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

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Summary

Background Diabetes mellitus is a major cause of death and disability worldwide and is a strong risk factor for stroke. Whether and to what extent the excess risk of stroke conferred by diabetes differs between the sexes is unknown. We did a systematic review and meta-analysis to estimate the relative effect of diabetes on stroke risk in women compared with men.

Methods We systematically searched PubMed for reports of prospective, population-based cohort studies published between Jan 1, 1966, and Dec 16, 2013. Studies were selected if they reported sex-specific estimates of the relative risk (RR) for stroke associated with diabetes, and its associated variability. We pooled the sex-specific RRs and their ratio comparing women with men using random-effects meta-analysis with inverse-variance weighting.

Findings Data from 64 cohort studies, representing 775 385 individuals and 12 539 fatal and non-fatal strokes, were included in the analysis. The pooled maximum-adjusted RR of stroke associated with diabetes was 2·28 (95% CI 1·93–2·69) in women and 1·83 (1·60–2·08) in men. Compared with men with diabetes, women with diabetes therefore had a greater risk of stroke—the pooled ratio of RRs was 1·27 (1·10–1·46; I^2=0%), with no evidence of publication bias. This sex differential was seen consistently across major predefined stroke, participant, and study subtypes.

Interpretation The excess risk of stroke associated with diabetes is significantly higher in women than men, independent of sex differences in other major cardiovascular risk factors. These data add to the existing evidence that men and women experience diabetes-related diseases differently and suggest the need for further work to clarify the biological, behavioural, or social mechanisms involved.

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Introduction

Diabetes mellitus is a global health concern; an estimated 347 million people worldwide are affected, and in 2008 diabetes accounted for 1·3 million deaths.[1–3] The incidence of diabetes is projected to increase by more than 50% in the next decade because of rapid increases in the prevalence of obesity and physical inactivity. As a result, diabetes is predicted to become the seventh leading cause of death in the world by 2030.[3,4]

The burden of diabetes as a major cause of premature illness and death is mostly caused by the associated increased risk of cardiovascular disease. Widely quoted estimates from WHO suggest that the cardiovascular risk in people with diabetes is two to three times higher than in those without the disease, and that cardiovascular diseases cause between 50% and 80% of deaths in people with diabetes.[3] However, these estimates are based on the assumption that diabetes confers the same degree of risk in women as in men, which is unlikely to be correct in view of the accruing evidence that women and men experience the disease differently.[4,5] Indeed, we have previously shown that the relative risk (RR) of diabetes-related coronary heart disease is substantially higher in women than in men, even after differences in other major cardiovascular risk factors have been taken into account.[6] Whether this sex difference also exists for stroke—which shares many of the same risk factors—remains uncertain. Findings from previous studies have been inconsistent, with some investigators reporting either a stronger,[7,8] similar,[9] or weaker effect of diabetes on stroke risk in women compared with men.[10,11]

In view of the substantial implications that any clinically important sex difference in the association between diabetes and stroke risk would have, we did a systematic review and meta-analysis of all available prospective data to estimate the relative effect of diabetes on stroke risk in women compared with men.

Methods

Search strategy and selection criteria

We systematically searched PubMed for reports published between Jan 1, 1966, and Dec 16, 2013, using a combined text and MeSH heading search strategy with the terms: "diabetes mellitus", "diabetes", "prediabetes", "impaired fasting glucose", "impaired glucose intolerance", "borderline diabetes," "blood glucose", "hemoglobin A, glycosylated", "cohort studies", "sex", "gender", "cardiovascular disease", "stroke", "cerebrovascular disease", "cerebrovascular attack", "cerebral ischemia", "brain ischemia", and "intracranial hemorrhage". We also checked

the reference lists of identified reports for other potentially relevant studies. Prospective studies were included if RRs, or equivalents, for the association between diabetes and stroke in men and women were reported. Studies were excluded if they had not adjusted at least for age, did not provide information about the variability around the point estimate, or were done in populations that predominantly consisted of individuals with a history of cardiovascular disease or other underlying pathological disorders.

When duplicate reports from the same study were identified, only the most recent publication, or the one with the longest follow-up period, was included. We also used individual participant data from four studies: the Scottish Heart Health Extended Cohort study (SHHEC),[12] the National Health And Nutrition Examination Survey III (NHANES III),[13] the Asia Pacific Cohort Studies Collaboration (APCSC),[14] and the Atherosclerosis Risk in Communities study (ARIC).[15] We contacted the authors of all the studies that provided sex-specific RRs to ask them to provide data adjusted for a predefined set of confounders. Authors of studies that had reported prospective data, but that had adjusted for, rather than stratified by, sex, were asked to provide separate results for men and women.

