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META-ANALYSIS

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

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Abstract
Aims/hypothesis A previous pooled analysis suggested that women with diabetes are at substantially increased risk of fatal CHD compared with affected men. Additional findings from several larger and more contemporary studies have since been published on the sex-specific associations between diabetes and incident CHD. We performed an updated systematic review with meta-analysis to provide the most reliable evidence of any sex difference in the effect of diabetes on subsequent risk of CHD.
Methods PubMed MEDLINE was systematically searched for prospective population-based cohort studies published between 1 January 1966 and 13 February 2013. Eligible studies had to have reported sex-specific RR estimates for incident CHD associated with diabetes and its associated variability that had been adjusted at least for age. Random-effects meta-analyses with inverse variance weighting were used to obtain sex-specific RRs and the RR ratio (RRR) (women:men) for incident CHD associated with diabetes.
Results Data from 64 cohorts, including 858,507 individuals and 28,203 incident CHD events, were included. The RR for incident CHD associated with diabetes compared with no diabetes was 2.82 (95% CI 2.35, 3.38) in women and 2.16 (95% CI 1.82, 2.56) in men. The multiple-adjusted RRR for incident CHD was 44% greater in women with diabetes than in men with diabetes (RRR 1.44 [95% CI 1.27, 1.63]) with no significant heterogeneity between studies (I^2=20%).
Conclusions/interpretation Women with diabetes have more than a 40% greater risk of incident CHD compared with men with diabetes. Sex disparities in pharmacotherapy are unlikely to explain much of the excess risk in women, but future studies are warranted to more clearly elucidate the mechanisms responsible for the substantial sex difference in diabetes-related risk of CHD.

Keywords Coronary heart disease · Diabetes · Meta-analysis · Risk factors · Sex differences · Systematic review

Abbreviations

APCSC	Asia Pacific Cohort Studies Collaboration
ARIC	Atherosclerosis Risk in Communities Study
NHANES III	National Health and Nutrition Examination Survey III
RRR	RR ratio
SHHEC	Scottish Heart Health Extended Cohort Study

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Introduction

A lack of sex-specific data from early epidemiological studies has typically led to the assumption that the associations between risk factors and disease outcomes are equivalent in women and men. But, increasingly, evidence to support the existence of clinically meaningful sex differences in the relationships between certain risk factors, such as smoking and diabetes [1–5], with chronic disease is becoming apparent, often with more detrimental effects of such risk factors in women than in men. Sex differences in risk factor–disease associations would not only have implications for patient management and treatment, but would also have repercussions on efforts to quantify the burden of disease due to specific risk factors, as most such studies use only a single estimate of risk that is uniformly applied to both men and women [6, 7].

In 2006, a systematic review of 37 cohort studies of the sex-specific effects of diabetes on risk of fatal CHD suggested that women with diabetes had a near 50% greater excess risk compared with their male equivalents, even after consideration of differences in baseline levels of other major risk factors [1]. Since that report, estimates from a number of large and more contemporary cohort studies have been published, with many reporting incident as well as fatal CHD outcomes [8–11].

Given the rising prevalence rates of diabetes worldwide, and the clinical implications that any important sex difference in the association between diabetes and future risk of CHD would have, we have performed an updated systematic review with meta-analysis of all available evidence to provide the most robust comparison of the sex-specific effect of diabetes on risk of incident CHD.

Methods

Search strategy and selection criteria A systematic search was performed in PubMed MEDLINE (www.ncbi.nlm.nih.gov) on 13 February 2013 using a combined text word and medical subject heading (MeSH) search strategy (electronic supplementary material [ESM] Methods). References were scanned to identify other potentially relevant studies. Prospective population-based studies were included if they had provided RRs (or equivalents) for the associations between diabetes and CHD in men and women. Studies were excluded if they had not adjusted for at least age or did not provide information on the variability around the point estimate. The search strategy and items for data extraction were defined and agreed by all authors. One author (S. A. E. Peters) did the search and extracted the data. Uncertainties regarding the inclusion/exclusion of manuscripts and data extraction were discussed by all authors and resolved by mutual consent. In addition, the authors had access to individual participant data from four studies: the Asia Pacific Cohort Studies Collaboration (APCSC) [12], the Atherosclerosis Risk in Communities Study (ARIC) [13], the National Health and Nutrition Examination Survey (NHANES) III [14] and the Scottish Heart Health Extended Cohort Study (SHHEC) [15].

