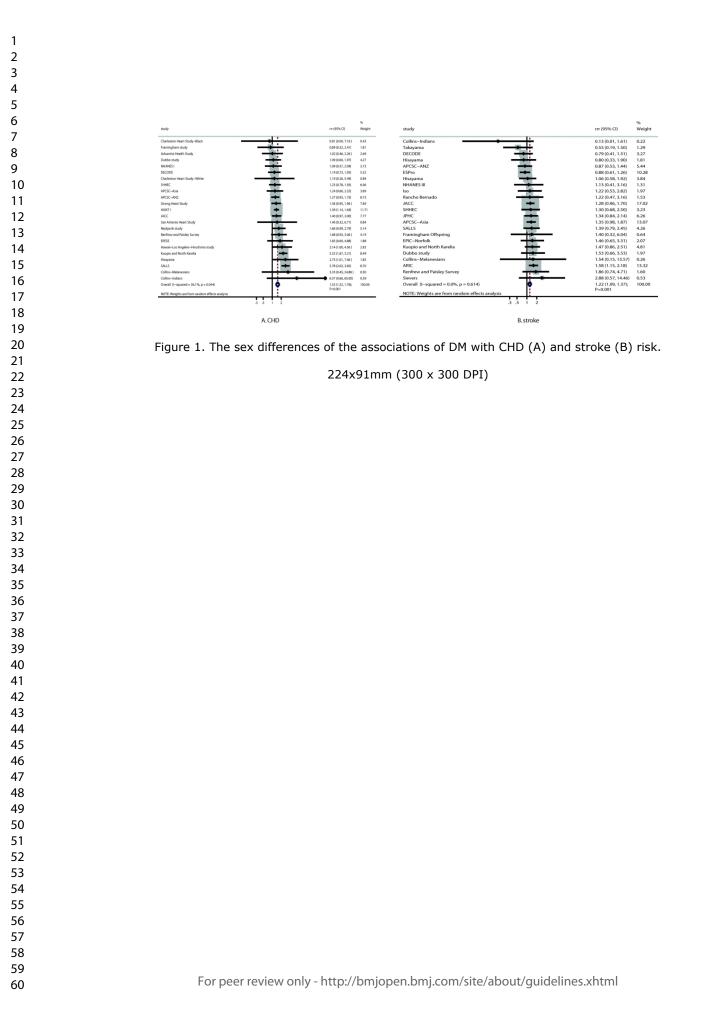
Supplemental 3: The summary results of DM and CHD, stroke, cardiac death, and all-cause mortality in men and women separately.

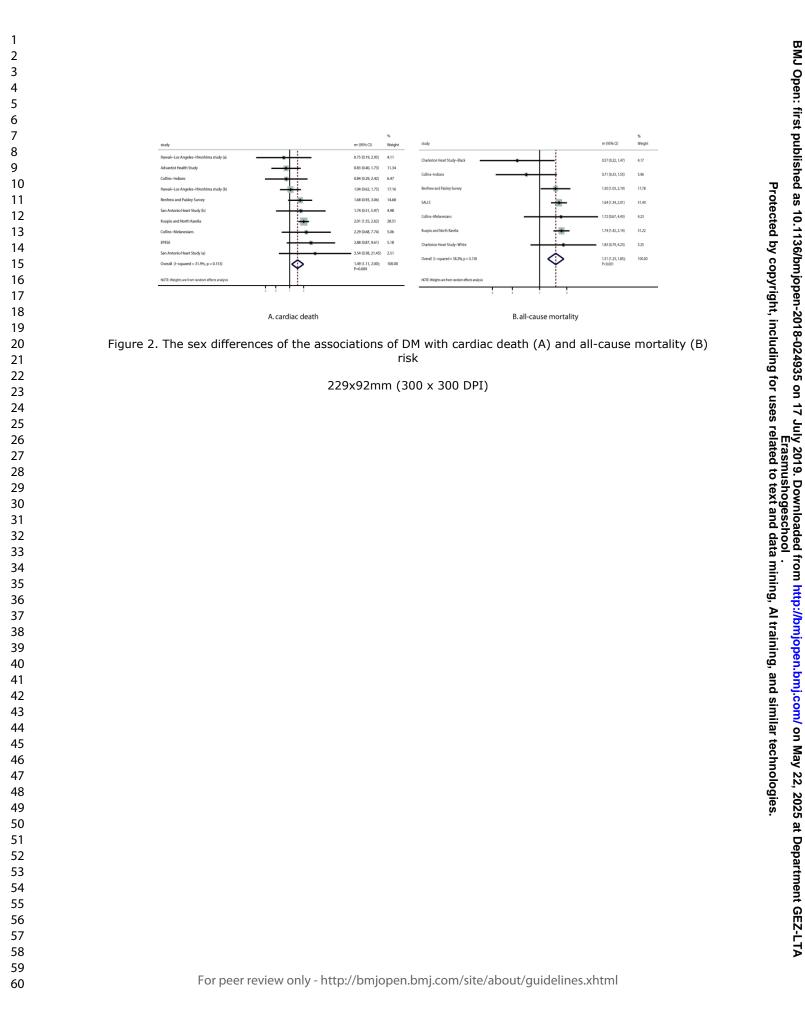
Supplemental 4: Sensitivity analyses for CHD, stroke, cardiac death, and all-cause mortality

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

Checklist S1: MOOSE Checklist

for peer terier on





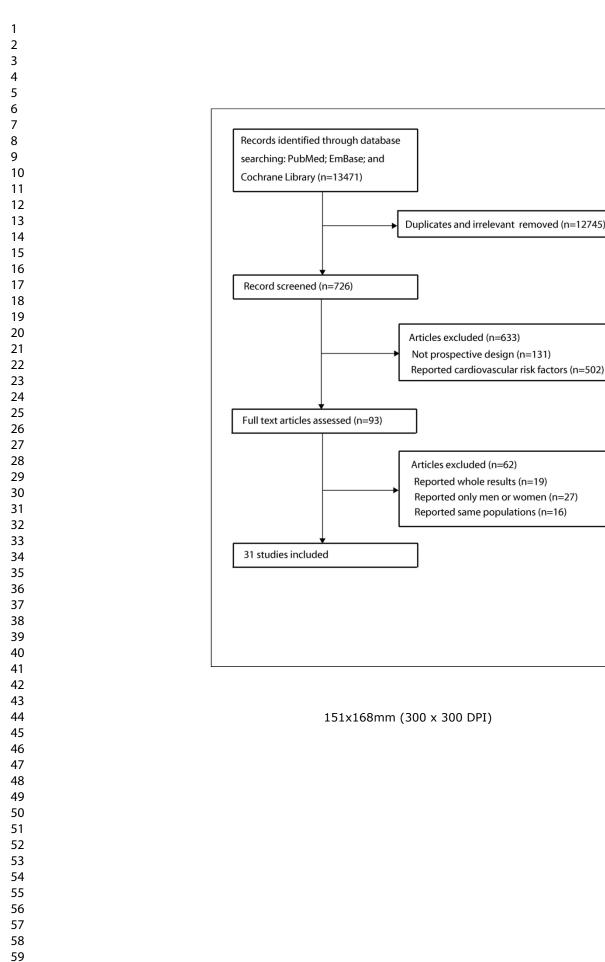
# Searching strategy in PubMed:

("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])

o per terien on t

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies

Page 34 of 45



ID	RR (95% CI)	Weig
EPESE	3.20 (1.46, 7.01)	3.45
Hisayama	3.46 (1.59, 7.54)	3.48
APCSC–Asia	1.82 (1.02, 3.25)	4.37
APCSC-ANZ	2.01 (1.55, 2.60)	5.87
Advantist Health Study	2.15 (1.33, 3.47)	4.86
DECODE	2.48 (1.69, 3.65)	5.32
Renfrew and Paisley Survey	1.97 (1.27, 3.08)	5.04
Collins–Indians	20.70 (2.51, 171.00)	0.89
Collins–Melanesians	5.36 (1.18, 24.30)	1.53
Kuopio and North Karelia	4.89 (3.84, 6.24)	5.93
San Antonio Heart Study	4.94 (1.33, 18.40)	1.88
Hawaii–Los Angeles–Hiroshima study	3.29 (1.79, 6.55)	4.04
Reykjavik study	2.23 (1.50, 3.32)	5.26
Charleston Heart Study–White	1.25 (0.35, 4.47)	1.97
Charleston Heart Study–Black	2.02 (0.90, 4.53)	3.36
Strong Heart Study	➡ 2.26 (1.73, 2.96)	5.83
HUNT 1	➡ 2.50 (2.10, 2.80)	6.24
Framingham study	5.40 (2.40, 12.30)	3.32
SALLS	8.03 (6.34, 10.18)	5.95
Dubbo study	1.67 (1.12, 2.48)	5.26
SHHEC	3.06 (2.18, 4.27)	5.54
NHANES I	2.59 (1.59, 4.22)	4.82
JACC	2.08 (1.58, 2.75)	5.80
Overall (I-squared = 83.8%, p = 0.000)	2.79 (2.25, 3.46)	100.0
	1	

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

Study		%
ID	RR (95% CI)	Weigl
EPESE	1.75 (0.97, 3.16)	3.02
Hisayama	<ul> <li>1.26 (0.67, 2.35)</li> </ul>	2.80
APCSC-Asi a	1.47 (1.15, 1.88)	6.31
APCSC-ANZ	<b>→</b> 1.58 (1.32, 1.90)	7.03
Advantist Health Study	• 2.11 (1.12, 4.00)	2.74
DECODE	2.09 (1.55, 2.82)	5.68
Renfrew and Paisley Survey	1.17 (0.78, 1.74)	4.57
Collins–Indians	3.15 (1.29, 7.69)	1.67
Collins-Melanesians	1.60 (0.43, 5.97 )	0.86
Kuopio and North Karelia	2.11 (1.70, 2.63)	6.63
San Antonio Heart Study	3.38 (1.56, 7.31)	2.09
Hawaii–Los Angeles–Hiroshima study	1.54 (1.03, 2.25)	4.68
Reykjavik study	1.34 (0.97, 1.87 )	5.35
Charleston Heart Study–White 🔶	1.05 (0.45, 2.44)	1.82
Charleston Heart Study–Black	2.48 (0.33, 18.67)	0.39
Strong Heart Study	1.66 (1.30, 2.12)	6.32
HUNT 1	➡ 1.80 (1.60, 2.10)	7.49
Framingham study	6.10 (3.40, 10.90)	3.08
SALLS	2.89 (2.34, 3.57)	6.71
Dubbo study	1.53 (0.99, 2.37 )	4.23
SHHEC	2.49 (1.84, 3.37 )	5.65
NHANES I	2.37 (1.55, 3.62)	4.35
JACC	1.49 (1.19, 1.88)	6.51
Overall (I-squared = 67.8%, p = 0.000)	1.87 (1.64, 2.12)	100.0
NOTE: Weights are from random effects analysis		

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

Study ID	RR (95% CI)	% Weight
Hisayama —	2.02 (1.07, 3.81)	3.89
Hisayama	1.90 (1.20, 3.00 )	5.09
APCSC-Asia	1.93 (1.45, 2.58)	6.38
APCSC-ANZ	1.41 (0.95, 2.08)	5.59
DECODE	• 2.37 (1.46, 3.84)	4.90
Renfrew and Paisley Survey	2.83 (1.63, 4.90)	4.43
Collins–Indians	▶ 2.88 (0.45, 18.40)	0.83
Collins–Melanesians	2.58 (0.44, 15.30)	0.90
Kuopio and North Karelia	3.91 (2.68, 5.72)	5.69
SALLS	4.37 (2.89, 6.59)	5.44
Dubbo study	2.05 (1.14, 3.66)	4.22
SHHEC	3.64 (2.29, 5.79)	5.05
lso	2.20 (1.20, 4.00)	4.10
Framingham Offspring	2.70 (0.80, 9.16)	1.68
ЈРНС —	2.19 (1.53, 3.12)	5.86
NHANES III	1.69 (0.90, 3.15)	3.94
ARI C	3.16 (2.55, 3.91)	6.89
EPIC–Norfolk —	2.12 (1.15, 3.89)	4.05
Sievers	2.30 (0.70, 8.30 )	1.64
Rancho Bernado	2.20 (1.00, 4.50)	3.25
Takayama 🔶	0.88 (0.36, 2.16)	2.62
ESPr o	1.53 (1.19, 1.97)	6.62
JACC	1.39 (1.13, 1.71)	6.93
Overall (I-squared = 70.0%, p = 0.000)	2.21 (1.85, 2.64)	100.00
NOTE Weights are from unders effects and usis		
NOTE: Weights are from random effects analysis	1	

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

1.80 (1.20, 2.60)       5         1.43 (1.23, 1.66)       7         1.62 (1.18, 2.22)       6         3.01 (1.95, 4.64)       4         1.52 (0.72, 3.21)       2         21.80 (4.08, 116.00)       0         ans       1.68 (0.38, 7.47)       0	3.61 5.35 7.58 6.05 4.92
Image: system of the system	5.35 7.58 6.05 4.92
Image: system of the system	7.58 6.05 4.92
ley Survey       1.62 (1.18, 2.22)       6         ans       1.62 (1.18, 2.22)       6         1.62 (1.18, 2.22)       1.62 (1.18, 2.22)       6         3.01 (1.95, 4.64)       4         21.80 (4.08, 116.00)       0         1.68 (0.38, 7.47)       0	6.05 4.92
ley Survey     3.01 (1.95, 4.64)     4       ans     1.52 (0.72, 3.21)     2       1.68 (0.38, 7.47)     0	4.92
ley Survey 1.52 (0.72, 3.21) 2 21.80 (4.08, 116.00) 0 ans 1.68 (0.38, 7.47) 0	
ans 21.80 (4.08, 116.00) 0 1.68 (0.38, 7.47) 0	
ans 1.68 (0.38, 7.47 ) 0	2.75
	0.75
	0.93
	5.43
	5.30
	3.61
	4.68
	3.73
	2.47
	6.15
	2.46
<b></b> 2.00 (1.57, 2.54) 6	6.79
1.45 (0.84, 2.49)	4.00
0.80 (0.30, 2.40)	1.70
• <u>1.80 (1.00, 3.20)</u> 3	3.73
	4.24
1.65 (0.99, 2.76) 4	
	6.57
1.75 (1.34, 2.27) 6	6.57 7.21
2.00 (1.57, 2.5 1.45 (0.84, 2.4 0.80 (0.30, 2.4	54) 49) 40) 20)

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

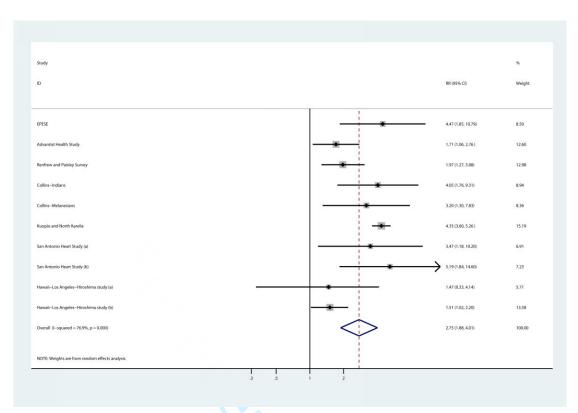


Figure S5. The summary results for DM and the risk of cardiac death in women

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

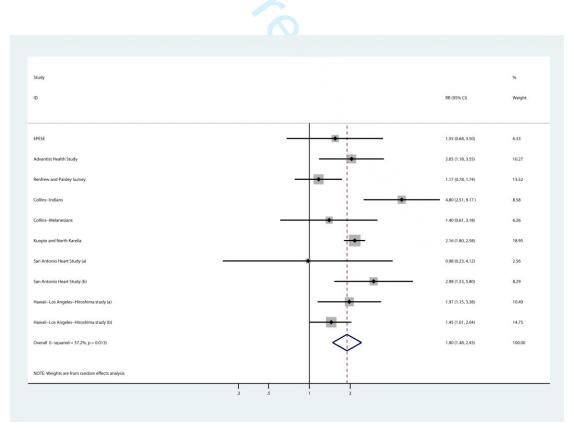


Figure S6. The summary results for DM and the risk of cardiac death in men

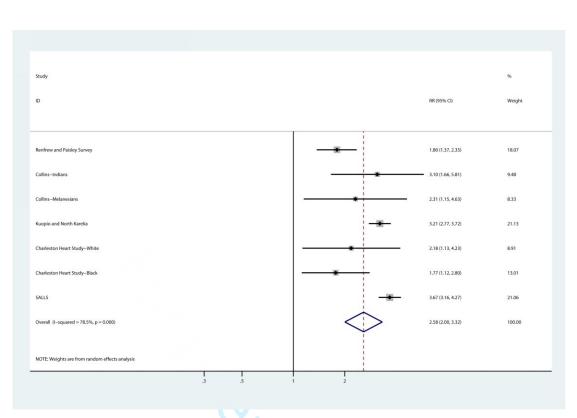


Figure S7. The summary results for DM and the risk of all-cause mortality in women