Data extraction and statistical analysis

The primary endpoint was combined fatal or non-fatal stroke, and the primary metrics were the pooled adjusted RRs and the women-to-men ratio of RRs for individuals with diabetes versus those without diabetes. To include the largest set of individuals and stroke endpoints, studies that reported either age-adjusted or multiple-adjusted results were included in our primary analyses. In pooling multiple-adjusted results, the set of adjustments made were allowed to vary by study, but had to include at least one other risk factor for stroke in addition to age.

For each study, we extracted the sex-specific RRs (with 95% CIs) for individuals with diabetes versus individuals without diabetes, from which we estimated the women-to-men ratio of RRs (and its 95% CI).[6,16] After log transformation of study-specific estimates, we generated pooled estimates across studies using random-effects meta-analysis. We used the inverse of the variance of the log RR to weight studies on the basis of an estimate of statistical size.[17] An identical approach was used for the ratio of RRs.

We did several sensitivity analyses: fatal stroke only, region (Asia or non-Asia), baseline year of data collection (pre-1985 or 1985 onwards), method of diabetes ascertainment (self-report or medical record), data source (aggregated data or individual participant data), and major stroke subtype (ischaemic or haemorrhagic). Using data from APCSC, ARIC, NHANES III, and SHHEC, we also did analyses by age (<60 years *vs* ≥60 years) and smoking status (current smoker *vs* non-smoker).

The I^2 statistic was used to estimate the percentage of variability across studies due to between-study heterogeneity. We used random-effects meta-regression analyses to assess whether differences in the mean duration of study follow-up, overall incidence of stroke, women-to-men ratio of stroke, prevalence of diabetes, or women-to-men ratio of diabetes prevalence contributed to heterogeneity between studies.[18,19] We used funnel plots to examine the presence of publication bias (ie, by plotting the natural log of the ratio of RRs against its standard error).

Using individual participant data from APCSC, ARIC, NHANES III, and SHHEC, we calculated stroke incidence rates in men and women with and without diabetes. Furthermore, to explore whether sex differences in other cardiovascular risk factors in individuals with and without diabetes might contribute to any sex difference seen in the RR for diabetes-associated stroke, we calculated the adjusted mean difference (with 95% CI) for systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, body-mass index (BMI), and waist circumference in participants with and without diabetes, by sex. We pooled these data in meta-analyses and weighted by the inverse of the variance. All statistical analyses were done with Stata (version 11.0).

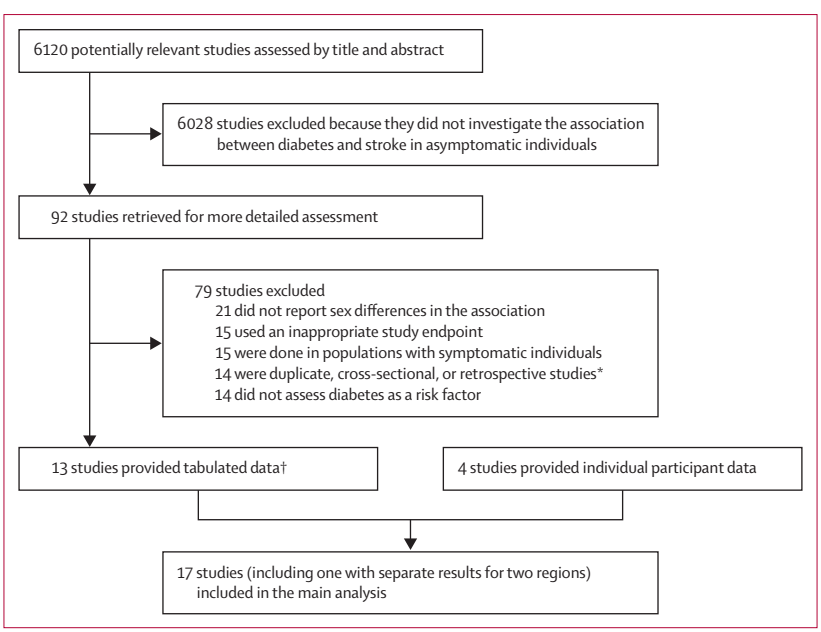

Figure 1: **Study selection**
*Including the four studies for which individual participant data were provided. †12 provided published data, and one unpublished data.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The systematic search identified 6120 articles, which were assessed by title and abstract. Of these, 92 articles

qualified for selection (figure 1). After full-text assessment, 12 studies provided published, and one study unpublished, summary data for sex differences in the association between diabetes and risk of stroke.[7–11,20–28] This database was extended with individual participant data from APCSC, ARIC, NHANES III, and SHHEC.[12–15]