Data extraction and statistical analysis For each study, we obtained the sex-specific RRs for individuals with diabetes vs individuals without diabetes and 95% CIs through extraction of RRs from the published manuscripts or through new statistical analyses on the available individual participant data. We subsequently used these RRs to estimate the women-to-men ratio of RRs (RRR) and 95% CIs [1]. The primary endpoint was incident CHD (either fatal or non-fatal) and the secondary endpoint was fatal CHD, to facilitate comparison with previous reviews. Multiple-adjusted results were used in our primary analyses. The set of multiple adjustments made were allowed to vary by study, but had to include at least one other risk factor in addition to age. After natural log transformation of study-specific estimates, pooled estimates across studies were obtained using random-effects meta-analysis. The inverse of the variance of the log RR and of the log RRR were used to weight studies according to an estimate of statistical size [16].

Sensitivity analyses were performed by age (≤60 vs >60 years), region (occidental cohort vs Oriental cohort) and baseline year of data collection (pre-1985 vs post-1985). The I^2 statistic was used to estimate the percentage of variability between studies due to between-study heterogeneity [17, 18]. Random-effects meta-regression analyses were used to assess whether differences in the mean duration of study follow-up, the incidence of CHD, the women-to-men ratio incidence of CHD, the overall prevalence of diabetes or the women-to-men ratio of diabetes prevalence contributed to heterogeneity between studies. We used funnel plots of the natural log of the RRR against its standard error to assess publication bias, and trim and fill analyses to adjust the RRRs for the presence of publication bias. All analyses were performed using Stata version 11.0 (SataCorp, College Station, TX, USA).

Results

Of the 8,183 articles that were identified through the systematic search, 116 articles qualified for full-text evaluation (Fig. 1). Of these, 18 articles provided information on sex differences in the association between diabetes and risk of CHD. These published data were extended with individual participant data from APCSC, ARIC, NHANES III and SHHEC. Overall, data from 64 cohorts, including 858,507