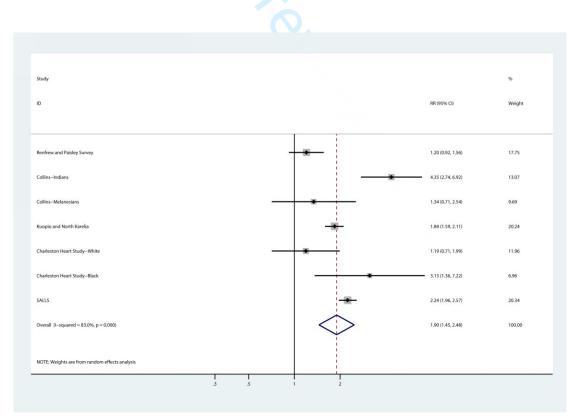
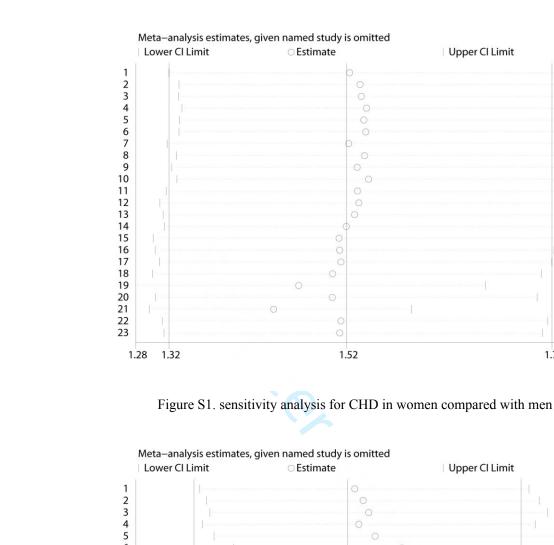


Figure S8. The summary results for DM and the risk of all-cause mortality in men

Upper CI Limit



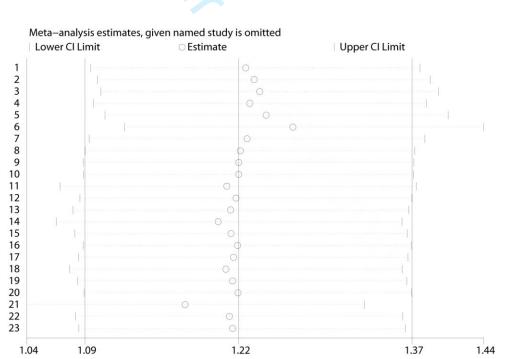


Figure S2. sensitivity analysis for stroke in women compared with men

1.81

1.76

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

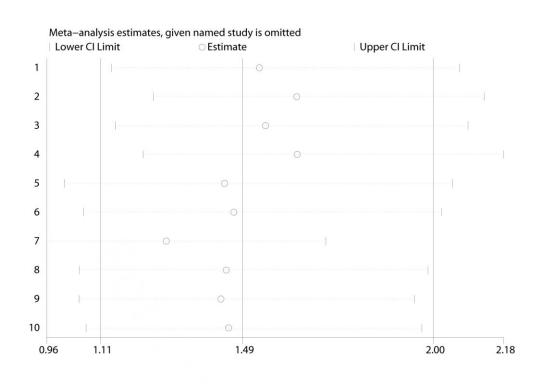


Figure S3. sensitivity analysis for cardiac death in women compared with men

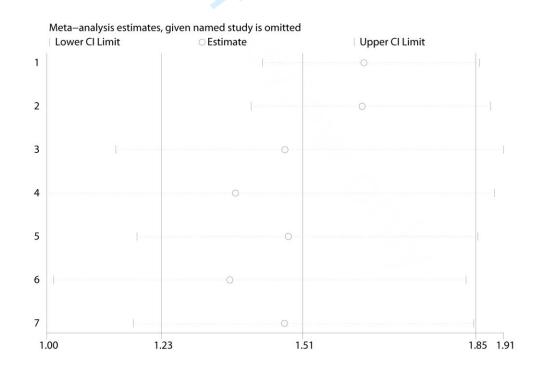
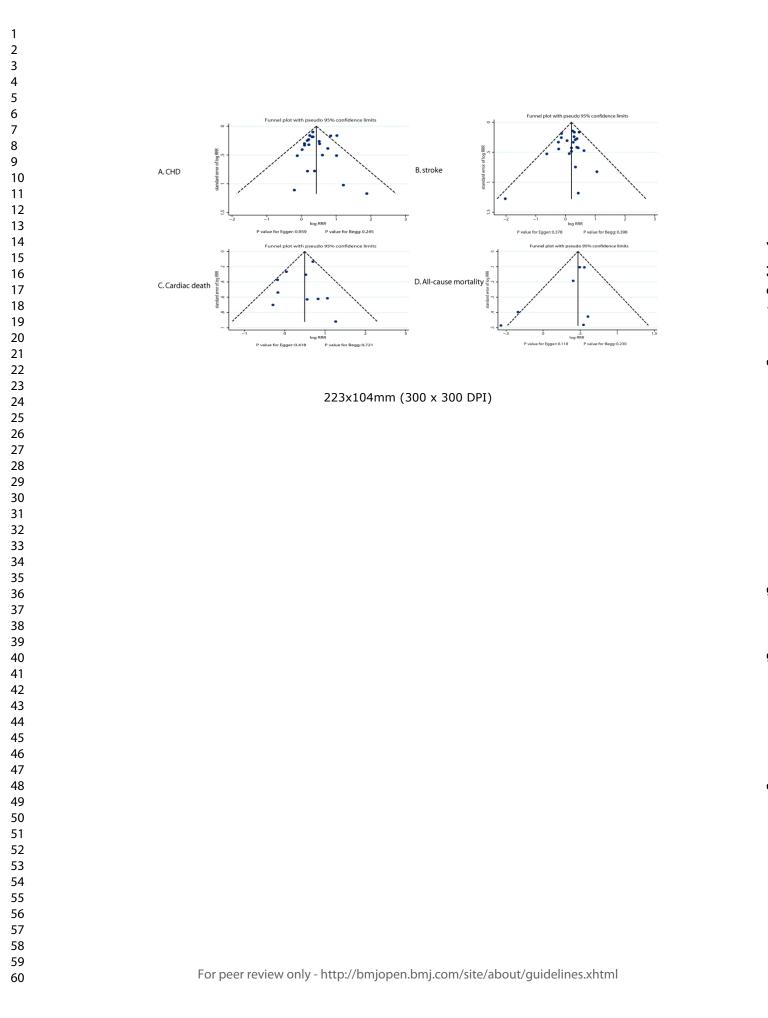


Figure S4. sensitivity analysis for all-cause mortality in women compared with men



# MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Metaanalyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported
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

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Assessment of heterogeneity	Yes	5
Description of statistical methods (eg complete description of fixed or	Yes	5
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		
Provision of appropriate tables and graphics	Yes	5
Reporting of results should include	1	I
Graphic summarizing individual study estimates and overall estimate	Yes	6-7
Table giving descriptive information for each study included	Yes	17-2
Results of sensitivity testing (eg subgroup analysis)	Yes	21-2
Indication of statistical uncertainty of findings	Yes	6-8
Reporting of discussion should include		1
Quantitative assessment of bias (eg publication bias)	Yes	8-
Justification for exclusion (eg exclusion of non-English language	No	8-10
citations)		
Assessment of quality of included studies	Yes	17-2
Strengths and weaknesses	Yes	10
Reporting of conclusions should include	1	I
Consideration of alternative explanations for observed results	Yes	8-9
Generalization of the conclusions (eg appropriate for the data presented	Yes	10
and within the domain of the literature review)		
Guidelines for future research	Yes	10
Disclosure of funding source	Yes	11
NA: Not Applicable	I	I

**BMJ** Open

# **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

Manuscript IDbmjopen-2018-024935.R1Article Type:ResearchDate Submitted by the Author:0-Mar-2019Complete List of Authors:wang, hao; First Affiliated Hospital of Dalian Medical University Sa, Ying; First Affiliated Hospital of Dalian Medical University ving, Qian; First Affiliated Hospital of Dalian Medical UniversitySecondary Subject Heading Diabetes and endocrinologyKewworket Medical Medical Micro Medical UniversitySex difference, diabetes mellitus, major cardiovascular outcomes, all-	Journal:	BMJ Open
Date Submitted by the Author:02-Mar-2019Complete 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 Cardiovascular medicine <b>Primary Subject Heading</b> Cardiovascular medicineSecondary Subject Heading:Diabetes and endocrinologyKowwords:Sex difference, diabetes mellitus, major cardiovascular outcomes, all-	Manuscript ID	bmjopen-2018-024935.R1
Author:U2-Mar-2019Complete 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 <b>Primary Subject Heading</b> Cardiovascular medicineSecondary Subject Heading:Diabetes and endocrinologyKowwords:Sex difference, diabetes mellitus, major cardiovascular outcomes, all-	Article Type:	Research
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 <b>Primary Subject Heading</b> :       Cardiovascular medicine         Secondary Subject Heading:       Diabetes and endocrinology         Sex difference, diabetes mellitus, major cardiovascular outcomes, all-		02-Mar-2019
Heading:       Cardiovascular medicine         Secondary Subject Heading:       Diabetes and endocrinology         Kouwords:       Sex difference, diabetes mellitus, major cardiovascular outcomes, all-	Complete List of Authors:	Ba, Ying; First Affiliated Hospital of Dalian Medical University Cai, Run-Ce; First Affiliated Hospital of Dalian Medical University
Sex difference, diabetes mellitus, major cardiovascular outcomes, all-		Cardiovascular medicine
	Secondary Subject Heading:	Diabetes and endocrinology
cause mortality, meta-analysis	Keywords:	Sex difference, diabetes mellitus, major cardiovascular outcomes, all-cause mortality, meta-analysis

# SCHOLARONE<sup>™</sup> Manuscripts

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

Hao Wang<sup>1\*</sup>, Ying Ba<sup>1</sup>, Run-Ce Cai<sup>1</sup>, Qian Xing<sup>1</sup>

<sup>1</sup>Department of endocrinology, First affiliated hospital of Dalian Medical University, Dalian, Liaoning province, China, 116000

\*Corresponding author: Hao Wang, Department of endocrinology, First affiliated hospital of Dalian Medical University, Dalian, Liaoning province, China, 116000. E-mail: <u>wanghaodl@126.com;</u>

reliez onz

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Running title: Sex difference of DM and major cardiovascular outcomes

Email:

Hao Wang: wanghaodl@126.com;

Ying Ba: <u>baying126@126.com;</u>

Run-Ce Cai: <u>clearance@sina.com</u>

Qian Xing: xingqiandl@163.com;

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

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

# 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

# **BMJ** Open

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

# **BMJ** Open

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

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

# **BMJ** Open

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

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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 sexspecific 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 ( $\geq 10000$ , < 10000), assessment of DM (self-reported, measured, both), follow-up duration ( $\geq 10$ , < 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.

#### **BMJ** Open

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).

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**

						BMJ Open		136/bmjop d by copyri		Page 8 of 45
6	1. Baseline c	characteristic	c of studies	included i	n the system	natic review and	1 meta-analysis	136/bmjopen-2018-024935 or 4 by copyright, including for		
7 8 Study 9 10	Publicatio n year	Country	Sample size	Number of DM	Age range	Percentage of women (%)	Assessment of DM	Follow Sup 17 duration (Spears	Adjusted factors	Study quality
11 NHANES I [26] _12	1988	US	7381	407	40-77	55.0	Self-reported	9.0 ted to	Age, SBP, smoking, BMI, TC	7
13 Rancho Bernado 14 [27] 15	1988	US	3778	320	50-79	54.0	Self-reported	duration (geargeschool 9.0 to text and data mining, Al training 10.0 to text and data mining, Al training 10.0 to text and data mining, Al training	Age, SBP, TC, smoking, obesity, family history, oestrogen use	6
16 ARIC [28] 17	1989	US	15732	1610	45-64	55.0	Measured	18.0 ata n	Age, SBP, smoking, BMI, TC	7
18 19 20 Study [29]	1992	US	27658	656	>25	63.0	Measured	nining, Al	Age, hypertension, smoking, BMI, PA	6
-21 22 Sievers [30]	1992	US	5131	1266	15-84	52.0	Measured	10.0 mjop	. Age	7
23 24 EPESE [31] 25 26	1993	US	2812	386	>65	58.0	Self-reported	10.0 training, and similar t	Age, AHT use, smoking, BMI, diabetes, angina, chest pain on exertion	6 1
<sup>27</sup> Charleston Heart <sup>28</sup> <sup>29</sup> Study-White [32]	1993	US	1394	38	>35	53.0	Measured	30.0 May		6
30 31 22Study-Black [32] 33	1993	US	787	37	>35	58.0	Measured	30.00 gies.	Age	6
34NHANES III [33] 35 36	1994	US	18603	1290	18-90	46.0	Self-reported or measured	13.0 at Depart	Age, SBP, smoking, BMI, TC	7
37         38         39         40         41         42         43         44         45			Fo	r peer reviev	w only - http://	/bmjopen.bmj.com	n/site/about/gui	tment GEZ-LTA delines.xhtml		

Page 9 of 45						BMJ Open		136/bmjopen-2 1 by copyright,		
1 2 3 <u>4</u>								018-02 includ		
5 Dubbo study [34] 6 7 8	1995	Australia	2805	206	>60	56.0	Measured	on 17 , or uses	triacylglycerols, ApoB, LPa, diabetes, self-rated health, prior CH	6
- <del>9</del> 1 <del>0</del> ollins-Indians [35] 11 12	1996	Fiji	1220	166	>20.0	55.0	Measured	July 2019. Downloaded fro Erasmushogeschool • 11.0text and data n 16.0text	Age, SBP, smoking, BMI, TC, survey area	6
1 <b>G</b> ollins-Melanesians 14 [35] 15	1996	Fiji	1324	65	>20.0	53.0	Measured	bownload shogeschutext and c	Age, SBP, smoking, BMI, TC, survey area	6
16 SALLS [36] 17	1998	Sweden	39055	174	25-74	51.0	Self-reported	16.0 lata	Age	6
18 19 Hawaii-Los 20 ngeles-Hiroshima 21 study [37] 22	2002	Japan	927	169	40-79	56.0	Measured	om http://bmjopen.l 10-1@ing, Al training, 17.0g,	Age, hypertension, smoking, BMI, TC, triacylglycerols, uric acid, ECG abnormalities	6
23 Reykjavik study 24 [38] 25 26	2002	Iceland	18519	295	32-60	52.0	Self-reported or measured	ning, and sim	Age, hypertension, smoking, BMI, TC, triacylglycerols, diabetes, glucose, prior CHD, LVH	8
<del>-27</del> 28APCSC-Asia [39] 29 30	2003	27 cohorts in Asia	436832	17763	>20	33.0	Self-reported or measured	7.0 frechr	Age, SBP, smoking, BMI, TC	7
31APCSC-Australia 32 33 <sup>and</sup> New Zealand 34 [39] 35 36 37	2003	9 cohorts in Australia and New Zealand	99624	4784	>20	45.0	Self-reported or measured	22, 2025 at Departme 7.0gies.	Age, SBP, smoking, BMI, TC	7
38 39 40 41 42 43 44 45			For	r peer review	' only - http://ł	omjopen.bmj.cc	om/site/about/guideli	ent GEZ-LTA lines.xhtml		

						BMJ Open		136/bmjopen-2018-0 1 by copyright, inclu	Pa	Page 10 of 45
1 2 3 <u>4</u>										
5 Framingham study 6 [40] 7	2003	2 cohorts in US	5243	229	35-75	52.0	Measured	20.0 for u	Age, hypertension, smoking, BMI, TC	7
8 Iso [41] 9 10 11 12	2004	Japan	10582	267	40-69	60.0	Measured	17 July 2019. Downloaded frc Erasmushogeschool . 25.0ext and data m 17.0 m	Age, hypertension, smoking, BMI, TC, HDL, skinfold, alcohol, community, menopause	8
18enfrew and Paisley 14 Survey [42] 15	2005	Scotland	15426	228	45-64	54.0	Self-reported or measured	25.0 text and c	Age, SBP, smoking, BMI, TC, SES	8
<sup>16</sup> Kuopio and North 17 18 Karelia [43] - <del>19</del>	2005	Finland	51735	1108	25-74	51.0	Self-reported	ini m	Age, SBP, smoking, BMI, TC, study year	8
2§trong Heart Study 21 [44] 22	2006	US	4372	724	45-74	61.0	Measured	ng Al train	Age, SBP, DBP, smoking, HDL, LDL, albuminuria	7
<ul> <li>Framingham</li> <li>Offspring [45]</li> </ul>	2006	US	2097	99	50-81	50.0	Measured	14.0 <b>g</b> , and	Age, SBP, AHT, CVD, atrial fibrillation, LVH, smoking	7
26 27 28 Study [46] 29	2007	US	4996	524	25-64	57.0	Measured	16.0m/ on l	Age, ethnicity	7
30 SHHEC [47]	2007	Scotland	13343	184	30-74	51.0	Measured	16.0nolo	Age, SBP, smoking, BMI, TC	7
3£PIC-Norfolk [48] 33 34	2008	UK	22516	441	40-79	55.0	Self-reported	10.000ies.		8
35 36 37 38								Departmer		
38 39 40 41								nt GEZ-LTA		
42 43 44 45			For	r peer review c	only - http://	bmjopen.bmj.cc	om/site/about/guideli			