Table 1 shows the baseline characteristics of all 64 cohorts included in the study. The year of the

	Location	Year of baseline data collection	Study duration (years)	n (% women)	Age range (years)	Number with diabetes (% women)	Ascertainment of diabetes	Number of strokes (% women)	Fatal or non-fatal strokes included	Maximum adjustment available
APCSC (Australia and New Zealand)[14]	Australia and New Zealand (nine cohorts)	1989–96	7	99 624 (45%)	20–104	4784 (31%)	Self-report or medical assessment	1671 (41%)	Both	Age, SBP, smoking, BMI, total cholesterol
APCSC (Asia)[14]	Asia (27 cohorts)	1961–93	7	436 832 (33%)	20–107	17 763 (23%)	Self-report or medical assessment	2872 (31%)	Both	Age, SBP, smoking, BMI, total cholesterol
ARIC[15]	USA	1987–89	18	15 732 (55%)	45–64	1610 (58%)	Medical assessment	930 (52%)	Both	Age, SBP, smoking, BMI, total cholesterol
DECODE[10]	Finland and Sweden (seven cohorts)	1987–2002	5–21	9278 (55%)	40–69	826 (47%)	Medical assessment	530 (34%)	Both	Age, hypertension, BMI, total cholesterol, HDL cholesterol, smoking
Dubbo[28]	Australia	1988–89	16	2006 (58%)	>60	142 (49%)	Medical assessment	286 (55%)	Both	Age, SBP, smoking, BMI, total cholesterol
EPIC–Norfolk[22]	UK	1993–97	10	22 516 (55%)	40–79	441 (37%)	Self-report	507 (49%)	Both	Age, SBP, smoking, BMI, total cholesterol, triglycerides
Framingham Offspring[25]	USA	1988–90	14	2097 (50%)	50–81	99 (29%)	Medical assessment	130 (42%)	Both	Age, SBP, antihypertensive use, CVD, atrial fibrillation, LVH, smoking
Hisayama (2010)[11]	Japan	1988	14	2421 (57%)	40–79	291 (46%)	Medical assessment	132 (54%)	Both	Age, SBP, smoking, BMI, total cholesterol, HDL cholesterol, alcohol intake, physical activity, ECG abnormalities
Hisayama (2000)[9]	Japan	1961	32	1621 (56%)	>40	130 (34%)	Medical assessment	298 (52%)	Both	Age
Iso et al[21]	Japan	1975–80	17	10 582 (60%)	40–69	267 (48%)	Medical assessment	400 (45%)	Fatal	Age, hypertension, smoking, BMI, total cholesterol, HDL cholesterol, skinfold, alcohol intake, community, menopause
JPHC[7]	Japan (two cohorts)	1990–93	12	35 657 (63%)	40–69	2034 (63%)	Medical assessment	904 (47%)	Both	Age, SBP, antihypertensive use, smoking, BMI, total cholesterol, HDL cholesterol, triglycerides, alcohol intake, fasting status, residential areas
Kuopio and North Karelia[8]	Finland (six cohorts)	1972–97	17	51 735 (51%)	25–74	1108 (46%)	Self-report	917 (47%)	Fatal	Age, SBP, smoking, BMI, total cholesterol, study year
NHANES III[13]	USA	1988	13	18 603 (46%)	18–90	1290 (38%)	Self-report or medical assessment	329 (42%)	Fatal	Age, SBP, smoking, BMI, total cholesterol
Rancho Bernado[24]	USA	1972–74	12	3778 (54%)	50–79	320 (39%)	Self-report	232	Both	Age, SBP, total cholesterol, smoking, obesity, family history, oestrogen use
Renfrew/ Paisley[20]	Scotland	1972–76	20	15 406 (54%)	45–64	NA	Self-report or medical assessment	1029 (54%)	Both	Age
Sievers et al[23]	USA	1965–84	10	5131 (52%)	15–84	1266 (58%)	Medical assessment	30 (50%)	Fatal	Age
SHHEC[12]	Scotland	1984–87	16	13 287 (51%)	30–74	184 (46%)	Medical assessment	1083 (43%)	Both	Age, SBP, smoking, BMI, total cholesterol
Takayama[26]	Japan	1992	7	29 079 (54%)	>35	1217 (35%)	Self-report	259 (51%)	Fatal	Age, hypertension, smoking, BMI, physical activity, education, energy intake, vegetables, fat, alcohol intake