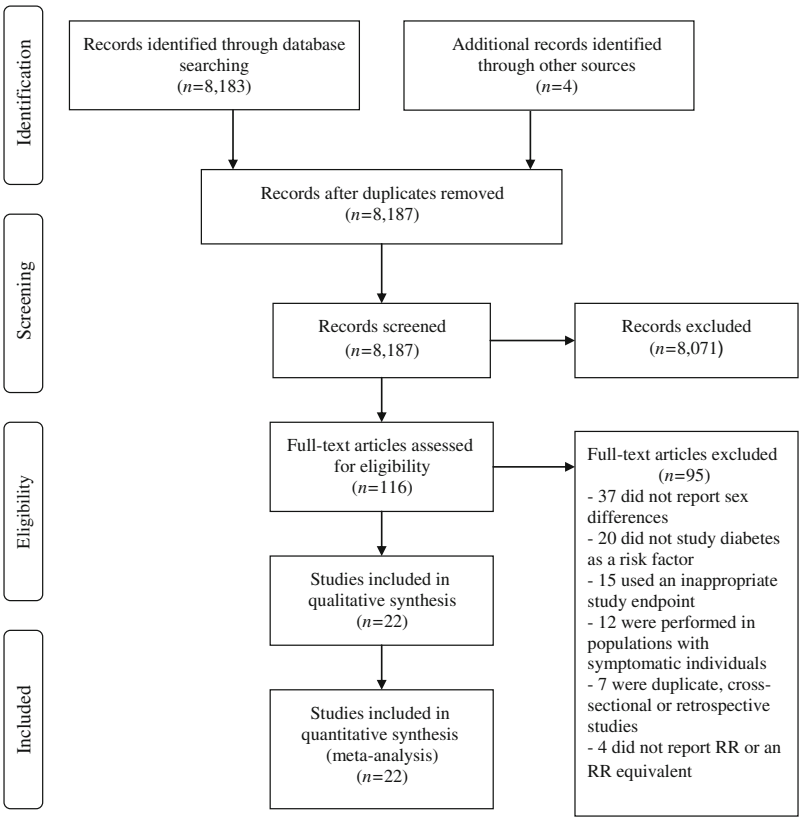

Fig. 1 Flow chart of the systematic review for the primary analysis

individuals (42% women) and 28,203 incident CHD events, were available (Table 1). Thirty cohorts were from Asia (55% of the individuals), 13 from Europe (23%), 11 from Australia, New Zealand or Pacific (12%) and 10 from the USA (10%). Individuals were between 20 and 107 years of age at baseline and the duration of follow-up ranged from 5 to 30 years. The average prevalence of diabetes at baseline was 3.4% among women and 4.8% among men.

Pooled estimates for the diabetes-related risk of combined incident CHD The overall summary RR for incident CHD associated with diabetes compared with no diabetes was 2.82 (95% CI 2.35, 3.38) in women and 2.16 (95% CI 1.82, 2.56) in men (ESM Fig. 1). The I^2 statistic for heterogeneity between studies was 83% in women and 86% in men, indicating substantial between-study heterogeneity. Exclusion of the four studies with only age-adjusted results reduced the between-study heterogeneity to 65% in women and 66% in men and mildly attenuated the RR estimates (RR 2.63 [95% CI 2.27, 3.06] in women and 1.85 [95% CI 1.64, 2.10] in men) (Fig. 2).

RRR for CHD in men and women with diabetes The pooled multiple-adjusted women-to-men RRR for incident CHD was 1.44 (95% CI 1.27, 1.63) (Fig. 3). Visual inspection of the funnel plot showed minimal evidence for publication bias (ESM Fig. 2), adjustment for which did not alter the results. There was no evidence that the pooled RRR varied materially by important study characteristics, namely: duration of study follow-up (p for heterogeneity=0.16); the proportion of CHD events within each study (p=0.76); the women-to-men ratio of the CHD event rate (p=0.93); the prevalence of diabetes (p=0.58); or the women-to-men ratio of diabetes prevalence (p=0.84) (ESM Fig. 3). In the sensitivity analyses there was no evidence that the multiple-adjusted RRRs for incident CHD differed materially by age or region (p value for interaction, 0.26 and 0.78, respectively); however, there was a borderline significant effect of year of cohort at study baseline on the RRR (p value for interaction=0.048; ESM Fig. 4).

Pooled estimates and RRR for the diabetes-related risk of fatal CHD In an analysis that included data from 52 cohorts, including 782,681 (91%) individuals and at least 16,877 fatal CHD events, the pooled multiple-adjusted RR estimates for fatal CHD associated with diabetes were 2.83 (95% CI 2.25, 3.54) in women and 2.04 (95% CI 1.72, 2.43) in men (ESM Fig. 5). The corresponding women-to-men RRR was 1.44 (95% CI 1.20, 1.73) (ESM Fig. 6).

Effect of adjustment for confounding on the relationship between diabetes and incident CHD A total of 47 cohorts, including 694,592 individuals (81%) and 16,492 CHD events, provided separate estimates of the association between diabetes and CHD that were age adjusted and then additionally adjusted for multiple confounders (Table 1). There was

Table 1 Characteristics of included studies separated by studies that contributed to earlier reviews and newly included or analysed studies