Page 11 of 45						BMJ Open		136/bmjopen-2 1 by copyright,		
1 2 3 4								includ		
5 Takayama [49] 6 7 8	2008	Japan	29079	1217	>35	54.0	Self-reported	17, Ises	Age, hypertension, smoking, BMI, PA, education, energy, vegetables, fat, alcohol	8
9 10 DECODE [50] 11 12 13	2009	7 cohorts in Finland and Sweden	9278	826	40-69	55.0	Measured	5-21ated to text and data r 14.04 data r	Age, hypertension, smoking, BMI, TC, HDL	6
14 Hisayama [51] 15 16	2010	Japan	2421	291	40-79	57.0	Measured	t geschool 14.0nd data	Age, SBP, smoking, BMI, TC, HDL, alcohol intake, PA,ECG abnormalities	7
<del>17</del> 18 JPHC [52] 19 20 21	2011	2 cohorts in Japan	35657	2034	40-69	63.0	Measured	12.0 <sup>m</sup> ining, Al tr	Age, SBP, AHT, smoking, BMI, TC, HDL, triglycerides, alcohol, fasting status, residential areas	8
22 23 24 -25	2012	Norway	47951	1992	>20	52.0	Self-reported	ainiopen.bn 17.0 <mark>1</mark> , an	Age, hypertension, smoking, BMI, CVD, PA	8
26 ESPro [54] 27 28	2017	Germany	105000	7190	>18	51.0	Self-reported or measured	14.0similar	Calendar year, age	7
29 JACC [55] 30 31 32 	2017	Japan	104910	5729	40-79	58.0	Self-reported	1 May 22, 2025 technologies.	Age, education, smoking, alcohol, PA, BMI, history of hypertension, or history of DM	8
34 *AHT 35							P, diastolic BP; LPa P, systolic BP; SES,	, lipoprotein	LVH, left ventricle hypertrophy; NA, status	
39 40 41 42 43			For	Deer review	w only - http://bi	miopen bmi co	om/site/about/guidel	GEZ-LTA		
44 45 46			TO	Peer revier	wonny - http://bl	njopen.omj.co	sin, site, about, guider			

# 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	RRR and 95%CI	P value	I-	P value for	P value for
		cohorts			square	heterogeneity	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	
	Self-reported	6	1.75 (1.29-2.37)	< 0.001	74.6	0.001	0.073
Assessment of DM	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	≥10	16	1.69 (1.41-2.04)	< 0.001	43.1	0.034	0.032
duration (years)	<10	6	1.22 (0.98-1.52)	0.078	0.0	0.948	
Adjusted other	Yes	19	1.45 (1.29-1.62)	< 0.001	6.6	0.375	<0.001
CVD risk factors	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<sup>2</sup>=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).

Variable	Group	Number of	RRR and 95%CI	P value	I-	P value for	P value for
		cohorts			square	heterogeneity	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	
	Self-reported	6	1.28 (1.04-1.58)	0.022	0.0	0.668	0.423
Assessment of DM	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	

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Follow-up	≥10	18	1.28 (1.11-1.47)	0.001	0.0	0.726	0.313
duration (years)	<10	4	1.09 (0.76-1.57)	0.627	36.0	0.196	-
Adjusted other	Yes	19	1.27 (1.11-1.44)	< 0.001	0.0	0.695	0.237
CVD risk factors	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  $\geq$  10000, used medical measure to assess DM, had a follow-up duration  $\geq$  10.0 years, adjusted for other cardiovascular risk factors, and was of high quality (Table 4).

Table 4. Subgroup analyses for cardiac death

-5								
5 7	Variable	Group	Number of	RRR and 95%CI	P value	I-	P value for	P value for
			cohorts			square	heterogeneity	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	
-								

2	
3	
4	
5	
6	
0	
7	
8	
-	
9	
	0
I	
1	1
1	2
I	<u>۲</u>
1	3
1	4
1	5
	6
1	7
	8
1	9
2	0
~	2
2	1
2	2
	~
2	
2	4
	5
2	6
5	-
2	7
2	8
	9
3	0
3	
3	2
3	2
3	4
	5
3	6
3	7
3	8
3	
4	0
4	
4	2
4	
4	4
Λ	5
	6
4	7
4	8
4	9
	-
5	
5	1
5	2
5	_
_	-
5	4
5	5
5	6
5	7
5	8
5	9

2								
3 4	Sample size	≥10000	2	1.96 (1.54-2.49)	< 0.001	0.0	0.591	0.015
5 6		<10000	8	1.18 (0.85-1.64)	0.322	0.0	0.433	
7 8		Self-reported	2	2.05 (1.59-2.64)	< 0.001	0.0	0.568	0.016
9 10 11	Assessment of DM	Measured	7	1.10 (0.78-1.54)	0.588	0.0	0.586	
12 13		Both	1	1.68 (0.93-3.06)	0.087	-	-	
14 15	Follow-up	≥10	8	1.57 (1.18-2.09)	0.002	21.8	0.256	0.257
16 17	duration (years)	<10	2	1.41 (0.42-4.68)	0.576	66.5	0.084	
18 19	Adjusted other	Yes	8	1.42 (1.02-1.98)	0.040	44.0	0.085	0.575
20 21	CVD risk factors	No	2	2.18 (0.79-6.03)	0.132	0.0	0.524	
22 23	Study quality	High	4	1.97 (1.56-2.48)	< 0.001	0.0	0.864	0.006
24 25 26	Study quanty	Low	6	1.10 (0.78-1.55)	0.593	0.0	0.417	
20								

# All-cause mortality

Data for the study that reported sex difference in an association between DM and subsequent allcause 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

55 56 56	Variable	Group	Number of	RRR and 95%CI	P value	I-	P value for	P value for
57			cohorts			square	heterogeneity	Meta-regression
58						(%)		
59						(, , ,		
60								

All-cause	Publication year	Before 2010	7	1.51 (1.23-1.85)	< 0.001	38.2	0.138	-		
nortality		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) 0.8	0.844	43.7	0.149					
		Self-reported	2	1.69 (1.46-1.95)	< 0.001	0.0	0.669	0.123		
	Assessment of DM	Measured	4	1.06 (0.59-1.90)	0.844	43.7	0.149			
		Both	1	1.50 (1.03-2.19)	0.035	-	-			
2 3 4 5	Follow-up	≥10	7	1.51 (1.23-1.85)	< 0.001	38.2	0.138	-		
	duration (years)	<10	0	-	-	-	-			
	Adjusted other	Yes	4	1.50 (1.12-2.01)	0.006	39.4	0.176	0.850		
	CVD risk factors	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		
	Study quanty	Low	5	1.25 (0.80-1.94)	0.329	53.3	0.073			
				0						
	<b><b>N</b> 111 <i>(</i>1</b>									
	Publication	bias								
		1 C 1 1 /	11 /	1 (1 ( ) 1 (		1. 6				
	Review of t	the funnel plots co	uld not ru	le out the potential fo	r publicatio	n bias for (	CHD, stroke,			
	cardiac deat	h, and all-cause me	ortality (Su	pplemental 6). The E	ger and Beg	g test resul	ts showed no			
			2 (							
	evidence of	publication bias f	or CHD (F	-value for Egger: 0.9	59; P-value	for Begg: 0	.245), stroke			
	$\frac{10000}{M} = \frac{1000}{M} = \frac{100}{M} = \frac$									
	(P-value loi	Eggel: 0.407, P-	value for r	segg. 0.398), cardiac	death (P-val	lue for Egg	el. 0.418, P-			
	value for Be	gg: 0.721), and all	-cause mo	rtality (P-value for Eg	ger: 0.118: P	-value for I	Begg: 0.230).			
					, <del>.</del> , <b>.</b>		<i></i>			
L	DISCUSS	ION								

# **Publication bias**

# **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

# **BMJ** Open

 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.

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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

# **BMJ** Open

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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

#### **BMJ** Open

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.

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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.

# Reference

 1. Yusuf S, Reddy S, Ounpuu S, et al. Global burden of cardiovascular diseases, I: general

# **BMJ** Open

considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001; 104: 2746-2753.

2. Chambless L, Keil U, Dobson A, et al. Population versus clinical view of case fatality from acute coronary heart disease: results from the WHO MONICA Project 1985-1990. Multinational MONItoring of Trends and Determinants in CArdiovascular Disease. Circulation 1997; 96: 3849-3859

3. Odutayo A, Wong CX, Hsiao AJ, et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016 Sep 6;354:i4482.

4. Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet 2016;388:465-75.

5. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol 2015;3:514-25.

6. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384:591-598.

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

7. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, Ezzati M, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet. 2014;383:970-83.

8. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-1847.

 Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care. 1993;16:434-44.

10. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with

#### **BMJ** Open

type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229-34.

Bartnik M, Norhammar A, Ryden L. Hyperglycaemia and cardiovascular disease. J Intern Med.
 2007; 262:145-56.

12. Goff DC Jr, Gerstein HC, Ginsberg HN, et al. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the action to control cardiovascular risk in diabetes (ACCORD) trial. Am J Cardiol 2007; 99: 4i-20i.

13. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia 2014;57:1542-51.

14. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. Lancet 2014;383:1973-80.

15. Walden CE, Knopp RH, Wahl PW, et al. Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations. N Engl J Med 1984;311:953-9.

16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology:a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group.JAMA. 2000; 283: 2008-12.

17. Wells G, Shea B, O' Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute 2009. Available:http://www.ohri.ca/programs/clinical\_epidemiology /oxford.htm.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177-88.

19. Ades AE, Lu G, Higgins JP. The interpretation of random-effects metaanalysis in decision models. Med Decis Making. 2005; 25: 646-54.

20. Woodward M. Epidemiology: study design and data analysis. 2nd edn. Boca Raton, FL, USA: Chapman and Hall/CRC, 2005.

# **BMJ** Open

21. Deeks JJ, Higgins JPT, Altman DG. Analyzing data and undertaking meta-analyses. In: Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions 5.0.1. Oxford, UK: The Cochrane Collaboration: 2008; chap 9.

22. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327: 557-60.

23. Tobias A. Assessing the influence of a single study in meta-analysis. Stata Tech Bull. 1999; 47:15-17.

24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315: 629-34.

25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50: 1088-1101.

26. Kleinman JC, Donahue RP, Harris MI, et al. Mortality among diabetics in a national sample. Am J Epidemiol 1988; 128:389-401.

27. Barrett-Connor E, Khaw KT. Diabetes mellitus: an independent risk factor for stroke? Am J Epidemiol 1988; 128: 116-23.

28. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. Am J Epidemiol 1989;129:687-702.

29. Fraser GE, Strahan TM, Sabate J, et al. Effects of traditional coronary risk factors on rates of incident coronary events in a low-risk population. The Adventist Health Study. Circulation 1992; 86:406-413.

30. Sievers ML, Nelson RG, Knowler WC, et al. Impact of NIDDM on mortality and causes of death in Pima Indians. Diabetes Care 1992; 15:1541-49.

31. Seeman T, de Mendes LC, Berkman L, et al. Risk factors for coronary heart disease among older men and women: a prospective study of community-dwelling elderly. Am J Epidemiol 1993; 138:1037-1049.

32. Keil JE, Sutherland SE, Knapp RG, et al. Mortality rates and risk factors for coronary disease in black as compared with white men and women. N Engl J Med 1993; 329:73-78.

33. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94.Series 1: programs and collection procedures. Vital Health Stat 11994; 32:1-407.

34. Simons LA, Friedlander Y, McCallum J, et al. Risk factors for coronary heart disease in the prospective Dubbo Study of Australian elderly. Atherosclerosis 1995; 117:107-118.

35. Collins VR, Dowse GK, Ram P, et al. Non-insulin-dependent diabetes and 11-year mortality in Asian Indian and Melanesian Fijians. Diabet Med 1996; 13:125-132.

36. Nilsson PM, Johansson SE, Sundquist J. Low educational status is a risk factor for mortality among diabetic people. Diabet Med 1998; 15:213-219.

37. Imazu M, Sumii K, Yamamoto H, et al. Influence of type 2 diabetes mellitus on cardiovascular disease mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Diabetes Res Clin Pract 2002; 57:61-69.

38. Jonsdottir LS, Sigfusson N, Gudnason V, et al. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. J Cardiovasc Risk 2002; 9:67-76.

39. Woodward M, Barzi F, Martiniuk A, et al. Cohort profile: the Asia Pacific Cohort Studies Collaboration. Int J Epidemiol 2006; 35:1412-16.

40. Natarajan S, Liao Y, Cao G, et al. Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. Arch Intern Med 2003; 163: 1735-1740.

41. Iso H, Imano H, Kitamura A, et al. Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. Diabetologia 2004; 47:2137-44.

42. Whiteley L, Padmanabhan S, Hole D, et al. Should diabetes be considered a coronary heart disease risk equivalent: results from 25 years of follow-up in the Renfrew and Paisley survey. Diabetes Care 2005; 28:1588-1593.

 43. Hu G, Jousilahti P, Qiao Q, et al. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. Diabetologia 2005; 48:856-861.

44. Lee ET, Howard BV, Wang W, et al. Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. Circulation 2006; 113: 2897-2905.

45. Najarian RM, Sullivan LM, Kannel WB, et al. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring study. Arch Intern Med 2006; 166: 106-11.

46. Hunt KJ, Williams K, Hazuda HP, et al. The metabolic syndrome and the impact of diabetes on coronary heart disease mortality in women and men: the San Antonio Heart Study. Ann Epidemiol 2007; 17:870-877.

47. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2007;93:172-176.

48. Myint PK, Sinha S, Luben RN, et al. Risk factors for first-ever stroke in the EPIC-Norfolk prospective population-based study. Eur J Cardiovasc Prev Rehabil 2008; 15:663-69.

49. Oba S, Nagata C, Nakamura K, et al. Selfreported diabetes mellitus and risk of mortality from all causes, cardiovascular disease, and cancer in Takayama: a population-based prospective cohort study in Japan. J Epidemiol 2008; 18: 197-203.

50. Hyvärinen M, Tuomilehto J, Laatikainen T, et al. The impact of diabetes on coronary heart disease differs from that on ischaemic stroke with regard to the gender. Cardiovasc Diabetol 2009; 8:17.

51. Doi Y, Ninomiya T, Hata J, et al. Impact of glucose tolerance status on development of ischemic stroke and coronary heart disease in a general Japanese population: the Hisayama study. Stroke 2010;41:203-209.

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

52. Cui R, Iso H, Yamagishi K, et al. Diabetes mellitus and risk of stroke and its subtypes among Japanese: the Japan public health center study. Stroke 2011; 42:2611-14.

53. Madssen E, Vatten L, Nilsen TI, et al. Abnormal glucose regulation and gender-specific risk of fatal coronary artery disease in the HUNT 1 study. Scand Cardiovasc J 2012; 46:219-225.

54. IcksA, ClaessenH, KvitkinaT, et al. Incidence and relative risk of stroke in the diabetic and the non-diabetic population between 1998 and 2014: A community-based stroke register. PLoSONE 2017; 12:e0188306.

55. Matsunaga M, Yatsuya H, Iso H, et al. Similarities and differences between coronary heart disease and stroke in the associations with cardiovascular risk factors: The Japan Collaborative Cohort Study. Atherosclerosis 2017;261:124-130.