APCSC=Asia Pacific Cohort Studies Collaboration. SBP=systolic blood pressure. BMI=body-mass index. ARIC=Atherosclerosis Risk in Communities study. DECODE=Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe study. HDL=high-density lipoprotein. EPIC-Norfolk=European Prospective Investigation into Cancer, Norfolk. CVD=cardiovascular disease. LVH=left-ventricular hypertrophy. ECG=electrocardiogram. JPHC=Japan Public Health Center study. NHANES III=National Health And Nutrition Examination Survey III. NA=not available. SHHEC=Scottish Heart Health Extended Cohort study.

Table 1: **Characteristics of included studies**

See Online for appendix

baseline survey ranged from 1961 to 2002, and duration of follow-up was between 5 and 32 years. Overall, data were available from 775 385 individuals, of whom 12 539 had a fatal or non-fatal stroke. The incidence of stroke was greater in individuals with diabetes than in those without (appendix p 1). Table 2 shows the age-adjusted

	Age-adjusted mean difference (95% CI)		Multiple-adjusted mean difference (95% CI)	
	Men	Women	Men	Women
Systolic blood pressure (mmHg)	5·33 (5·09 to 5·58)	6·79 (6·40 to 7·18)	4·18 (3·93 to 4·44)	4·70 (4·26 to 5·14)
Total cholesterol (mmol/L)	0·22 (0·20 to 0·23)	0·24 (0·22 to 0·27)	0·15 (0·13 to 0·17)	0·14 (0·11 to 0·17)
HDL cholesterol (mmol/L)	−0·09 (−0·11 to −0·08)	−0·16 (−0·17 to −0·14)	−0·06 (−0·08 to −0·05)	−0·11 (−0·13 to −0·09)
BMI (kg/m²)	1·01 (0·97 to 1·06)	2·00 (1·91 to 2·09)	0·64 (0·59 to 0·68)	1·66 (1·57 to 1·75)
Waist circumference (cm)	5·27 (4·79 to 5·75)	9·06 (8·53 to 9·59)	0·45 (0·21 to 0·70)	2·20 (1·90 to 2·50)

Pooled data from the Asia Pacific Cohort Studies Collaboration,[14] Atherosclerosis Risk in Communities study,[15] National Health and Nutrition Examination Survey III,[13] and Scottish Heart Health Extended Cohort study.[12] Multiple-adjusted mean differences are, where appropriate, adjusted for age, systolic blood pressure, smoking, body-mass index (BMI), and total cholesterol. HDL=high-density lipoprotein.

Table 2: **Age-adjusted and multiple-adjusted mean difference in baseline risk factor levels among men and women with and without diabetes**