Study name	Country	Baseline study (years)	Follow-up (years)	Study size, n (% female)	Age (years)	Diabetes, n (% female)	Ascertainment of diabetes	CHD events, n (% female)	F or NF	Maximum adjustment available
Studies that contributed to earlier reviews										
Advantist Health Study [39]	USA	1974	6	27,658 (63)	25+	656	Measured	302 (55)	F	Age, hypertension, smoking, BMI, PA
Charleston Heart Study–White [40]	USA	1960–61	30	1,394 (53)	35+	38 (42)	Measured	257 (42)	F	Age
Charleston Heart Study–Black [40]	USA	1960–61	30	787 (58)	35+	37 (70)	Measured	134 (46)	F	Age
Collins et al–Indians [41]	Fiji	1980	11	1,220 (55)	20+	166 (52)	Measured	NA	F	Age, SBP, smoking, BMI, TC, survey area
Collins et al–Melanesians [41]	Fiji	1980	11	1,324 (53)	20+	65 (66)	Measured	NA	F	Age, SBP, smoking, BMI, TC, survey area
Dubbo study [42]	Australia	1988	5	2,805 (56)	60+	206 (49)	Measured	463 (48)	F and NF	Age, AHT use, BMI, TC, HDL, triacylglycerols, ApoB, LP_a, diabetes, self-rated health, prior CHD
EPESE [43]	USA	1982	6	2,812 (58)	65+	386 (60)	Self-reported	230 (55)	F	Age, AHT use, smoking, BMI, diabetes, angina, chest pain on exertion
Framingham study [44]	USA (2 cohorts)	1970–75	20	5,243 (52)	35–75	229 (42)	Measured	395 (29)	F	Age, hypertension, smoking, BMI, TC
Hawaii–Los Angeles–Hiroshima study [45]	Japan	1976–84	10–18	917 (56)	40–79	169 (54)	Measured	43 (33)	F	Age, hypertension, smoking, BMI, TC, triacylglycerols, uric acid, ECG abnormalities
NHANES I [46]	USA	1971–75	9	7,381 (55)	40–77	407 (54)	Self-reported	350 (36)	F	Age, SBP, smoking, BMI, TC
Reykjavik study [47]	Iceland	1967	17	18,519 (52)	32–60	295 (49)	Self-reported, partly measured	2,406 (29)	F and NF	Age, hypertension, smoking, BMI, TC, triacylglycerols, diabetes, glucose, prior CHD, LVH
SALLS [48]	Sweden	1979–85	16	39,055 (51)	25–74	174 (51)	Self-reported	1,520 (31)	F	Age
Newly included or analysed studies										
APCSC–ANZ [49]	Pool of 9 cohorts	1989–96	7	99,624 (45)	20–104	4,784 (31)	Self-reported or measured	3,953 (31)	F and NF	Age, SBP, smoking, BMI, TC
APCSC–Asia [49]	Pool of 27 cohorts	1961–93	7	436,832 (33)	20–107	17,763 (23)	Self-reported or measured	1,195 (27)	F and NF	Age, SBP, smoking, BMI, TC
ARIC [13]	USA	1987–89	18	15,732 (55)	45–64	1,610 (58)	Measured	1,616 (42)	F and NF	Age, SBP, smoking, BMI, TC
DECODE study [10]	Finland and Sweden (7 cohorts)	1987–02	5–21	9,278 (55)	40–69	826 (47)	Measured	530 (34)	F and NF	Age, hypertension, smoking, BMI, TC, HDL
Hisayama [9]	Japan	1988	14	2,421 (57)	40–79	291 (46)	Measured	171 (34)	F and NF	Age, SBP, smoking, BMI, TC, HDL, alcohol intake, PA, ECG abnormalities
HUNT 1 [11]	Norway	1984–86	17	47,951 (52)	20+	1,992 (57)	Self-reported	4,723 (39)	F	Age, hypertension, smoking, BMI, CVD, PA
Kuopio and North Karelia [50]	Finland	1972–97	17	51,735 (51)	25–74	1,108 (46)	Self-reported	3,039 (31)	F	Age, SBP, smoking, BMI, TC, study year
NHANES III [14]	USA	1988	13	18,603 (46)	18–90	1,290 (38)	Self-reported, partly Measured	973 (51)	F	Age, SBP, smoking, BMI, TC
Renfrew and Paisley Survey [51]	Scotland	1972–76	25	15,426 (54)	45–64	228 (51)	Self-reported, partly measured	2,357 (59)	F	Age, SBP, smoking, BMI, TC, SES
San Antonio Heart Study [52]	USA	1979–88	16	4,996 (57)	25–64	524 (58)	Measured	121 (43)	F	Age, ethnicity