## **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

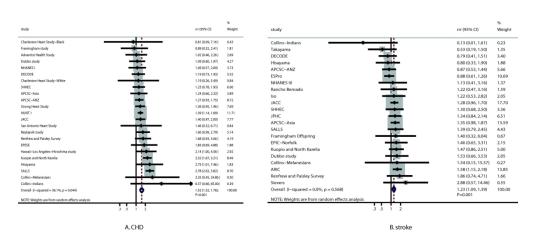
Supplemental 3: NOS scale for included studies

**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

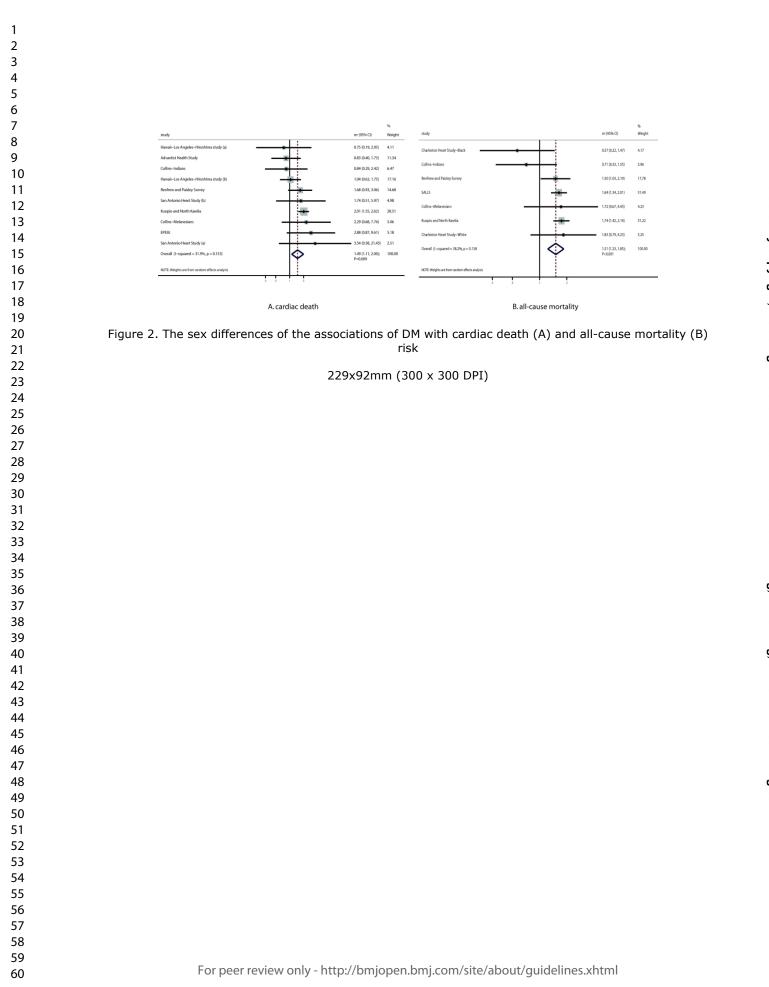
Supplemental 6: Funnel plots for CHD, stroke, cardiac death, and all-cause mortality.

Checklist S1: MOOSE Checklist





217x91mm (300 x 300 DPI)

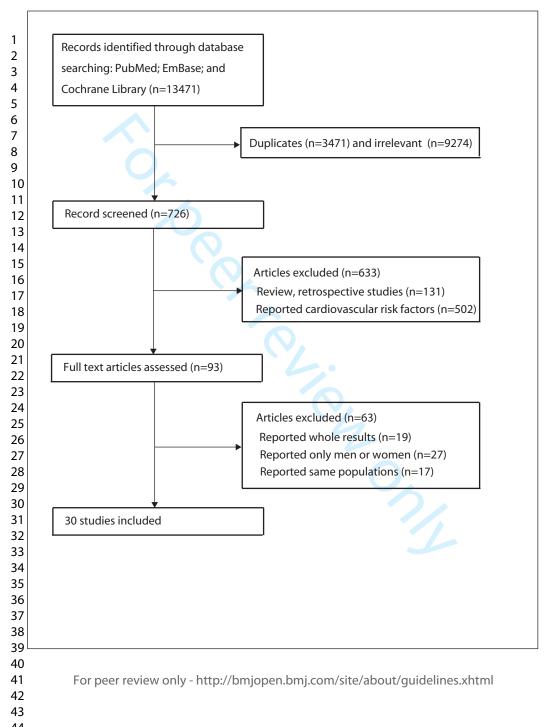


Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies

## 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])

o per teriez ony



				BMJ Open	d by copyright	136/bmjope		Pag	ge 32 of 45
1 2 3 4 5 Table S	S1. Quality scores of pr	prospective cohort stu	dies using Newcastle	-Ottawa Scale.	right, including	n-2018-024			
6 Study			Selection		Comparability 🤤	<u> </u>	Outcome		NOS
7 8	Representativene	Selection of the	Ascertainment	Demonstration that	Comparability on	⊐ ⊐Assessment	Adequate	Adequate	Overall
9	ss of the exposed	non exposed	of DM	outcomes was not present	the basis of the <b>a</b>		follow-up	follow-up	score
10	cohort	cohort		at start of study	design or analysis	- m<	duration	rate	
11 12 HANES I [26]	1	1	1	0	1 <b>t</b>	<b>19</b> . 1	1	1	7
Rancho Bernado [27]	0	1	1	0	1 <b>text</b>	shog 1	1	1	6
14 15 ARIC [28]	1	1	1	0	1 <b>ano</b>	nloa Jesc	1	1	7
1 <b>≜</b> dvantist Health	1	0	1	1	1 data		0	1	6
17 Study [29]			<u>'-C</u>	<u> </u>	3	fro			
<sup>18</sup> 19 Sievers [30]	0	1	1		1 <b>ning</b>		1	1	7
20 EPESE [31]	0	1	1	1	<b>&gt;</b>		0	1	6
<sup>2</sup> Charleston Heart	0	1	1		1 traini	bm 1 jop	1	0	6
22 25 25 25 22 25				VIA		<u> </u>			
2 <b>C</b> harleston Heart	0	1	1	1		<b>n. b</b> 1	1	0	6
<sup>25</sup> Study-Black [32]				V	I and s				
26 29 HANES III [33]	1	1	1	0			1	1	7
<b>28</b> ubbo study [34]	0	1	1	1	1 lar te	. J -	0	1	6
Çollins-Indians [35]	0	1	1	0	1 60	May 1	1	1	6
Gollins-Melanesians	0	1	1	0	1 <b>Dologi</b> e	<b>22</b> , 1	1	1	6
32 [35]					gies	2025			
<sup>33</sup> SALLS [36]	1	1	1	0	1	<b>5</b> at 1	1	0	6
35 Hawaii-Los	0	1	1	0	1	Depa	1	1	6
Angeles-Hiroshima						parti			
Angeles-Hiroshima 37 38 study [37]						men			
39									_
40 41						EZ-L			
41 42						TA			
43		Fc	or peer review only - '	http://bmjopen.bmj.com/site/ab	oout/quidelines.xhtml				
44 45			<b>•</b> • •						
45									

Page 33 of 45				BMJ Open		136/bmjopen-2 1 by copyright,				
1 2 3 4						018-02 includ				
Reykjavik study [38]	1	1	1	1	1	2493 ling	1	1	1	8
APCSC-Asia [39]	1	1	1	0	1	5 on for L	1	1	1	7
APCSC-Australia	1	1	1	0	1		1	1	1	7
9and New Zealand						July E s rel				
10 [39] 			×			ras atec				
Fzamingham study	0	1	1	1	1	19. [ mu: 1 to	1	1	1	7
13 [40]						Jow shoc text				
14 15 Iso [41]	1	1	1	1	1	17 July 2019. Downloaded from http: Erasmushogeschool . Ises related to text and data mining, A	1	1	1	8
Renfrew and Paisley	1	1	1	1	1	ndec hoo 1 dat	1	1	1	8
17 Survey [42]			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u> </u>		l fro l . ta m				
Kuopio and North	1	1	1	1	1	m http vining,	1	1	1	8
20 Karelia [43]				the second						
	0	1	1	1	1		1	1	1	7
Strong Heart Study 22 23 [44]				Vi		ainir				
24 Framingham	0	1	1	1	1	/bmjop <mark>e</mark> n.bmj. I training, and	1	1	1	7
25 <sub>Offspring</sub> [45]				<u> </u>	1/	en.bmj.o 19, and s				
26 San Antonio Heart	0	1	1	1	1		1	1	1	7
28 Study [46]					5					
<sup>29</sup> SHHEC [47]	1	1	1	0	1	May ech	1	1	1	7
<del>30</del> FPIC-Norfolk [48]	1	1	1	1	1	22 0lc	1	1	1	8
32Takayama [49]	1	1	1	1	2	, 2025 ogies.	1	0	1	8
<sup>33</sup> DECODE [50] -34	0	1	1	1	1	<u>s</u> . 25 at	1	0	1	6
35Hisayama [51]	0	1	1	1	1	t De	1	1	1	7
36 JPHC [52]	1	1	1	1	1	part	1	1	1	8
<sup>37</sup> <sub>38</sub> HUNT 1 [53]	1	1	1	1	1	tmen	1	1	1	8
39						nt Gl				
40						GEZ-LTA				
41 42						.TA				
43		Fc	st poor review only - t	nttp://bmjopen.bmj.com/site/ab	oout/quidelines.xht	·				
44			peer review only in	ttp://pmjopen.omj.com/sic/ao	Out/guideimes.and	1111				
45										

				BMJ Open		136/bmjopen-2018-02493 J by copyright, including		Pa	age 34 of 45
1						open yrigh			
2 3						-2018 It, inc			
4						3-024			
5 ESPro [54]	1	1	1	1	1	- <u>-</u>	1	0	7
6 JACC [55]	1	1	1	1	1	<b>♀</b> <u>0</u> 1	1	1	8
8						n 17 July 2019. Downloaded from http://bmjopen.bmj.com/ on May 22, 2025 a Erasmushogeschool . uses related to text and data mining, Al training, and similar technologies.			
9 10						uly 2 Era			
11						2019 ed t			
12 13						. Do usho o te			
14						wnlo oges xt ar			
15 16						bade Scho nd d			
17						ed fr ata r			
18						nini			
19 20						http ng, '			
21						Al tr			
22						njop ainii			
23 24						<mark>en.</mark> k			
25						and			
26 27						simi			
28						/ on			
29 30						May			
31						1 22, 10lo			
32						202 gies			
33 34						ā.			
35						Dep			
36 37						Departm			
38						nent			
39									
40 41						GEZ-LTA			
42						ĨĂ			
43		Fc	or peer review only - ht	tp://bmjopen.bmj.com/si	te/about/guidelines.xht	ml			
44									

Study		RR (95% CI)	% We
EPESE		3.20 (1.46, 7.01)	3.45
Hisayama		3.46 (1.59, 7.54)	3.48
APCSC–Asia		1.82 (1.02, 3.25)	4.3
APCSC-ANZ		2.01 (1.55, 2.60)	5.87
Advantist Health Study		2.15 (1.33, 3.47)	4.86
DECODE		2.48 (1.69, 3.65)	5.32
Renfrew and Paisley Survey		1.97 (1.27, 3.08)	5.04
Collins–Indians		20.70 (2.51, 171.00)	0.89
Collins–Melanesians		5.36 (1.18, 24.30)	1.5
Kuopio and North Karelia		4.89 (3.84, 6.24)	5.93
San Antonio Heart Study		4.94 (1.33, 18.40)	1.8
Hawaii–Los Angeles–Hiroshima study		3.29 (1.79, 6.55)	4.0
Reykjavik study		2.23 (1.50, 3.32)	5.2
Charleston Heart Study–White		1.25 (0.35, 4.47)	1.9
Charleston Heart Study–Black		2.02 (0.90, 4.53)	3.3
Strong Heart Study	-	2.26 (1.73, 2.96)	5.8
HUNT 1	-	2.50 (2.10, 2.80)	6.24
Framingham study	+ •	5.40 (2.40, 12.30)	3.3
SALLS	-	8.03 (6.34, 10.18)	5.9
Dubbo study		1.67 (1.12, 2.48)	5.26
SHHEC		3.06 (2.18, 4.27)	5.54
NHANES I		2.59 (1.59, 4.22)	4.8
JACC		2.08 (1.58, 2.75)	5.8
Overall (I–squared = 83.8%, p = 0.000)	$\diamond$	2.79 (2.25, 3.46)	100
NOTE: Weights are from random effects analysis			

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

Study		%
ID	RR (95% CI)	Weig
EPESE	• 1.75 (0.97, 3.16)	3.02
Hisayama	1.26 (0.67, 2.35)	2.80
APCSC-Asi a	1.47 (1.15, 1.88)	6.31
APCSC-ANZ		7.03
Advantist Health Study	◆ 2.11 (1.12, 4.00)	2.74
DECODE	2.09 (1.55, 2.82)	5.68
Renfrew and Paisley Survey	1.17 (0.78, 1.74)	4.57
Collins–Indians	3.15 (1.29, 7.69)	1.67
Collins-Melanesians	1.60 (0.43, 5.97)	0.86
Kuopio and North Karelia	2.11 (1.70, 2.63)	6.63
San Antonio Heart Study	3.38 (1.56, 7.31)	2.09
Hawaii–Los Angeles–Hiroshima study	1.54 (1.03, 2.25)	4.68
Reykjavik study	1.34 (0.97, 1.87)	5.35
Charleston Heart Study–White	1.05 (0.45, 2.44)	1.82
Charleston Heart Study–Black	2.48 (0.33, 18.67)	0.39
Strong Heart Study	1.66 (1.30, 2.12)	6.32
HUNT 1	<b>→</b> 1.80 (1.60, 2.10)	7.49
Framingham study	6.10 (3.40, 10.90)	3.08
SALLS	2.89 (2.34, 3.57)	6.71
Dubbo study	1.53 (0.99, 2.37)	4.23
SHHEC	2.49 (1.84, 3.37)	5.65
NHANES I	2.37 (1.55, 3.62)	4.35
JACC	1.49 (1.19, 1.88)	6.51
Overall (I-squared = 67.8%, p = 0.000)	1.87 (1.64, 2.12)	100.
NOTE: Weights are from random effects analysis		

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

Study			%
ID		RR (95% CI)	Weigl
Hisayama		2.02 (1.07, 3.81 )	4.14
APCSC–Asia		1.93 (1.45, 2.58)	6.66
APCSC-ANZ	+ • - :	1.41 (0.95, 2.08)	5.87
DECODE	· · · ·	2.37 (1.46, 3.84)	5.17
Renfrew and Paisley Survey		2.83 (1.63, 4.90)	4.69
Collins–Indians		2.88 (0.45, 18.40)	0.90
Collins–Melanesians		2.58 (0.44, 15.30)	0.97
Kuopio and North Karelia	· · · · ·	3.91 (2.68, 5.72)	5.97
SALLS	· · · · · ·	4.37 (2.89, 6.59)	5.71
Dubbo study		2.05 (1.14, 3.66)	4.47
SHHEC		3.64 (2.29, 5.79)	5.32
lso		2.20 (1.20, 4.00)	4.35
Framingham Offspring		2.70 (0.80, 9.16)	1.81
JPHC		2.19 (1.53, 3.12)	6.14
NHANES III		1.69 (0.90, 3.15)	4.19
ARIC	· · · ·	3.16 (2.55, 3.91)	7.17
EPIC-Norfolk		2.12 (1.15, 3.89)	4.30
Sievers		2.30 (0.70, 8.30)	1.77
Rancho Bernado		2.20 (1.00, 4.50)	3.47
Takayama		0.88 (0.36, 2.16)	2.81
ESPro		1.53 (1.19, 1.97)	6.90
JACC		1.39 (1.13, 1.71 )	7.21
Overall (I-squared = 71.3%, p = 0.000)	$\diamond$	2.23 (1.85, 2.69)	100.0
NOTE: Weights are from random effects analysis			

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

Study ID	RR (95% CI)	% Weigh
	200 A	
Hisayama –	★ 2.54 (1.40, 4.63)	3.86
APCSC-Asia	• 1.43 (1.23, 1.66)	7.86
APCSC-ANZ	1.62 (1.18, 2.22)	6.34
DECODE	3.01 (1.95, 4.64)	5.20
Renfrew and Paisley Survey	1.52 (0.72, 3.21)	2.96
Collins–Indians	21.80 (4.08, 116.00)	0.82
Collins–Melanesians	1.68 (0.38, 7.47)	1.01
Kuopio and North Karelia	2.66 (1.82, 3.88)	5.73
SALLS	3.15 (2.13, 4.67)	5.59
Dubbo study	1.34 (0.74, 2.45)	3.86
SHHEC	2.80 (1.77, 4.44)	4.96
lso	1.80 (1.00, 3.20)	3.98
Framingham Offspring	1.93 (0.86, 4.33)	2.67
JPHC -	1.64 (1.21, 2.23)	6.45
NHANES III	1.49 (0.66, 3.34)	2.66
ARIC	2.00 (1.57, 2.54)	7.08
EPIC–Norfolk	1.45 (0.84, 2.49)	4.27
Sievers	0.80 (0.30, 2.40)	1.84
Rancho Bernado	• 1.80 (1.00, 3.20)	3.98
Takayama	1.65 (0.99, 2.76)	4.51
ESPro –	← 1.75 (1.34, 2.27)	6.86
JACC 🔸	1.09 (0.90, 1.33)	7.49
Overall (I-squared = 68.5%, p = 0.000)	1.85 (1.57, 2.16)	100.00
NOTE: Weights are from random effects analysis	1	