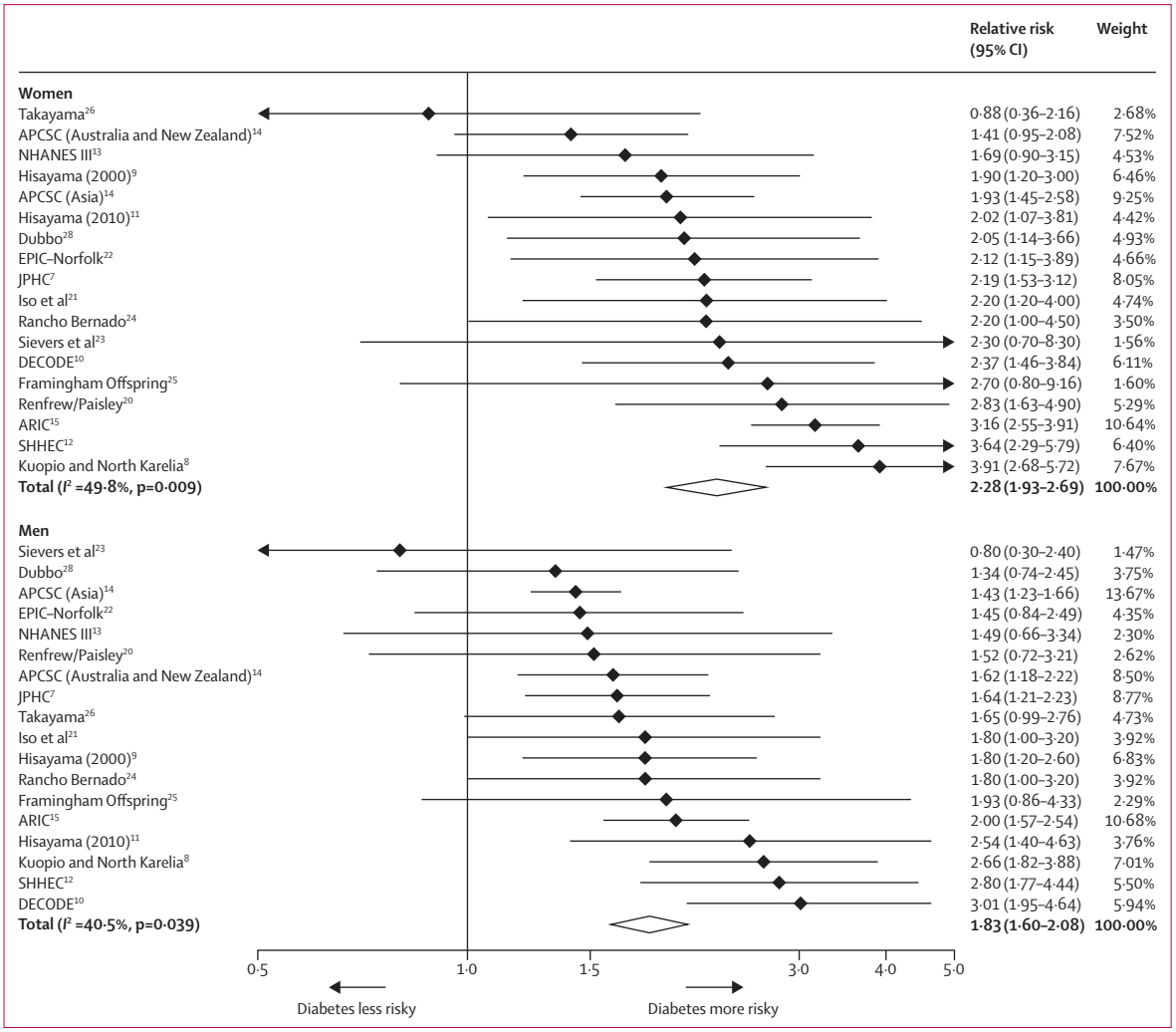

Figure 2: **Maximum-adjusted pooled relative risk for any stroke, comparing individuals with diabetes to those without diabetes**

Box sizes are in proportion to study weights. Asia Pacific Cohort Studies Collaboration (APCSC) provided separate estimates for cohorts from Asia and Australia and New Zealand. NHANES III=National Health And Nutrition Examination Survey III. EPIC–Norfolk=European Prospective Investigation into Cancer, Norfolk. JPHC=Japan Public Health Center study. DECODE=Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe. ARIC=Atherosclerosis Risk in Communities study. SHHEC=Scottish Heart Health Extended Cohort study.

and multiple-adjusted mean differences in cardiovascular risk factors for men and women with and without diabetes from those studies for which individual participant data were available. Compared with individuals without diabetes, those with diabetes had higher systolic blood pressure, total cholesterol, BMI, and waist circumference, and lower HDL cholesterol. The mean difference for each of these risk factors—particularly the anthropometric variables—was greater for women than for men (table 2, appendix pp 2–3).

The overall maximum-adjusted pooled RR based on all available data for combined fatal and non-fatal stroke associated with diabetes was 2·28 (95% CI 1·93–2·69) for women and 1·83 (1·60–2·08) for men (figure 2). The I^2 statistic for heterogeneity between studies was 50% in women and 41% in men, suggesting substantial between-study heterogeneity. Exclusion of the three studies with results adjusted for age only did not reduce the between-study heterogeneity and did not change the RR estimates (2·27 [1·88–2·74] for women and 1·87 [1·61–2·16] for men; appendix p 4). To determine whether adjustment for other cardiovascular risk factors might have had a stronger effect in women than in men, we repeated the analyses using data from 55 cohorts (738 082 individuals, and 10 311 strokes) for which both age-adjusted and multiple-adjusted results were available (appendix p 5). Overall, adjustment resulted in a similar amount of attenuation (of less than 10%) in both women and men: the age-adjusted RR was 2·46 (1·83–3·32) for women and 1·96 (1·64–2·36) for men, decreasing to 2·37 (1·88–3·00) for women and 1·90 (1·61–2·25) for men in the multiple-adjusted models.