Table 1 (continued)

Study name	Country	Baseline study (years)	Follow-up (years)	Study size, n (% female)	Age (years)	Diabetes, n (% female)	Ascertainment of diabetes	CHD events, n (% female)	F or NF	Maximum adjustment available
SHHEC [15]	Scotland	1,984–87	16	13,343 (51)	30–74	184 (46)	Measured	2,595 (39)	F and NF	Age, SBP, smoking, BMI, TC
Strong Heart Study [53]	USA	1989–91	12	4,372 (61)	45–74	714 (52)	Measured	724 (52)	F and NF	Age, SBP, DBP, smoking, HDL, LDL, albuminuria
Takayama [8]	Japan	1992	7	29,079 (54)	>35	1,217 (35)	Self-reported	106 (45)	F	Age, hypertension, smoking, BMI, PA, education, total energy intake, intake of vegetables, fat and alcohol

AHT, anti-hypertensive; ANZ, Australia and New Zealand; ApoB, apolipoprotein B; CVD, cardiovascular disease; DBP, diastolic BP; DECODE, Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe; EPESE, (National Institute on Aging) Established Populations for Epidemiologic Studies of the Elderly; F, fatal; HUNT, Nord-Trøndelag health study; LP_a, lipoprotein a; LVH, left ventricle hypertrophy; NA, not available; NF, not fatal; PA, physical activity; SALLS, Swedish Annual Level-of-Living Survey; SBP, systolic BP; SES, socioeconomic status