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

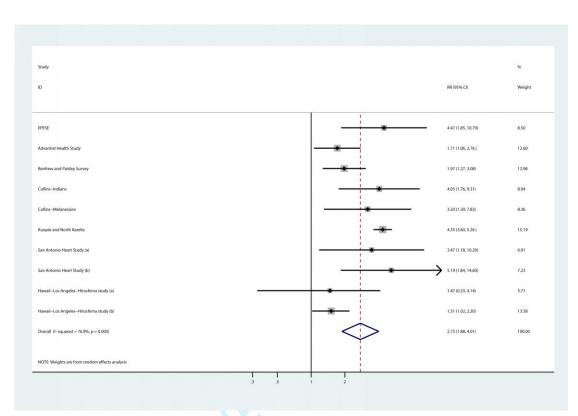


Figure S5. The summary results for DM and the risk of cardiac death in women

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

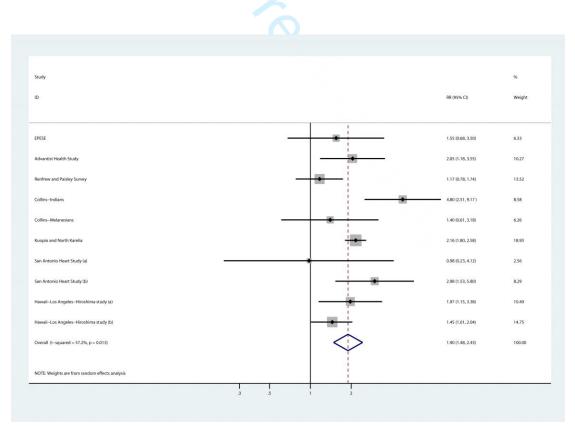


Figure S6. The summary results for DM and the risk of cardiac death in men

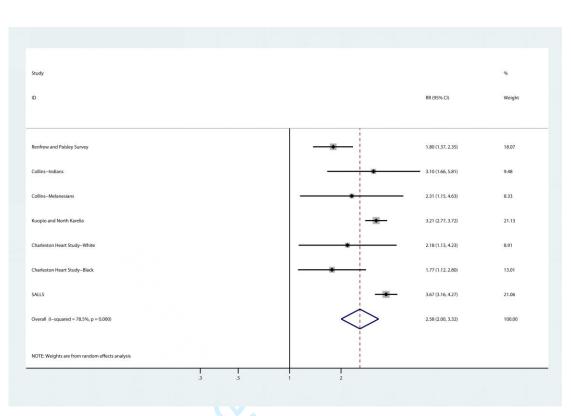


Figure S7. The summary results for DM and the risk of all-cause mortality in women

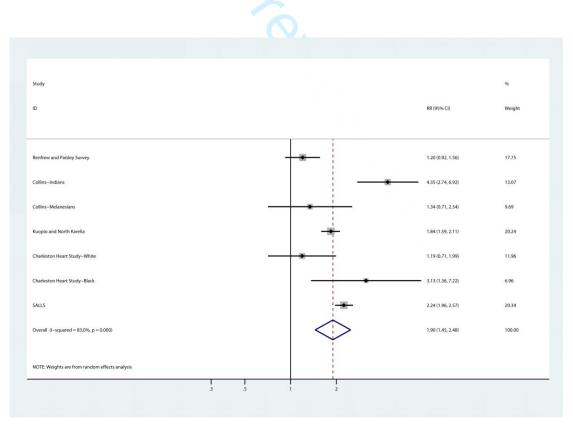


Figure S8. The summary results for DM and the risk of all-cause mortality in men

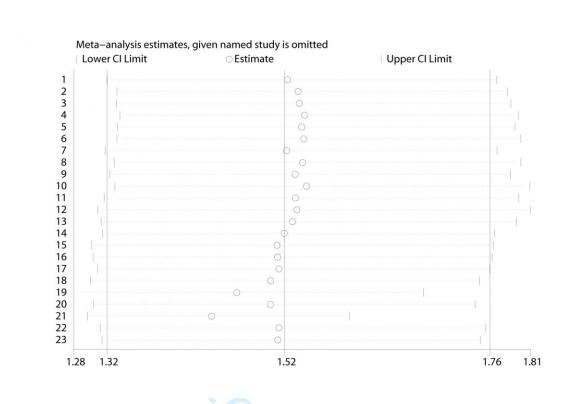


Figure S1. sensitivity analysis for CHD in women compared with men

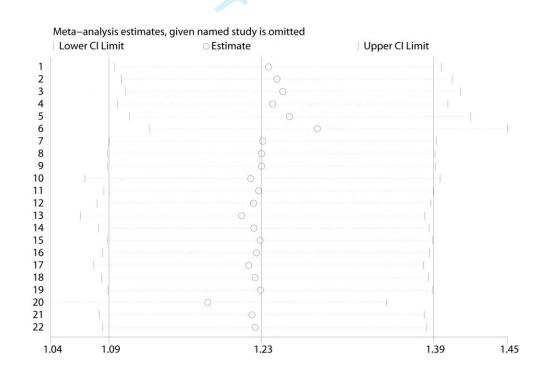


Figure S2. sensitivity analysis for stroke in women compared with men

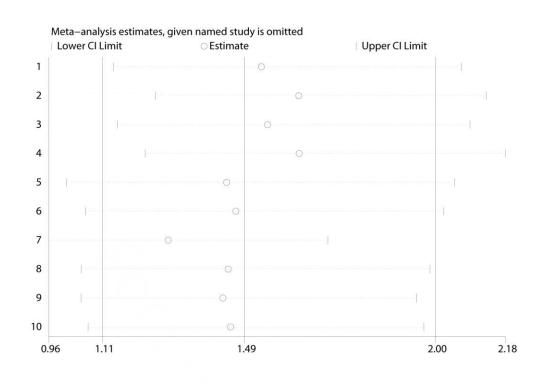


Figure S3. sensitivity analysis for cardiac death in women compared with men

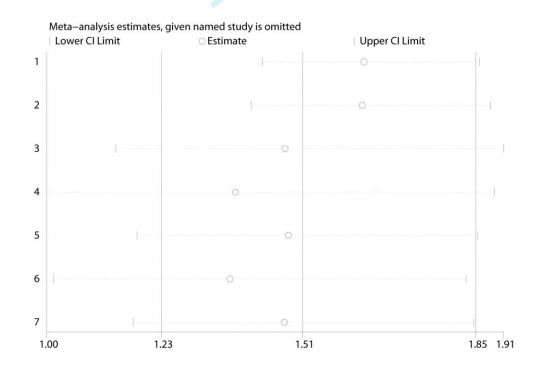
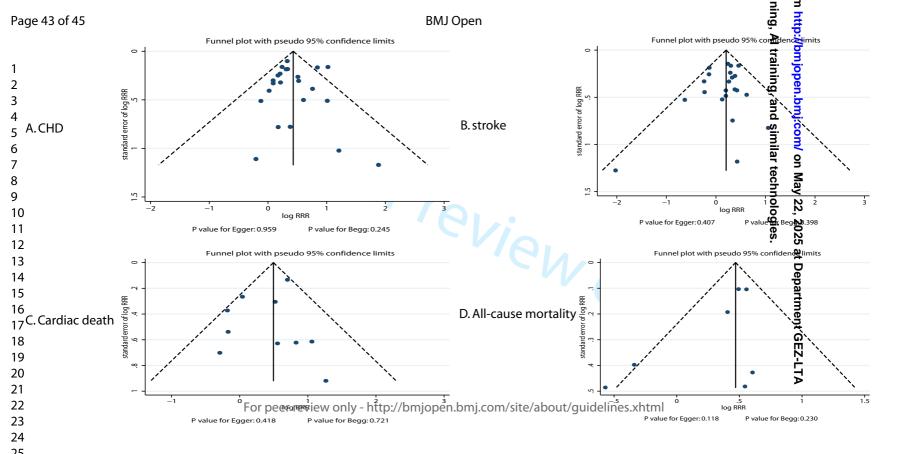


Figure S4. sensitivity analysis for all-cause mortality in women compared with men



## MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Metaanalyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reported	
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	

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Assessment of heterogeneity	Yes	5
Description of statistical methods (eg complete description of fixed or	Yes	5
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		
Provision of appropriate tables and graphics	Yes	5
Reporting of results should include	1	I
Graphic summarizing individual study estimates and overall estimate	Yes	6-7
Table giving descriptive information for each study included	Yes	17-2
Results of sensitivity testing (eg subgroup analysis)	Yes	21-2
Indication of statistical uncertainty of findings	Yes	6-8
Reporting of discussion should include		1
Quantitative assessment of bias (eg publication bias)	Yes	8-
Justification for exclusion (eg exclusion of non-English language	No	8-10
citations)		
Assessment of quality of included studies	Yes	17-2
Strengths and weaknesses	Yes	10
Reporting of conclusions should include	1	I
Consideration of alternative explanations for observed results	Yes	8-9
Generalization of the conclusions (eg appropriate for the data presented	Yes	10
and within the domain of the literature review)		
Guidelines for future research	Yes	10
Disclosure of funding source	Yes	11
NA: Not Applicable	I	I

**BMJ** Open

# **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
<b>Primary Subject Heading</b> :	Cardiovascular medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Sex difference, diabetes mellitus, major cardiovascular outcomes, all- cause mortality, meta-analysis

## SCHOLARONE<sup>™</sup> Manuscripts

2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
27
20
29
30
31
32
33
34
35
36
27
37 38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
52
55 54
54 55
56
57
58
59
60

# 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

Hao Wang1\*, Ying Ba1, Run-Ce Cai1, Qian Xing1

<sup>1</sup>Department of endocrinology, First affiliated hospital of Dalian Medical University, Dalian, Liaoning province, China, 116000

\*Corresponding author: Hao Wang, Department of endocrinology, First affiliated hospital of Dalian Medical University, Dalian, Liaoning province, China, 116000. E-mail: <u>wanghaodl@126.com</u>;

Running title: Sex difference of DM and major cardiovascular outcomes

Email:

Hao Wang: wanghaodl@126.com;

Ying Ba: baying126@126.com;

Run-Ce Cai: clearance@sina.com

Qian Xing: xingqiandl@163.com;

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

## ABSTRACT

## **BMJ** Open

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

**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

## **BMJ** Open

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

#### **BMJ** Open

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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.

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

#### 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

## **BMJ** Open

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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<sup>2</sup> 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:

#### **BMJ** Open

 publication year (2010 or after, and before 2010); country (Eastern or Western countries); sample size ( $\geq 10,000, < 10,000$ ); assessment of DM (self-reported, measured, or both); follow-up duration ( $\geq 10, < 10$  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.

ere

## 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**

#### **BMJ** Open

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies

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 followup period was 5.0–30.0 years, while 787 to 436,832 individuals were included in each study. Fortyone 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 selfreported 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).

Page 9 of 45						BMJ Open		136/bmjopen 4 by copyrigh		
6	1. Baseline c	characteristi	c of studies	included i	n the system	natic review and	l meta-analysis	136/bmjopen-2018-024935 or y by copyright, including for u		
<del>7</del> 8 Study 9 10	Publicatio n year	Country	Sample size	Number of DM	Age range	Percentage of women (%)	Assessment of DM	Follow Sin 1	Adjusted factors	Study quality
<sup>11</sup> NHANES I [26] 12	1988	US	7381	407	40-77	55.0	Self-reported	9.0 <b>to</b>	Age, SBP, smoking, BMI, TC	7
<sup>13</sup> Rancho Bernado 14 15 [27]	1988	US	3778	320	50-79	54.0	Self-reported	duration (striggarding 2019). Downloaded from http://bmj 9.0 to text and data mining, Al traii	Age, SBP, TC, smoking, obesity, family history, oestrogen use	6
<del>-16</del> 17 ARIC [28]	1989	US	15732	1610	45-64	55.0	Measured	18.0 at a from	Age, SBP, smoking, BMI, TC	7
-18 19Advantist Health	1992	US	27658	656	>25	63.0	Measured	6.0 g	Age, hypertension, smoking, BMI, PA	6
20 Study [29] 21						0	•	o://bn Al tr:		
22 Sievers [30] 23	1992	US	5131	1266	15-84	52.0	Measured	10.0 ing	Age	7
24 EPESE [31] 25 26 27	1993	US	2812	386	>65	58.0	Self-reported	6.0 and sin	Age, AHT use, smoking, BMI, diabetes, angina, chest pain on exertion	6
28Charleston Heart <sup>29</sup> Study-White [32] 30	1993	US	1394	38	>35	53.0	Measured	30.0 <mark>r techn</mark>	Age	6
<sup>31</sup> Charleston Heart 32 33Study-Black [32]	1993	US	787	37	>35	58.0	Measured	ologies.	Age	6
-34 35NHANES III [33] 36 37	1994	US	18603	1290	18-90	46.0	Self-reported or measured	13.0 Departme	Age, SBP, smoking, BMI, TC	7
38 39 40 41 42 43 44 45			Fo	r peer reviev	v only - http://	/bmjopen.bmj.com	n/site/about/guid	ent GEZ-LTA delines.xhtml		

						BMJ Open		136/bmjopen-2 1 by copyright,		Page 10 of 45
1 2 3 4								-2018-02 t, includ		
5 Dubbo study [34] 6 7 8 9	1995	Australia	2805	206	>60	56.0	Measured	<b>1935 on 17 J</b> 5.0 <b>g for uses</b>	Age, AHT use, BMI, TC, HDL, triacylglycerols, ApoB, LPa, diabetes, self-rated health, prior CH	6
1©ollins-Indians [35] 11 12	1996	Fiji	1220	166	>20.0	55.0	Measured	11.099. Downloaded from Erasmushogeschool . 11.011 and data mi	Age, SBP, smoking, BMI, TC, survey area	6
<sup>1</sup> Collins-Melanesians 14 15 [35]	1996	Fiji	1324	65	>20.0	53.0	Measured	11.0 and di	Age, SBP, smoking, BMI, TC, survey area	6
16 17 SALLS [36]	1998	Sweden	39055	174	25-74	51.0	Self-reported	16.0 <sup>a</sup> from 16.0 <sup>a</sup>	Age	6
18 19 Hawaii-Los 20Angeles-Hiroshima 21 22 study [37]	2002	Japan	927	169	40-79	56.0	Measured	1 http://bmjo 10-199, Al train		, 6
23 24 Reykjavik study 25 [38] 26 27	2002	Iceland	18519	295	32-60	52.0	Self-reported or measured	ing, and similar		, 8
28 29 <sup>APCSC-Asia [39]</sup> 30 31	2003	27 cohorts in Asia	436832	17763	>20	33.0	Self-reported or measured	on May 22, 7.0 technolo	Age, SBP, smoking, BMI, TC	7
32APCSC-Australia 33 34 35 [39] 36 37 38 39 40	2003	9 cohorts in Australia and New Zealand	99624	4784	>20	45.0	Self-reported or measured	2025 at Department gies.	Age, SBP, smoking, BMI, TC	7
41 42 43 44 45			For	' peer review	/ only - http://b	mjopen.bmj.c	com/site/about/guideli	GEZ-LTA lines.xhtml		

Page 11 of 45						BMJ Open		136/bm, 1 by cop		
1 2 3 4								136/bmjopen-2018-024935 d by copyright, including f 20.0		
5 Framingham study 6 [40] 7	2003	2 cohorts in US	5243	229	35-75	52.0	Measured	20.00 for use	Age, hypertension, smoking, BMI, TC	7
8 Iso [41] 9 10 11 12	2004	Japan	10582	267	40-69	60.0	Measured	17.0 Uly 2019. Downloaded from http://bmjop Erasmushogeschool . 25.0 and data mining, Al trainii 12.0 trainii	Age, hypertension, smoking, BMI, TC, HDL, skinfold, alcohol, community, menopause	8
Renfrew and Paisley 14 15 Survey [42]	2005	Scotland	15426	228	45-64	54.0	Self-reported or measured	25.0th and d	Age, SBP, smoking, BMI, TC, SES	8
<ul> <li>16</li> <li>1 ⊀uopio and North</li> <li>18 Karelia [43]</li> <li>19</li> </ul>	2005	Finland	51735	1108	25-74	51.0	Self-reported	ata 17.0a mining	Age, SBP, smoking, BMI, TC, study year	8
28strong Heart Study 21 22 [44]	2006	US	4372	724	45-74	61.0	Measured	12.0Al traini	Age, SBP, DBP, smoking, HDL, LDL, albuminuria	7
23 24 Framingham 25 Offspring [45] 26	2006	US	2097	99	50-81	50.0	Measured	ng, and si	Age, SBP, AHT, CVD, atrial fibrillation, LVH, smoking	7
<sup>2</sup> San Antonio Heart <sup>28</sup> 29 Study [46]	2007	US	4996	524	25-64	57.0	Measured	14.0 and similar techr	Age, ethnicity	7
<del>30</del> 31 SHHEC [47]	2007	Scotland	13343	184	30-74	51.0	Measured	16.0 <mark>00</mark> 22,	Age, SBP, smoking, BMI, TC	7
- <del>32</del> 3£PIC-Norfolk [48] 34 35	2008	UK	22516	441	40-79	55.0	Self-reported	<u>gies</u> 10.0 <u>5</u> at De	Age, SBP, smoking, BMI, TC, triglycerides	8
36 37 38 39 40 41 42 43 44 45 46			Foi	r peer review	only - http://l	bmjopen.bmj.co	om/site/about/guideli	partment GEZ-LTA		