The pooled maximum-adjusted RR for diabetes was significantly higher in women than in men (ratio of RRs 1·27, 95% CI 1·10–1·46; figure 3). There was no evidence of publication bias (p=0·65; appendix p 6). Exclusion of the three studies that provided only age-adjusted estimates had no appreciable effect on the pooled ratio of RRs (multiple-adjusted ratio of RRs 1·26, [1·09–1·47]). The pooled ratio of RRs did not vary substantially by duration of study follow-up (p for heterogeneity=0·44); proportion of stroke events (p=0·93); women-to-men ratio of stroke event rate (p=0·47); baseline prevalence of diabetes (p=0·59); or women-to-men ratio of diabetes prevalence (p=0·07; appendix p 7). Additionally, the ratio of RRs did not differ significantly by region age, smoking status, year of study baseline, stroke subtype, method of diabetes ascertainment, or data source (figure 4).

The pooled sex-specific RR estimates for fatal stroke associated with diabetes were 2·29 (95% CI 1·73–3·04) for women and 1·74 (1·45–2·08) for men (appendix p 8). The corresponding ratio of RRs (women to men) was 1·32 (0·97–1·79; appendix p 9). The I^2 statistic for heterogeneity between studies was 27%, with no evidence of publication bias (p=0·76; appendix p 10). The pooled ratio of RRs did not vary by duration of study follow-up (p=0·34), proportion of stroke events (p=0·79), women-to-men ratio of stroke event rate (p=0·84), baseline prevalence of diabetes (p=0·24), or women-to-men ratio of diabetes prevalence (p=0·052; appendix p 11).