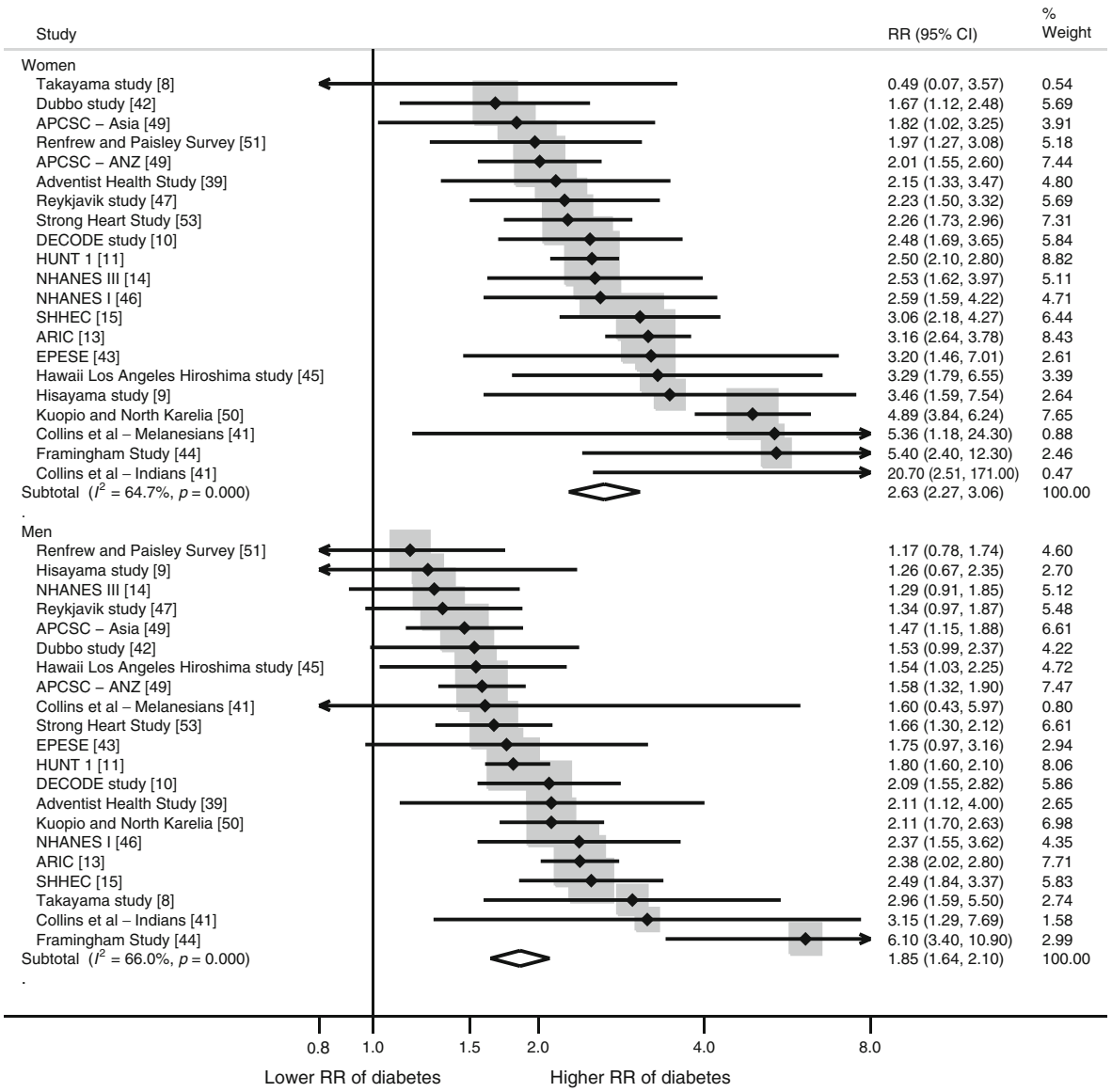

Fig. 2 Multiple-adjusted pooled RR for incident CHD, comparing individuals with diabetes with those without diabetes. ANZ, Australia and New Zealand; EPESE, (National Institute on Aging) Established Populations for Epidemiologic Studies of the Elderly; HUNT, Nord-Trøndelag health study

variation in the confounders that were adjusted for in the individual studies but, aside from age, most adjusted for blood pressure, cigarette smoking, BMI and lipids. As shown in ESM Fig. 7, adjustment for major cardiovascular risk factors had only a small effect and attenuated the age-adjusted RR of diabetes for CHD to a similar extent in women (12%) and men (11%).

Discussion

The present analysis of 64 cohorts, including nearly 900,000 individuals and over 28,000 incident CHD events, confirms the greater excess risk of CHD in women with diabetes compared with men with diabetes. The current estimate of 44% greater RR for incident CHD in women with diabetes compared with their male counterparts is comparable with the previous estimate of 46% excess risk for fatal CHD reported in a meta-analysis that was restricted to 37 cohorts and fatal CHD events, with about one-third the number of events available in the current review [1]. The sex difference in diabetes-related risk for CHD was consistent across subgroups defined by age and region and remained unchanged after excluding non-fatal CHD events. Furthermore, as the level of attenuation of the age-adjusted summary risk estimates was both moderate and equivalent in women and men the observed sex difference is unlikely to be driven by residual confounding. Recently, we