							BMJ Open		136/bmj 1 by cop	Pa	ge 12 of 45
1 2 3 4									136/bmjopen-2018-024935 J by copyright, including for 7.0 7.0		
5 6 7 8	Takayama [49]	2008	Japan	29079	1217	>35	54.0	Self-reported	on 17 J or uses	Age, hypertension, smoking, BMI, PA, education, energy, vegetables, fat, alcohol	8
11 12 13	DECODE [50]	2009	7 cohorts in Finland and Sweden	9278	826	40-69	55.0	Measured	related to text and data m	Age, hypertension, smoking, BMI, TC, HDL	6
<del>-14</del> 15 16 17	Hisayama [51]	2010	Japan	2421	291	40-79	57.0	Measured	and chool , 14.0d data	Age, SBP, smoking, BMI, TC, HDL, alcohol intake, PA,ECG abnormalities	7
18 19 20 21 22	JPHC [52]	2011	2 cohorts in Japan	35657	2034	40-69	63.0	Measured	mining, Al training, and 17.00, a	Age, SBP, AHT, smoking, BMI, TC, HDL, triglycerides, alcohol, fasting status, residential areas	8
23 24 25	HUNT 1 [53]	2012	Norway	47951	1992	>20	52.0	Self-reported	17.0 <b>g</b> , and	Age, hypertension, smoking, BMI, CVD, PA	8
26 27 28 29	ESPro [54]	2017	Germany	105000	7190	>18	51.0	Self-reported or measured	14.0m/ on M	Calendar year, age	7
30 31 32 33 -34	JACC [55]	2017	Japan	104910	5729	40-79	58.0	Self-reported	fay 22, 2025 at 19.00ogies.	Age, education, smoking, alcohol, PA, BMI, history of hypertension, or history of DM	8
35 36 37 38 39 40 41 42								P, diastolic BP; LPa, P, systolic BP; SES,	art	LVH, left ventricle hypertrophy; NA, status	
42 43 44 45 46				Fo	r peer reviev	w only - http://br	njopen.bmj.cc	om/site/about/guideli	nes.xhtml		

## 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<sup>2</sup> = 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	RRR and 95%CI	P value	I-	P value for	P value for
		cohorts			square	heterogeneity	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	
	Self-reported	6	1.75 (1.29-2.37)	< 0.001	74.6	0.001	0.073
Assessment of DM	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	≥10	16	1.69 (1.41-2.04)	< 0.001	43.1	0.034	0.032
duration (years)	<10	6	1.22 (0.98-1.52)	0.078	0.0	0.948	
Adjusted other	Yes	19	1.45 (1.29-1.62)	< 0.001	6.6	0.375	<0.001
CVD risk factors	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	
Strol	ke						
Twee	nty studies repor	ted sex differ	ences in the associa	tion between	n DM and	subsequent ris	k for
strok	e. The pooled re	sults in men ar	nd women with DM	were statistic	cally signi	ficant (Supplem	ental
file 4	). The pooled RI	RR (female to	male) suggested that	women with	n DM had	an increased ris	k for
strok	e compared to m	nen with DM (	RRR 1.23 [95% CI	1.09–1.39]; I	P = 0.001)	(Figure 1B), an	id no
evide	ence of heteroge	neity was obse	erved ( $I^2 = 0.0\%$ ; P =	• 0.568). Ser	sitivity an	alysis indicated	l that
the c	onclusion was r	ot affected by	sequential exclusio	n of each st	udy from	the pooled ana	lyses
(Supj	plemental file 5)	. Subgroup an	alysis indicated no s	ex difference	es in the	relationship betw	ween
DM	and stroke risk	for pooled st	tudies published in	2010 or af	ter, condu	icted in the Ea	stern
hemi	sphere, sample s	sizes < 10,000	, those that used bo	th self-repor	ted and n	neasured parame	eters,
durat	ion of follow-up	o < 10.0 years,	no adjustments for	other cardiov	ascular ri	sk factors, and t	hose
of lov	1. (T 1 1	2)					
	w quality (Table	5).					
Table	w quality (Table e 3. Subgroup an		ke				
Table Variable			ke RRR and 95%CI	P value	I-	P value for	P value for
	e 3. Subgroup an	alyses for stro		P value	square	P value for heterogeneity	
Variable	e 3. Subgroup an Group	alyses for stro Number of cohorts	RRR and 95%CI	Ç	square (%)	heterogeneity	Meta-regressio
	e 3. Subgroup an	alyses for stro		P value 0.001	square		
Variable	e 3. Subgroup an Group	alyses for stro Number of cohorts	RRR and 95%CI	Ç	square (%)	heterogeneity	Meta-regressio
Variable	e 3. Subgroup an Group Before 2010	alyses for stro Number of cohorts 18	RRR and 95%CI 1.29 (1.11-1.50)	0.001	square (%) 0.0	heterogeneity 0.640	Meta-regressio
Variable Publication year	e 3. Subgroup an Group Before 2010 2010 or after	alyses for stro Number of cohorts 18 4	RRR and 95%CI 1.29 (1.11-1.50) 1.11 (0.89-1.40)	0.001	square (%) 0.0 18.1	heterogeneity 0.640 0.300	Meta-regressio
Variable Publication year	e 3. Subgroup an Group Before 2010 2010 or after Western	alyses for stro Number of cohorts 18 4 15	RRR and 95%CI 1.29 (1.11-1.50) 1.11 (0.89-1.40) 1.23 (1.05-1.44)	0.001 0.353 0.011	square (%) 0.0 18.1 0.0	heterogeneity 0.640 0.300 0.587	Meta-regressio
Variable Publication year Country	e 3. Subgroup an Group Before 2010 2010 or after Western Eastern	alyses for stro Number of cohorts 18 4 15 7	RRR and 95%CI 1.29 (1.11-1.50) 1.11 (0.89-1.40) 1.23 (1.05-1.44) 1.20 (0.97-1.49)	0.001 0.353 0.011 0.091	square (%) 0.0 18.1 0.0 14.7	heterogeneity 0.640 0.300 0.587 0.318	Meta-regressio 0.269 0.998
Variable Publication year Country	e 3. Subgroup an Group Before 2010 2010 or after Western Eastern ≥10000	alyses for stro Number of cohorts 18 4 15 7 14	RRR and 95%CI 1.29 (1.11-1.50) 1.11 (0.89-1.40) 1.23 (1.05-1.44) 1.20 (0.97-1.49) 1.25 (1.10-1.42)	0.001 0.353 0.011 0.091 <0.001	square (%) 0.0 18.1 0.0 14.7 0.0	heterogeneity 0.640 0.300 0.587 0.318 0.531	Meta-regressio

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

 **BMJ** Open

	Both	5	1.09 (0.85-1.41)	0.484	21.3	0.279	
Follow-up	≥10	18	1.28 (1.11-1.47)	0.001	0.0	0.726	0.313
duration (years)	<10	4	1.09 (0.76-1.57)	0.627	36.0	0.196	
Adjusted other	Yes	19	1.27 (1.11-1.44)	< 0.001	0.0	0.695	0.237
CVD risk factors	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
Study quanty _	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  $\geq 10,000$ , used medical measures to assess DM, had a follow-up duration  $\geq 10.0$ years, was adjusted for other cardiovascular risk factors, and was of high quality (Table 4).

Table 4. Subgroup analyses for cardiac death

46			-					
47	Variable	Group	Number of	RRR and 95%CI	P value	I-	P value for	P value for
48 49			cohorts			square	heterogeneity	Meta-regression
50 51						(%)		-
52 53	Publication year	Before 2010	10	1.49 (1.11-2.00)	0.009	31.9	0.153	-
54 55		2010 or after	0	-	-	-	-	
56 57 58	Country	Western	7	1.84 (1.45-2.32)	< 0.001	3.6	0.399	0.010
58 59 60		Eastern	3	0.97 (0.62-1.51)	0.891	0.0	0.870	

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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	
	Self-reported	2	2.05 (1.59-2.64)	< 0.001	0.0	0.568	0.016
Assessment of DM	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	≥10	8	1.57 (1.18-2.09)	0.002	21.8	0.256	0.257
duration (years)	<10	2	1.41 (0.42-4.68)	0.576	66.5	0.084	
Adjusted other	Yes	8	1.42 (1.02-1.98)	0.040	44.0	0.085	0.575
CVD risk factors	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
enary quanty	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 allcause 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

Variable	Group	Number of	RRR and 95%CI	P value	I-	P value for	P value for
		cohorts			square	heterogeneity	Meta-regression
					(%)		
					(,0)		
	Variable	Variable Group	1	1	1	1	cohorts square heterogeneity

2									
<sup>3</sup> All-cause	Publication year	Before 2010	7	1.51 (1.23-1.85)	< 0.001	38.2	0.138	-	
5mortality 6		2010 or after	0	-	-	-	-		
7 8 9	Country	Western	6	1.63 (1.41-1.88)	< 0.001	8.2	0.364	0.039	
10 11		Eastern	1	0.71 (0.33-1.55)	0.394	-	-		
12 13	Sample size	≥10000	3	1.66 (1.46-1.90)	< 0.001	0.0	0.772	0.050	
14 15		<10000	4	1.06 (0.59-1.90)	0.844	43.7	0.149		Prote
16 17	Assessment of	Self-reported	2	1.69 (1.46-1.95)	< 0.001	0.0	0.669	0.123	ected t
18 19 20	Assessment of DM	Measured	4	1.06 (0.59-1.90)	0.844	43.7	0.149		- уу сор
21 22		Both	1	1.50 (1.03-2.19)	0.035	-	-		yright
23 24	Follow-up	≥10	7	1.51 (1.23-1.85)	< 0.001	38.2	0.138	-	inclu
25 26	duration (years)	<10	0	-	-	-	-		ding fo
27 28 20	Adjusted other	Yes	4	1.50 (1.12-2.01)	0.006	39.4	0.176	0.850	or uses
29 30 31	CVD risk factors	No	3	1.33 (0.75-2.36)	0.321	57.6	0.095		Éra s relate
32 33	Study quality	High	2	1.69 (1.41-2.02)	< 0.001	0.0	0.490	0.414	smush ed to t
34 35		Low	5	1.25 (0.80-1.94)	0.329	53.3	0.073		noges ext an
36 37									chool d data
38 39 40	Publication	bias							mining,
41 42	A review of	the funnel plots c	ould not r	ule out the potential for	or publicatio	n bias for (	CHD, stroke,		Al trai
43 44	cardiac deat	th, and all-cause	mortality	(Supplemental file 6)	. The Egge	r and Begg	g test results		ning, a
45 46 47	revealed no	evidence of public	ation bias	for CHD (Egger $P = 0$ .	959; Begg P	<b>e</b> = 0.245), s	troke (Egger		, and sir
47 48 49	P = 0.407; B	egg P = 0.398), can	diac death	h (Egger P = 0.418; Beg	g P = 0.721)	, and all-ca	use mortality		nilar te
50 51 52 53 54	(Egger P = 0	0.118; Begg P = 0.	230).						Erdsmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

#### **Publication bias**

## **DISCUSSION**

#### **BMJ** Open

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies

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 metaanalysis [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

#### **BMJ** Open

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.

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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

#### **BMJ** Open

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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.

## Reference

#### **BMJ** Open

1. Yusuf S, Reddy S, Ounpuu S, et al. Global burden of cardiovascular diseases, I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001; 104: 2746-2753.

 Chambless L, Keil U, Dobson A, et al. Population versus clinical view of case fatality from acute coronary heart disease: results from the WHO MONICA Project 1985-1990. Multinational MONItoring of Trends and Determinants in CArdiovascular Disease. Circulation 1997; 96: 3849-

3. Odutayo A, Wong CX, Hsiao AJ, et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016 Sep 6;354:i4482.

4. Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. Lancet 2016;388:465-75.

5. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol 2015;3:514-25.

6. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014;384:591-598.

7. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, Ezzati M, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet. 2014;383:970-83.

8. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-1847.

 Stamler J, Vaccaro O, Neaton JD, et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the multiple risk factor intervention trial. Diabetes Care. 1993;16:434-44.

 10. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229-34.

Bartnik M, Norhammar A, Ryden L. Hyperglycaemia and cardiovascular disease. J Intern Med.
 2007; 262:145-56.

12. Goff DC Jr, Gerstein HC, Ginsberg HN, et al. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the action to control cardiovascular risk in diabetes (ACCORD) trial. Am J Cardiol 2007; 99: 4i-20i.

13. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia 2014;57:1542-51.

14. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. Lancet 2014;383:1973-80.

15. Walden CE, Knopp RH, Wahl PW, et al. Sex differences in the effect of diabetes mellitus on lipoprotein triglyceride and cholesterol concentrations. N Engl J Med 1984;311:953-9.

16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (MOOSE) group.JAMA. 2000; 283: 2008-12.

17. Wells G, Shea B, O' Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute 2009. Available:http://www.ohri.ca/programs/clinical\_epidemiology /oxford.htm.

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177-88.

19. Ades AE, Lu G, Higgins JP. The interpretation of random-effects metaanalysis in decision models. Med Decis Making. 2005; 25: 646-54.

#### **BMJ** Open

20. Woodward M. Epidemiology: study design and data analysis. 2nd edn. Boca Raton, FL, USA: Chapman and Hall/CRC, 2005.

21. Deeks JJ, Higgins JPT, Altman DG. Analyzing data and undertaking meta-analyses. In: Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions 5.0.1. Oxford, UK: The Cochrane Collaboration: 2008; chap 9.

22. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ.2003; 327: 557-60.

23. Tobias A. Assessing the influence of a single study in meta-analysis. Stata Tech Bull. 1999; 47:15-17.

24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315: 629-34.

25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50: 1088-1101.

26. Kleinman JC, Donahue RP, Harris MI, et al. Mortality among diabetics in a national sample. Am J Epidemiol 1988; 128:389-401. Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

27. Barrett-Connor E, Khaw KT. Diabetes mellitus: an independent risk factor for stroke? Am J Epidemiol 1988; 128: 116-23.

28. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. Am J Epidemiol 1989;129:687-702.

29. Fraser GE, Strahan TM, Sabate J, et al. Effects of traditional coronary risk factors on rates of incident coronary events in a low-risk population. The Adventist Health Study. Circulation 1992; 86:406-413.

30. Sievers ML, Nelson RG, Knowler WC, et al. Impact of NIDDM on mortality and causes of death in Pima Indians. Diabetes Care 1992; 15:1541-49.

31. Seeman T, de Mendes LC, Berkman L, et al. Risk factors for coronary heart disease among older

men and women: a prospective study of community-dwelling elderly. Am J Epidemiol 1993; 138:1037-1049.

32. Keil JE, Sutherland SE, Knapp RG, et al. Mortality rates and risk factors for coronary disease in black as compared with white men and women. N Engl J Med 1993; 329:73-78.

33. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94.Series 1: programs and collection procedures. Vital Health Stat 11994; 32:1-407.

34. Simons LA, Friedlander Y, McCallum J, et al. Risk factors for coronary heart disease in the prospective Dubbo Study of Australian elderly. Atherosclerosis 1995; 117:107-118.

35. Collins VR, Dowse GK, Ram P, et al. Non-insulin-dependent diabetes and 11-year mortality in Asian Indian and Melanesian Fijians. Diabet Med 1996; 13:125-132.

36. Nilsson PM, Johansson SE, Sundquist J. Low educational status is a risk factor for mortality among diabetic people. Diabet Med 1998; 15:213-219.

37. Imazu M, Sumii K, Yamamoto H, et al. Influence of type 2 diabetes mellitus on cardiovascular disease mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Diabetes Res Clin Pract 2002; 57:61-69.

38. Jonsdottir LS, Sigfusson N, Gudnason V, et al. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. J Cardiovasc Risk 2002; 9:67-76.

39. Woodward M, Barzi F, Martiniuk A, et al. Cohort profile: the Asia Pacific Cohort Studies Collaboration. Int J Epidemiol 2006; 35:1412-16.

40. Natarajan S, Liao Y, Cao G, et al. Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. Arch Intern Med 2003; 163: 1735-1740.

41. Iso H, Imano H, Kitamura A, et al. Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. Diabetologia 2004; 47:2137-44.

#### **BMJ** Open

42. Whiteley L, Padmanabhan S, Hole D, et al. Should diabetes be considered a coronary heart disease risk equivalent: results from 25 years of follow-up in the Renfrew and Paisley survey. Diabetes Care 2005; 28:1588-1593.

43. Hu G, Jousilahti P, Qiao Q, et al. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. Diabetologia 2005; 48:856-861.

44. Lee ET, Howard BV, Wang W, et al. Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. Circulation 2006; 113: 2897-2905.

45. Najarian RM, Sullivan LM, Kannel WB, et al. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring study. Arch Intern Med 2006; 166: 106-11.

46. Hunt KJ, Williams K, Hazuda HP, et al. The metabolic syndrome and the impact of diabetes on coronary heart disease mortality in women and men: the San Antonio Heart Study. Ann Epidemiol 2007; 17:870-877.

47. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2007;93:172-176.

48. Myint PK, Sinha S, Luben RN, et al. Risk factors for first-ever stroke in the EPIC-Norfolk prospective population-based study. Eur J Cardiovasc Prev Rehabil 2008; 15:663-69.