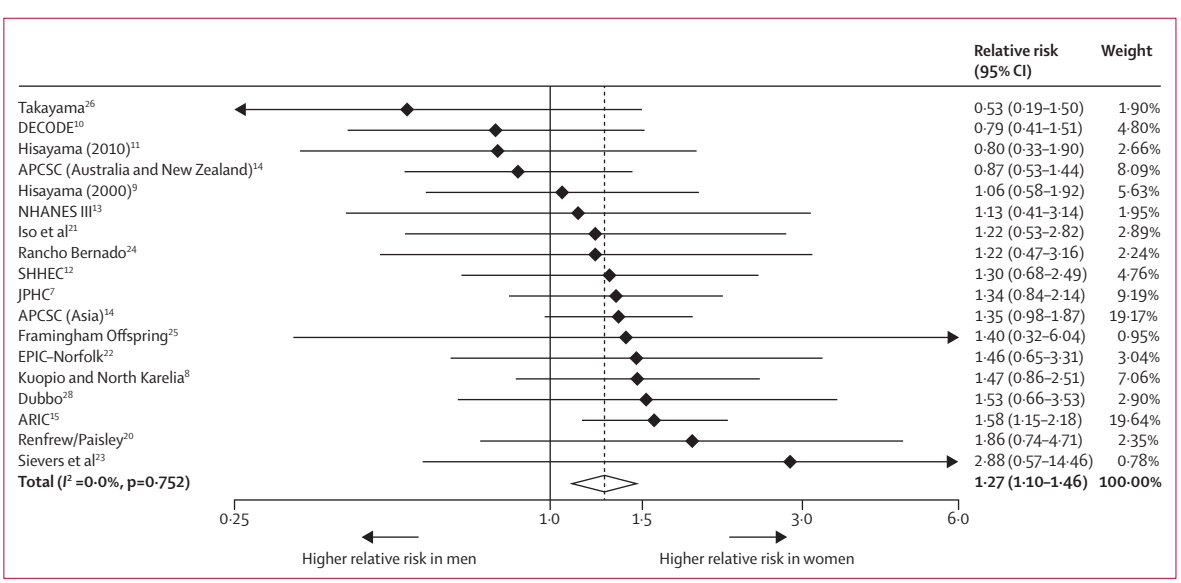

Figure 3: **Maximum-adjusted women-to-men ratio of relative risks for any stroke, comparing individuals with diabetes to those without diabetes**
Box sizes are in proportion to study weights. Asia Pacific Cohort Studies Collaboration (APCSC) provided separate estimates for cohorts from Asia and Australia and New Zealand. DECODE=Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe. NHANES III=National Health And Nutrition Examination Survey III. SHHEC=Scottish Heart Health Extended Cohort study. JPHC=Japan Public Health Center study. EPIC–Norfolk=European Prospective Investigation into Cancer, Norfolk. ARIC=Atherosclerosis Risk in Communities study.

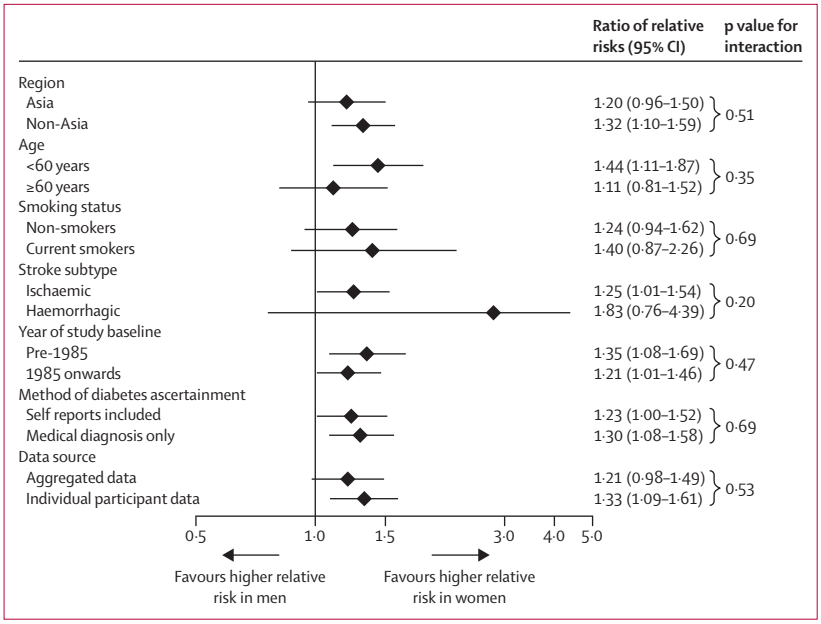

Figure 4: **Sensitivity analyses**

Discussion

In this pooled analysis of 64 cohorts, with data for more than three-quarters of a million individuals and more than 12 000 fatal and non-fatal stroke events, diabetes was a stronger risk factor for stroke in women than in men. Compared with men with diabetes, women with diabetes had a 27% greater RR for stroke when baseline differences in other major cardiovascular risk factors were taken into account. This sex difference in diabetes-related stroke risk was apparent and consistent across a wide range of prespecified subgroups. These findings add to the accumulating evidence for appreciable and clinically relevant differences in how diabetes affects the risk of cardiovascular disease in men and women.[6]

In our analysis, as in previous reports,[29–37] differences in major cardiovascular risk factors in individuals with and without diabetes were greater among women than among men. Historically, men with diabetes or cardiovascular disease were diagnosed earlier and more often treated with aspirin, statins, and antihypertensive treatments than were women, and were therefore more likely to achieve recommended treatment targets for risk factors.[38–42] As such, the excess risk of stroke in women with diabetes might be expected to be an underestimate of the real sex difference, especially in older studies in which sex disparities in treatment are most pronounced. However, our analysis did not show a difference in the excess risk of diabetes-related stroke in women between cohorts with baseline data collection before 1985 and from 1985 onwards. Moreover, data from more recent studies suggest that even when treated similarly, women with diabetes remain less likely than men to achieve target values for systolic blood pressure, low-density lipoprotein (LDL) and HDL cholesterol, fasting glucose, and glycated haemoglobin.[43,44] However, sex differences in cardiovascular risk factors are unlikely to wholly account for the greater excess risk of diabetes-related stroke seen in women. In our analysis, adjustment for major cardiovascular risk factors resulted in a similar degree of attenuation in the age-adjusted estimate, of less than 10%, for both women and men. This result implies that although some residual confounding probably persists (as in all observational cohorts), it is marginal and unlikely to differentially affect women more than men.