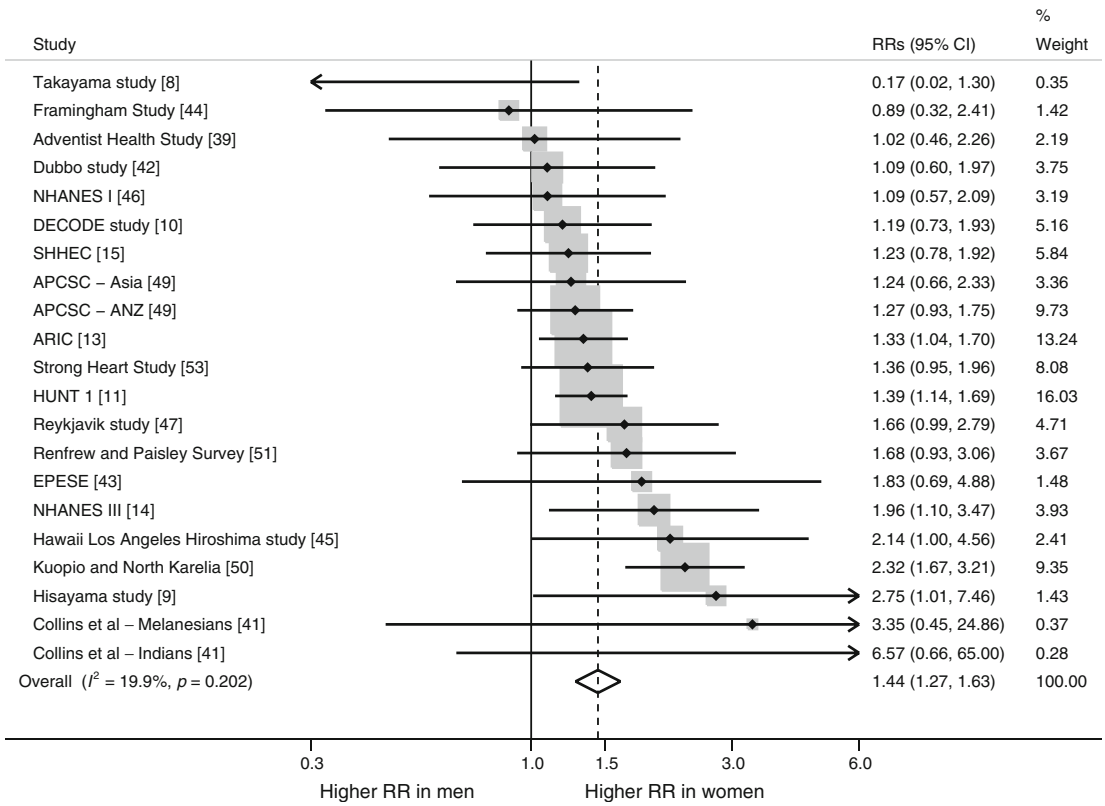

Fig. 3 Multiple-adjusted women-to-men RRR for incident CHD, comparing individuals with diabetes to those without diabetes. ANZ, Australia and New Zealand; EPESE, (National Institute on Aging) Established Populations for Epidemiologic Studies of the Elderly; HUNT, Nord-Trøndelag health study

have shown that the excess risk of stroke in individuals with diabetes is more than 25% greater in women than in men [4]; taken together with these current data, there is convincing evidence that diabetes poses a greater relative risk for cardiovascular diseases in women than men.

There is considerable uncertainty as to the mechanisms responsible for the observed greater coronary hazard conferred by diabetes in women compared with men. It has long been speculated that there is a widespread sex disparity in the management and treatment of cardiovascular risk factors in individuals with diabetes, to the detriment of women. Historically, women with diabetes were more likely to have a more adverse cardiovascular risk profile and were less likely to achieve the recommended levels of risk factors compared with male counterparts; in particular, this may have affected the sex-specific estimates from the older cohort studies that were established when there were significant disparities in treatment between sexes [19–22]. Indeed, the results of the present study provide some marginal evidence that the excess risk of diabetes in women was more pronounced in cohorts with baseline data collection before 1985 than in cohorts with baseline data collection after 1985. However, even though treatment has become more equitable between the sexes, when treated similarly diabetic women are still less likely than men to achieve target values for cardiovascular risk factors [23–25]. This might suggest that it is not the higher levels of cardiovascular risk factors or the relative undertreatment in women alone that account for all of the excess risk of CHD induced by diabetes in women.