49. Oba S, Nagata C, Nakamura K, et al. Selfreported diabetes mellitus and risk of mortality from all causes, cardiovascular disease, and cancer in Takayama: a population-based prospective cohort study in Japan. J Epidemiol 2008; 18: 197-203.

50. Hyvärinen M, Tuomilehto J, Laatikainen T, et al. The impact of diabetes on coronary heart disease differs from that on ischaemic stroke with regard to the gender. Cardiovasc Diabetol 2009; 8:17.

51. Doi Y, Ninomiya T, Hata J, et al. Impact of glucose tolerance status on development of ischemic stroke and coronary heart disease in a general Japanese population: the Hisayama study. Stroke 2010;41:203-209.

52. Cui R, Iso H, Yamagishi K, et al. Diabetes mellitus and risk of stroke and its subtypes among Japanese: the Japan public health center study. Stroke 2011; 42:2611-14.

53. Madssen E, Vatten L, Nilsen TI, et al. Abnormal glucose regulation and gender-specific risk of fatal coronary artery disease in the HUNT 1 study. Scand Cardiovasc J 2012; 46:219-225.

54. IcksA, ClaessenH, KvitkinaT, et al. Incidence and relative risk of stroke in the diabetic and the non-diabetic population between 1998 and 2014: A community-based stroke register. PLoSONE 2017; 12:e0188306.

55. Matsunaga M, Yatsuya H, Iso H, et al. Similarities and differences between coronary heart disease and stroke in the associations with cardiovascular risk factors: The Japan Collaborative Cohort Study. Atherosclerosis 2017;261:124-130.

Y.C.Z.ONI

#### **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).

Supplemental file 1: Search strategy in PubMed.

Supplemental file 2: Flowchart illustrating the study selection process.

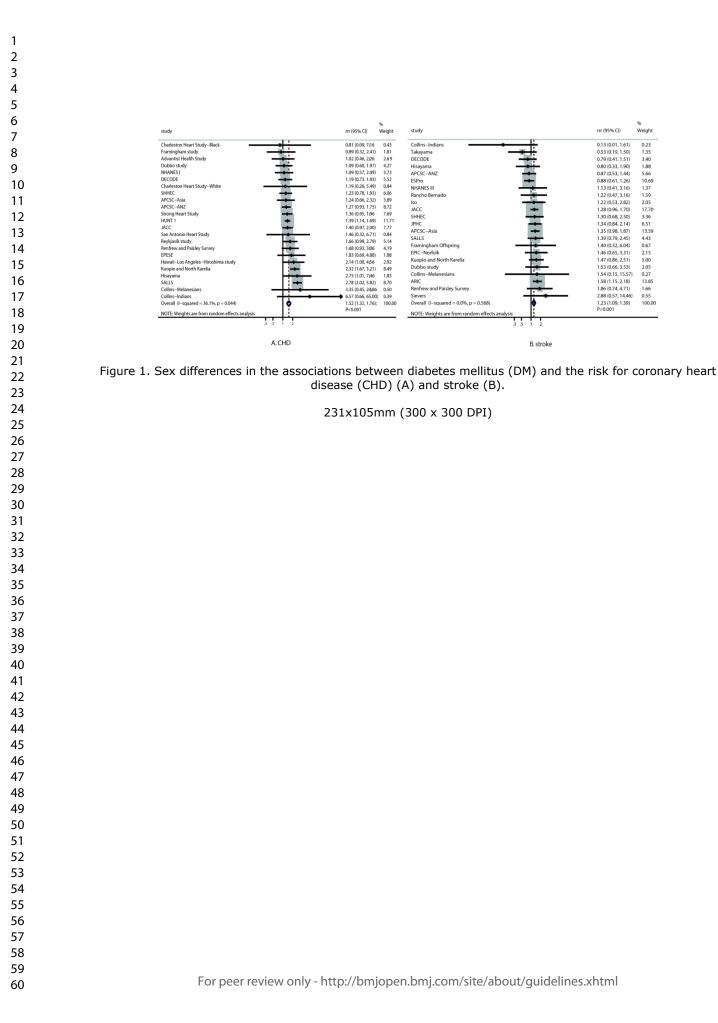
Supplemental file 3: Newcastle-Ottawa scale for included studies.

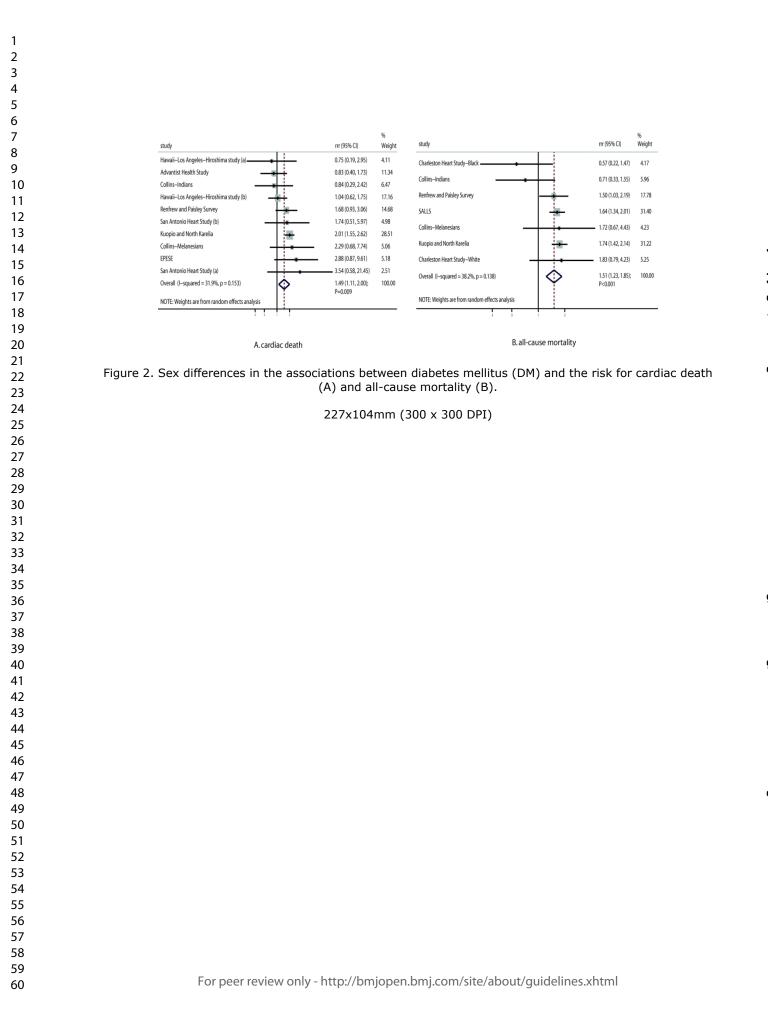
Supplemental file 4: Summary of results for diabetes mellitus (DM) and coronary heart disease (CHD) stroke, cardiac death, and all-cause mortality in men and women separately.

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 allcause mortality. rezien onz

Checklist S1: MOOSE Checklist



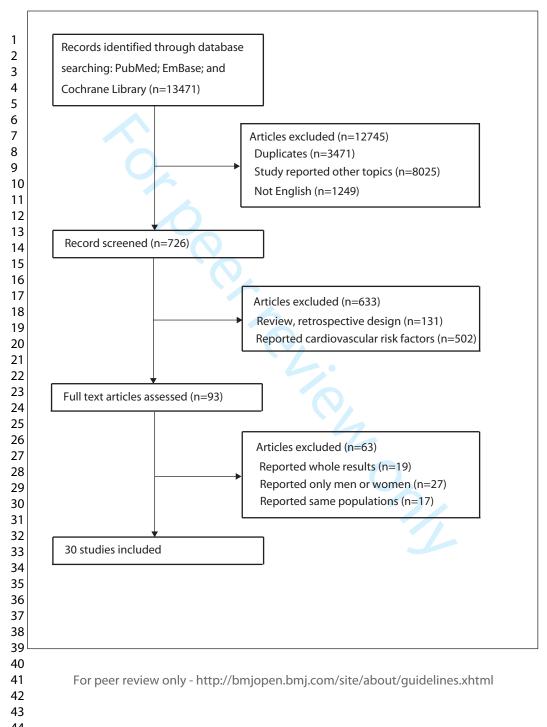


Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies

#### 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])

o per teriez ony



				BMJ Open	d by copyright	136/bmjope		Pag	ge 32 of 45
1 2 3 4 5 Table S	S1. Quality scores of pr	prospective cohort stu	dies using Newcastle	-Ottawa Scale.	right, including	n-2018-024			
6 Study			Selection		Comparability 🤤	<u> </u>	Outcome		NOS
7 8	Representativene	Selection of the	Ascertainment	Demonstration that	Comparability on	⊐ ⊐Assessment	Adequate	Adequate	Overall
9	ss of the exposed	non exposed	of DM	outcomes was not present	the basis of the <b>a</b>		follow-up	follow-up	score
10	cohort	cohort		at start of study	design or analysis	- m<	duration	rate	
11 12 HANES I [26]	1	1	1	0	1 <b>t</b>	<b>19</b> . 1	1	1	7
Rancho Bernado [27]	0	1	1	0	1 <b>text</b>	shog 1	1	1	6
14 15 ARIC [28]	1	1	1	0	1 <b>ano</b>	nloa Jesc	1	1	7
1 <b>≜</b> dvantist Health	1	0	1	1	1 data		0	1	6
17 Study [29]			<u>'-C</u>	<u> </u>	3	fro			
<sup>18</sup> 19 Sievers [30]	0	1	1		1 <b>ning</b>		1	1	7
20 EPESE [31]	0	1	1	1	<b>&gt;</b>		0	1	6
<sup>2</sup> Charleston Heart	0	1	1		1 traini	bm 1 jop	1	0	6
22 25 25 25 22 25				VIA		<u> </u>			
2 <b>C</b> harleston Heart	0	1	1	1		<b>n.</b> 1 <b>b n</b>	1	0	6
<sup>25</sup> Study-Black [32]				V	1 and s				
26 29 HANES III [33]	1	1	1	0			1	1	7
<b>28</b> ubbo study [34]	0	1	1	1	1 lar te	. J -	0	1	6
Çollins-Indians [35]	0	1	1	0	1 60	May 1	1	1	6
Gollins-Melanesians	0	1	1	0	1 <b>Dologi</b> e	<b>22</b> , 1	1	1	6
32 [35]					gies	2025			
<sup>33</sup> SALLS [36]	1	1	1	0	1	<b>5</b> at 1	1	0	6
35 Hawaii-Los	0	1	1	0	1	Depa	1	1	6
Angeles-Hiroshima						parti			
Angeles-Hiroshima 37 38 study [37]						men			
39									_
40 41						EZ-L			
41 42						TA			
43		Fc	or peer review only - '	http://bmjopen.bmj.com/site/ab	oout/quidelines.xhtml				
44 45			<b>•</b> • •						
45									

Page 33 of 45				BMJ Open		136/bmjopen-2 1 by copyright,				
1 2 3 4						018-02 includ				
Reykjavik study [38]	1	1	1	1	1	2493 ling	1	1	1	8
APCSC-Asia [39]	1	1	1	0	1	5 on for L	1	1	1	7
APCSC-Australia	1	1	1	0	1		1	1	1	7
9and New Zealand						July E s rel				
10 [39] 			×			ras atec				
Fzamingham study	0	1	1	1	1	19. [ mu: 1 to	1	1	1	7
13 [40]						Jow shoc text				
14 15 Iso [41]	1	1	1	1	1	17 July 2019. Downloaded from http: Erasmushogeschool . Ises related to text and data mining, A	1	1	1	8
Renfrew and Paisley	1	1	1	1	1	ndec hoo 1 dat	1	1	1	8
17 Survey [42]			~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	<u> </u>		l fro l . ta m				
Kuopio and North	1	1	1	1	1	m http vining,	1	1	1	8
20 Karelia [43]				the second						
	0	1	1	1	1		1	1	1	7
Strong Heart Study 22 23 [44]				Via		ainir				
24 Framingham	0	1	1	1	1	/bmjop <mark>e</mark> n.bmj. I training, and	1	1	1	7
25 <sub>Offspring</sub> [45]				<u> </u>	1/	en.bmj.o 19, and s				
26 San Antonio Heart	0	1	1	1	1		1	1	1	7
28 Study [46]					5					
<sup>29</sup> SHHEC [47]	1	1	1	0	1	May ech	1	1	1	7
<del>30</del> FPIC-Norfolk [48]	1	1	1	1	1	22 0lc	1	1	1	8
32Takayama [49]	1	1	1	1	2	, 2025 ogies.	1	0	1	8
<sup>33</sup> DECODE [50] -34	0	1	1	1	1	<u>s</u> . 25 at	1	0	1	6
35Hisayama [51]	0	1	1	1	1	t De	1	1	1	7
36 JPHC [52]	1	1	1	1	1	part	1	1	1	8
<sup>37</sup> <sub>38</sub> HUNT 1 [53]	1	1	1	1	1	tmen	1	1	1	8
39						nt Gl				
40						GEZ-LTA				
41 42						.TA				
43		Fc	st poor review only - t	nttp://bmjopen.bmj.com/site/ab	oout/quidelines.xht	·				
44			peer review only in	ttp://pmjopen.omj.com/sic/ao	Out/guideimes.and	[]]]]				
45										

				BMJ Open		136/bmjopen-2018-02493 J by copyright, including		Pa	age 34 of 45
1						open yrigh			
2 3						-2018 It, inc			
4						3-024			
5 ESPro [54]	1	1	1	1	1	- <u>-</u>	1	0	7
6 JACC [55]	1	1	1	1	1	<b>♀</b> <u>0</u> 1	1	1	8
8						n 17 July 2019. Downloaded from http://bmjopen.bmj.com/ on May 22, 2025 a Erasmushogeschool . uses related to text and data mining, Al training, and similar technologies.			
9 10						uly 2 Era			
11						2019 ed t			
12 13						. Do usho o te			
14						wnlo oges xt ar			
15 16						bade Scho nd d			
17						ed fr ata r			
18						nini			
19 20						http ng, '			
21						Al tr			
22						njop ainii			
23 24						<mark>en.</mark> k			
25						and			
26 27						simi			
28						/ on			
29 30						May			
31						1 22, 10lo			
32						202 gies			
33 34						ā.			
35						Dep			
36 37						Departm			
38						nent			
39									
40 41						GEZ-LTA			
42						ĨĂ			
43		Fc	or peer review only - ht	tp://bmjopen.bmj.com/si	te/about/guidelines.xht	ml			
44									

Study		RR (95% CI)	% We
EPESE		3.20 (1.46, 7.01)	3.45
Hisayama		3.46 (1.59, 7.54)	3.48
APCSC–Asia		1.82 (1.02, 3.25)	4.3
APCSC-ANZ		2.01 (1.55, 2.60)	5.87
Advantist Health Study		2.15 (1.33, 3.47)	4.86
DECODE		2.48 (1.69, 3.65)	5.32
Renfrew and Paisley Survey		1.97 (1.27, 3.08)	5.04
Collins–Indians		20.70 (2.51, 171.00)	0.89
Collins–Melanesians		5.36 (1.18, 24.30)	1.5
Kuopio and North Karelia		4.89 (3.84, 6.24)	5.93
San Antonio Heart Study		4.94 (1.33, 18.40)	1.8
Hawaii–Los Angeles–Hiroshima study		3.29 (1.79, 6.55)	4.0
Reykjavik study		2.23 (1.50, 3.32)	5.2
Charleston Heart Study–White		1.25 (0.35, 4.47)	1.9
Charleston Heart Study–Black		2.02 (0.90, 4.53)	3.3
Strong Heart Study	-	2.26 (1.73, 2.96)	5.8
HUNT 1	-	2.50 (2.10, 2.80)	6.24
Framingham study	+ •	5.40 (2.40, 12.30)	3.3
SALLS	-	8.03 (6.34, 10.18)	5.9
Dubbo study		1.67 (1.12, 2.48)	5.26
SHHEC		3.06 (2.18, 4.27)	5.54
NHANES I		2.59 (1.59, 4.22)	4.8
JACC		2.08 (1.58, 2.75)	5.8
Overall (I–squared = 83.8%, p = 0.000)	$\diamond$	2.79 (2.25, 3.46)	100
NOTE: Weights are from random effects analysis			