Sex differences in diabetes-related changes in the progression of atherosclerosis or in more novel risk factors (such as markers of coagulation and inflammation, lipid peroxidation, and endothelial function), for which we had insufficient data to explore, might also be involved.[30,45–48] Mansfield and colleagues[46] investigated sex differences in coagulation and fibrinolysis in individuals with diabetes and reported that women had significantly higher factor VII and plasminogen activator inhibitor 1 (also known as serpin E1) activity than men.[46] Similarly, data from the British Regional Heart Study and the British Women's Heart Health Study[34] showed a greater adverse effect of diabetes in women than in men on markers of coagulation, fibrinolysis, lipids, and blood pressure, which were mediated by greater changes in central adiposity and insulin resistance in women.[34] In support of this finding, results from other studies suggest that despite women having a greater body-fat percentage per unit of BMI than men,[49] they conversely have greater insulin sensitivity at sites associated with insulin resistance, namely the liver and skeletal muscle.[50] These data support the idea that women have further to travel metabolically and physiologically than men to transition from normoglycaemia to a deranged glycaemic state;[34] in other words, the metabolic and vascular risk factor profile of women has to deteriorate to a greater extent than that of men before the onset of overt diabetes occurs.

Women have a much more favourable cardiovascular risk profile than men, but this pattern can be reversed with deterioration in glycaemic control. A previous study[51] has shown that years before the manifestation of overt diabetes, individuals who have impaired glucose tolerance—particularly women—have a more adverse cardiovascular profile than those with normal glucose tolerance—the so-called ticking-clock hypothesis. Findings from studies in non-diabetic men and women before they transition to a state of impaired glucose tolerance suggest that women who progress from normoglycaemia to prediabetes have greater endothelial dysfunction than men, as well as more severe hypertension and more fibrinolysis and thrombosis.[52] We propose that the diabetes-related excess risk of stroke in women is due to their having a chronically raised cardiovascular risk profile in the prediabetic state, which is more likely to go undetected and therefore untreated than in men, rather than by any substantial sex difference in the effects and

complications of diabetes per se. If confirmed, the implementation of sex-specific interventions before diabetes becomes manifest—such as increased screening for prediabetes in women—could have a substantial effect on the prevention of vascular events.

This meta-analysis provides the most definitive and convincing evidence so far of a sex difference in diabetes-related risk of stroke. The findings were robust and applicable across a broad range of populations. Limitations of our study are inherent to the use of published data, including the absence of standardisation in study design, duration, endpoint definition, study populations, and the extent of adjustment for confounding across studies. Moreover, the studies included in this meta-analysis generally did not report on, or adjust for, the use of antidiabetic drugs. But because women were historically more likely to be undertreated than men, the net effect is likely to have been to underestimate the true excess risk of stroke in women with diabetes. Thus our estimate might be regarded as a lower bound for this excess risk.

An important limitation of these data, which warrants further investigation by future studies, was our inability to examine the potential contribution that a woman's obstetric and gynaecological history might have on the excess risk of stroke. Additionally, because a standard definition of diabetes was not used across studies, ascertainment of diabetes probably varied between—but importantly, not within—studies. Hence, the use of the ratio of RRs (comparing women with men) remains valid. Finally, we were unable to assess whether the excess risk of stroke in women with diabetes varied with different indices of glycaemic control or duration of diabetes because of insufficient data for these variables.

Future prospective cohort studies can address many of the limitations of this meta-analysis by exploring the role of sex differences in individuals in the prediabetic state and their contribution to vascular risk. Ideally, such studies would include a large number of men and women free from diabetes and stroke at recruitment, with detailed information about risk factors, including medical treatment, taken at baseline and several times during follow-up, which should continue until a sufficient number of stroke events had occurred. Detailed gynaecological histories should also be recorded to allow the effect of complications in pregnancy and menopause to be studied.

Although costly, such studies would be free of the major drawbacks of our meta-analysis. They would allow for detailed exploration of the sex-specific differences in the cardiovascular risk trajectories between individuals who develop impaired glucose tolerance and overt diabetes and those who remain normoglycaemic during follow-up, and how these sex differences contribute to stroke risk. Population-based big data studies, such as the UK Biobank, are well suited to investigation of these issues and, on maturation, should be mined to find out why diabetes confers a stronger coronary and cerebrovascular hazard in women than in men.

Contributors

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.

Conflicts of interest

We declare that we have no conflicts of interest.

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