Alternatively, sex differences in diabetes-related changes in the levels of cardiovascular risk factors may play an important role. Indeed, there is accumulating evidence to support the hypothesis that women's metabolic and vascular risk factor profile has to deteriorate to a greater extent, i.e. that women have to 'travel further', than men to become diabetic. Several studies have shown that the difference in both traditional and novel cardiovascular risk factor levels in people with and without diabetes is significantly greater in women than in men [26–32]. Furthermore, in the prediabetic state where glucose tolerance may already be impaired but does not meet all diagnostic criteria of diabetes, risk factor levels are more elevated in women than in men [33, 34]. Several studies have suggested that men develop diabetes at a lower BMI compared with women [32, 35–37]. For example, in the UK General Practice Research Database, the BMI of individuals at the time of diabetes diagnosis was, on average, 1.8 kg/m^2

higher in women than in men [37]. Similarly, data from the UK Prospective Diabetes Study indicated that men with newly diagnosed diabetes were significantly less obese compared with newly diagnosed women [35]. It is conceivable, therefore, that the diabetes-related excess risk of CHD in women is not due to significant sex differences in the physiological effects and complications of diabetes. Rather, we hypothesise that the excess risk in women is due to a combination of both a greater deterioration in cardiovascular risk factor levels and a chronically elevated cardiovascular risk profile in the prediabetic state, driven by greater levels of adiposity in women compared with men. If confirmed, the implementation of sex-specific interventions before diabetes becomes manifest—such as increased screening for prediabetes, especially in women, combined with more stringent follow-up of women at high risk for diabetes, such as women with a history of gestational diabetes—could have a substantial impact on the prevention of CHD. Moreover, physicians may be more likely to recognise the early symptoms of CHD in men than women because of men's higher absolute risk, and thus sex differences in medication use and risk factor control may still exist [38]. Greater awareness of early symptoms of CHD in women and sex-specific therapeutic risk factor management, irrespective of the presence of diabetes, is optimal for improving clinical outcomes in both women and men.

Strengths and limitations A key strength of this meta-analysis, aside from its size, is the wide diversity of studies that were included, increasing the generalisability of the study findings. In contrast to previous reviews, we included both fatal and non-fatal CHD events, but even after excluding non-fatal events the estimate remained materially unchanged. Finally, the inclusion of only those studies that provided sex-specific estimates for men and women avoided any study confounding that would have been introduced if we had included estimates for men and women derived from different studies. There are, however, several limitation of this review. First, while it may be possible that we missed some small relevant cohorts through our search using just one database, there was no evidence of publication bias (as shown by the funnel plots), suggesting that the impact of bias arising from failure to include some cohorts was marginal. Other forms of bias that are not detected by funnel plots may have arisen, for example in the use of only one author to extract all of the data from published reports. However, where there was uncertainty in the data extraction process, all three authors reviewed the paper independently until internal consensus was reached. Further limitations of this study are inherent to the use of published data and include the lack of standardisation in study design and duration, endpoint definition, level of adjustment for confounding and information on medication use and the intensity of other cardiovascular risk factor management across studies. However, as our sensitivity analysis comparing the pooled age-adjusted and multiple-adjusted summary estimates showed, confounding is unlikely to have been an important contributor to the observed sex difference in diabetes-related risk of CHD.

Conclusion Diabetes confers a significantly greater relative risk of incident CHD in women than in men. Higher levels of cardiovascular risk factors and relative undertreatment in women compared with men are unlikely to account for all of the excess risk observed in women. Instead, we propose that a greater deterioration in cardiovascular risk profile combined with more prolonged exposure to adverse levels of cardiovascular risk factors among prediabetic women compared with their male equivalents, possibly driven by greater levels of adiposity, may be responsible for the excess risk of diabetes-related CHD in women. Further studies are warranted to determine the actual mechanisms responsible for the difference in diabetes-related coronary risk between the sexes.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement SAEP searched the scientific literature, did the statistical analyses, participated in data interpretation and drafted the report. RRH and MW conceived the study, contributed data, participated in data interpretation and made important revisions to the draft report. All authors gave final approval of the version to be published and are responsible for the integrity of the work as a whole.

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