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

Study		%
ID	RR (95% CI)	Weig
EPESE	• 1.75 (0.97, 3.16)	3.02
Hisayama	1.26 (0.67, 2.35)	2.80
APCSC-Asi a	1.47 (1.15, 1.88)	6.31
APCSC-ANZ		7.03
Advantist Health Study	◆ 2.11 (1.12, 4.00)	2.74
DECODE	2.09 (1.55, 2.82)	5.68
Renfrew and Paisley Survey	1.17 (0.78, 1.74)	4.57
Collins–Indians	3.15 (1.29, 7.69)	1.67
Collins-Melanesians	1.60 (0.43, 5.97)	0.86
Kuopio and North Karelia	2.11 (1.70, 2.63)	6.63
San Antonio Heart Study	3.38 (1.56, 7.31)	2.09
Hawaii–Los Angeles–Hiroshima study	1.54 (1.03, 2.25)	4.68
Reykjavik study	1.34 (0.97, 1.87)	5.35
Charleston Heart Study–White	1.05 (0.45, 2.44)	1.82
Charleston Heart Study–Black	2.48 (0.33, 18.67)	0.39
Strong Heart Study	1.66 (1.30, 2.12)	6.32
HUNT 1	<b>→</b> 1.80 (1.60, 2.10)	7.49
Framingham study	6.10 (3.40, 10.90)	3.08
SALLS	2.89 (2.34, 3.57)	6.71
Dubbo study	1.53 (0.99, 2.37)	4.23
SHHEC	2.49 (1.84, 3.37)	5.65
NHANES I	2.37 (1.55, 3.62)	4.35
JACC	1.49 (1.19, 1.88)	6.51
Overall (I-squared = 67.8%, p = 0.000)	1.87 (1.64, 2.12)	100.
NOTE: Weights are from random effects analysis		

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

Study			%
ID		RR (95% CI)	Weigl
Hisayama		2.02 (1.07, 3.81 )	4.14
APCSC–Asia		1.93 (1.45, 2.58)	6.66
APCSC-ANZ	+ • - :	1.41 (0.95, 2.08)	5.87
DECODE	· · · ·	2.37 (1.46, 3.84)	5.17
Renfrew and Paisley Survey		2.83 (1.63, 4.90)	4.69
Collins–Indians		2.88 (0.45, 18.40)	0.90
Collins–Melanesians		2.58 (0.44, 15.30)	0.97
Kuopio and North Karelia	· · · · ·	3.91 (2.68, 5.72)	5.97
SALLS	· · · · · ·	4.37 (2.89, 6.59)	5.71
Dubbo study		2.05 (1.14, 3.66)	4.47
SHHEC		3.64 (2.29, 5.79)	5.32
lso		2.20 (1.20, 4.00)	4.35
Framingham Offspring		2.70 (0.80, 9.16)	1.81
JPHC		2.19 (1.53, 3.12)	6.14
NHANES III		1.69 (0.90, 3.15)	4.19
ARIC	· · · ·	3.16 (2.55, 3.91)	7.17
EPIC-Norfolk		2.12 (1.15, 3.89)	4.30
Sievers		2.30 (0.70, 8.30)	1.77
Rancho Bernado		2.20 (1.00, 4.50)	3.47
Takayama		0.88 (0.36, 2.16)	2.81
ESPro		1.53 (1.19, 1.97)	6.90
JACC		1.39 (1.13, 1.71 )	7.21
Overall (I-squared = 71.3%, p = 0.000)	$\diamond$	2.23 (1.85, 2.69)	100.0
NOTE: Weights are from random effects analysis			

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

Study ID	RR (95% CI)	% Weigh
	200 A	
Hisayama –	★ 2.54 (1.40, 4.63)	3.86
APCSC-Asia	• 1.43 (1.23, 1.66)	7.86
APCSC-ANZ	1.62 (1.18, 2.22)	6.34
DECODE	3.01 (1.95, 4.64)	5.20
Renfrew and Paisley Survey	1.52 (0.72, 3.21)	2.96
Collins–Indians	21.80 (4.08, 116.00)	0.82
Collins–Melanesians	1.68 (0.38, 7.47)	1.01
Kuopio and North Karelia	2.66 (1.82, 3.88)	5.73
SALLS	3.15 (2.13, 4.67)	5.59
Dubbo study	1.34 (0.74, 2.45)	3.86
SHHEC	2.80 (1.77, 4.44)	4.96
lso	1.80 (1.00, 3.20)	3.98
Framingham Offspring	1.93 (0.86, 4.33)	2.67
JPHC -	1.64 (1.21, 2.23)	6.45
NHANES III	1.49 (0.66, 3.34)	2.66
ARIC	2.00 (1.57, 2.54)	7.08
EPIC–Norfolk	1.45 (0.84, 2.49)	4.27
Sievers -	0.80 (0.30, 2.40)	1.84
Rancho Bernado	• 1.80 (1.00, 3.20)	3.98
Takayama	1.65 (0.99, 2.76)	4.51
ESPro –	← 1.75 (1.34, 2.27)	6.86
JACC 🔸	1.09 (0.90, 1.33)	7.49
Overall (I-squared = 68.5%, p = 0.000)	1.85 (1.57, 2.16)	100.00
NOTE: Weights are from random effects analysis	1	

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

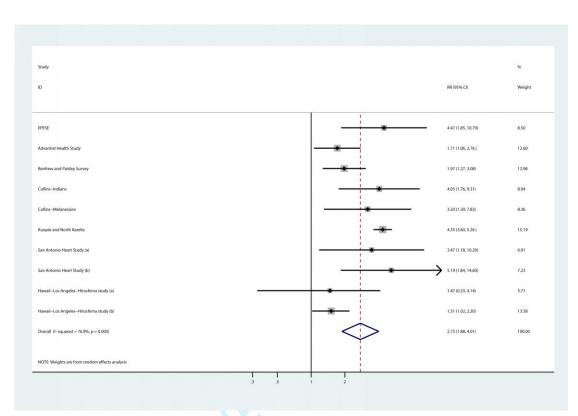


Figure S5. The summary results for DM and the risk of cardiac death in women

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

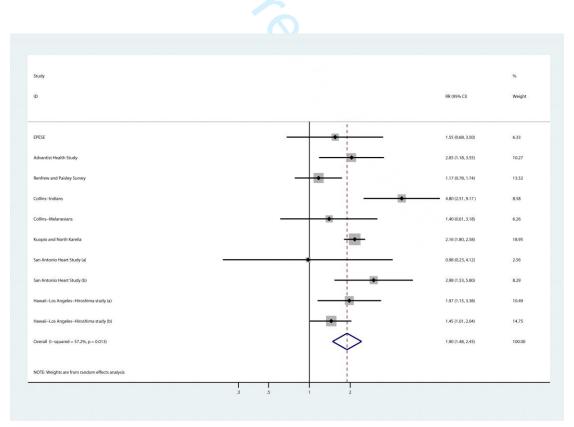


Figure S6. The summary results for DM and the risk of cardiac death in men

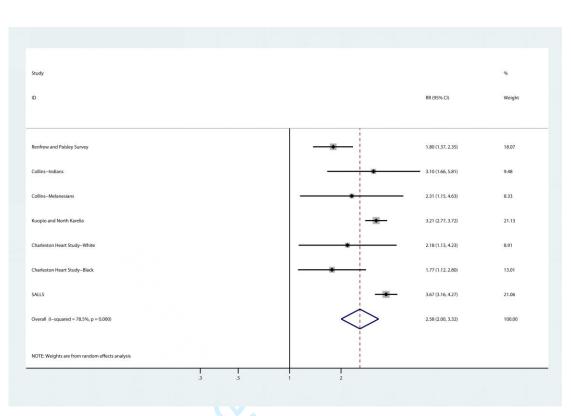


Figure S7. The summary results for DM and the risk of all-cause mortality in women

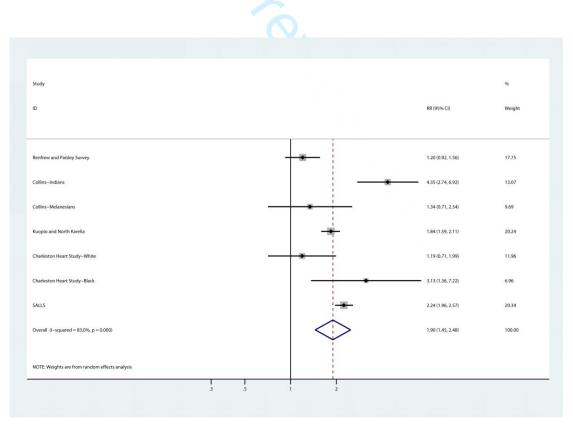
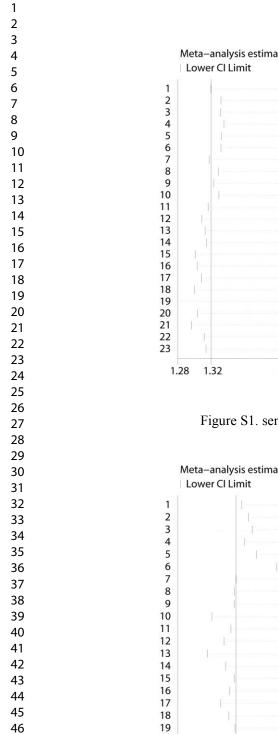
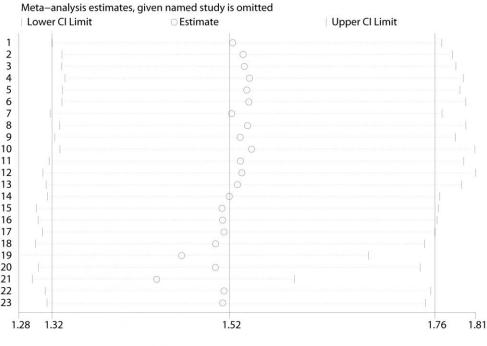
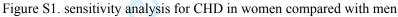


Figure S8. The summary results for DM and the risk of all-cause mortality in men







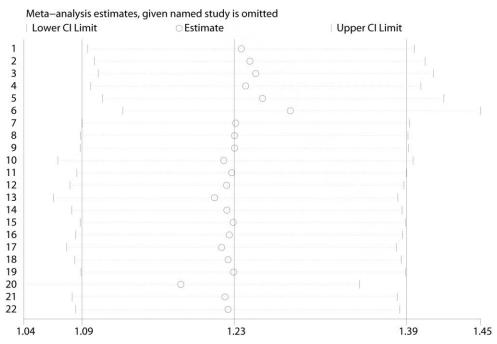


Figure S2. sensitivity analysis for stroke in women compared with men

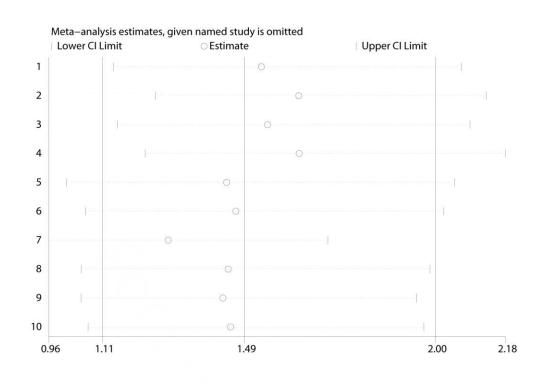


Figure S3. sensitivity analysis for cardiac death in women compared with men

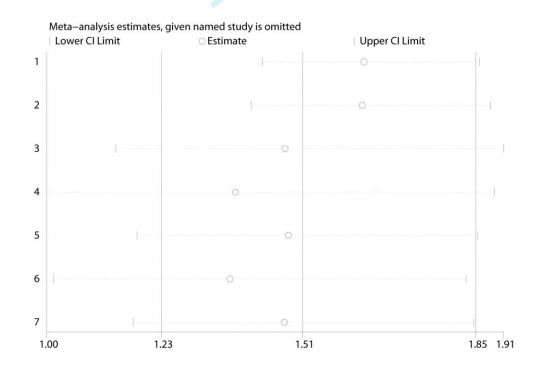
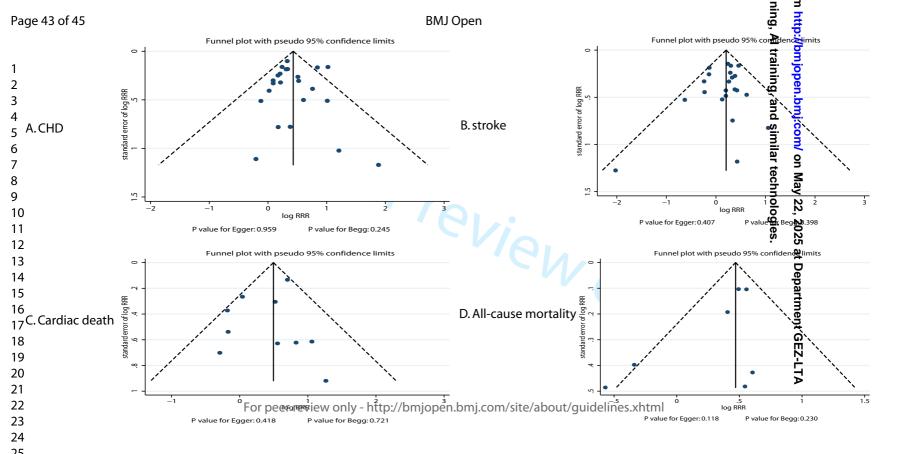


Figure S4. sensitivity analysis for all-cause mortality in women compared with men



# MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Metaanalyses of Observational Studies

Reporting Criteria	Reported (Yes/No)	Reporte
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 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 Provision of appropriate tables and graphics <b>Reporting of results should include</b> Graphic summarizing individual study estimates and overall estimate Table giving descriptive information for each study included Results of sensitivity testing (eg subgroup analysis) Indication of statistical uncertainty of findings <b>Reporting of discussion should include</b> Quantitative assessment of bias (eg publication bias) Justification for exclusion (eg exclusion of non-English language	Yes Yes Yes Yes Yes Yes Yes Yes	
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 Provision of appropriate tables and graphics <b>Reporting of results should include</b> Graphic summarizing individual study estimates and overall estimate Table giving descriptive information for each study included Results of sensitivity testing (eg subgroup analysis) Indication of statistical uncertainty of findings <b>Reporting of discussion should include</b> Quantitative assessment of bias (eg publication bias) Justification for exclusion (eg exclusion of non-English language	Yes Yes Yes Yes Yes	5 6-7 17-2 21-2
account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated Provision of appropriate tables and graphics <b>Reporting of results should include</b> Graphic summarizing individual study estimates and overall estimate Table giving descriptive information for each study included Results of sensitivity testing (eg subgroup analysis) Indication of statistical uncertainty of findings <b>Reporting of discussion should include</b> Quantitative assessment of bias (eg publication bias) Justification for exclusion (eg exclusion of non-English language	Yes Yes Yes Yes	6-7 17-2 21-2
cumulative meta-analysis) in sufficient detail to be replicated Provision of appropriate tables and graphics <b>Reporting of results should include</b> Graphic summarizing individual study estimates and overall estimate Table giving descriptive information for each study included Results of sensitivity testing (eg subgroup analysis) Indication of statistical uncertainty of findings <b>Reporting of discussion should include</b> Quantitative assessment of bias (eg publication bias) Justification for exclusion (eg exclusion of non-English language	Yes Yes Yes Yes	6-7 17-2 21-2
Provision of appropriate tables and graphics <b>Reporting of results should include</b> Graphic summarizing individual study estimates and overall estimate Table giving descriptive information for each study included Results of sensitivity testing (eg subgroup analysis) Indication of statistical uncertainty of findings <b>Reporting of discussion should include</b> Quantitative assessment of bias (eg publication bias) Justification for exclusion (eg exclusion of non-English language	Yes Yes Yes Yes	6-7 17-2 21-2
Reporting of results should includeGraphic summarizing individual study estimates and overall estimateTable giving descriptive information for each study includedResults of sensitivity testing (eg subgroup analysis)Indication of statistical uncertainty of findingsReporting of discussion should includeQuantitative assessment of bias (eg publication bias)Justification for exclusion (eg exclusion of non-English language	Yes Yes Yes Yes	6-7 17-2 21-2
Graphic summarizing individual study estimates and overall estimate Table giving descriptive information for each study included Results of sensitivity testing (eg subgroup analysis) Indication of statistical uncertainty of findings <b>Reporting of discussion should include</b> Quantitative assessment of bias (eg publication bias) Justification for exclusion (eg exclusion of non-English language	Yes Yes Yes	21-2
Table giving descriptive information for each study includedResults of sensitivity testing (eg subgroup analysis)Indication of statistical uncertainty of findingsReporting of discussion should includeQuantitative assessment of bias (eg publication bias)Justification for exclusion (eg exclusion of non-English language	Yes Yes Yes	21-2
Results of sensitivity testing (eg subgroup analysis)         Indication of statistical uncertainty of findings         Reporting of discussion should include         Quantitative assessment of bias (eg publication bias)         Justification for exclusion (eg exclusion of non-English language	Yes Yes	21-2
Indication of statistical uncertainty of findings Reporting of discussion should include Quantitative assessment of bias (eg publication bias) Justification for exclusion (eg exclusion of non-English language	Yes	
Reporting of discussion should include         Quantitative assessment of bias (eg publication bias)         Justification for exclusion (eg exclusion of non-English language		6-8
Quantitative assessment of bias (eg publication bias) Justification for exclusion (eg exclusion of non-English language	Ves	
Justification for exclusion (eg exclusion of non-English language	Ves	
	105	8-
	No	8-10
citations)		
Assessment of quality of included studies	Yes	17-2
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 presente	d Yes	10
and within the domain of the literature review)		
Guidelines for future research	Yes	10
Disclosure of funding source	Yes	11
Disclosure of funding source		