Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis

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Summary

Background **Studies have suggested sex differences in the mortality rate associated with type 1 diabetes. We did a meta-analysis to provide reliable estimates of any sex differences in the effect of type 1 diabetes on risk of all-cause mortality and cause-specific outcomes.**

Methods **We systematically searched PubMed for studies published between Jan 1, 1966, and Nov 26, 2014. Selected studies reported sex-specific estimates of the standardised mortality ratio (SMR) or hazard ratios associated with type 1 diabetes, either for all-cause mortality or cause-specific outcomes. We used random effects meta-analyses with inverse variance weighting to obtain sex-specific SMRs and their pooled ratio (women to men) for all-cause mortality, for mortality from cardiovascular disease, renal disease, cancer, the combined outcome of accident and suicide, and from incident coronary heart disease and stroke associated with type 1 diabetes.**

Findings **Data from 26 studies including 214 114 individuals and 15 273 events were included. The pooled women-to-men ratio of the SMR for all-cause mortality was 1·37 (95% CI 1·21–1·56), for incident stroke 1·37 (1·03–1·81), for fatal renal disease 1·44 (1·02–2·05), and for fatal cardiovascular diseases 1·86 (1·62–2·15). For incident coronary heart disease the sex difference was more extreme; the pooled women-to-men ratio of the SMR was 2·54 (95% CI 1·80–3·60). No evidence suggested a sex difference for mortality associated with type 1 diabetes from cancer, or accident and suicide.**

Interpretation **Women with type 1 diabetes have a roughly 40% greater excess risk of all-cause mortality, and twice the excess risk of fatal and nonfatal vascular events, compared with men with type 1 diabetes.**

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Introduction

Type 1 diabetes is one of the most common chronic autoimmune disorders that typically manifests in early childhood and adolescence.[1] The age-adjusted incidence of type 1 diabetes varies widely between populations from as low as 0·1 per 100 000 people per year in China to 40·9 in Finland.[2] By contrast with other common autoimmune diseases, there is no female bias in the incidence of type 1 diabetes.[2] In the USA, around 15 000 children and a similar number of adults are diagnosed with type 1 diabetes every year.[3] Aside from the enormous psychological and health burden on the individual patients, the disease costs the health-care system an estimated US$14·9 billion annually.[4] Worldwide, the incidence of type 1 diabetes in children younger than 14 years of age is estimated to have increased by 3% each year since 1989.[5]

Treatment of type 1 diabetes is through self-administration of intensive insulin therapy in conjunction with clinical management of blood pressure and blood lipid levels, and early monitoring and treatment of complications.[6] However, despite improvements in treatment and management, type 1 diabetes remains associated with increased mortality rates compared with the general population.[7] In affected children and adolescents, mortality rates that are largely driven by acute metabolic complications associated with diabetes, such as ketoacidosis and hypoglycaemia, are double those of non-affected individuals of similar age.[8] At older ages, compared with the general population, mortality rates in individuals with type 1 diabetes are even higher, largely because of chronic complications of diabetes, such as cardiovascular disease.[9] Indeed, the cardiovascular mortality rate in elderly people with type 1 diabetes is more than ten-times greater than in elderly people in the general population.[9]

Sex differences in the effect of type 1 diabetes on the excess risk of mortality have been documented[7,9,10–12] but the pattern varies by age group and outcome studied.[7] Reports also exist of sex differences in the ability of individuals with type 1 diabetes to adequately control their diabetes—most often to the detriment of women. Whether or not this finding translates into increased vascular risk in women with type 1 diabetes compared with men with type 1 diabetes is unknown, but there is some evidence that women with type 1 diabetes incur a greater excess risk of cardiovascular disease than do men.[12] Although previous reports have detailed patterns of mortality in patients with type 1 diabetes, this study is the first meta-analysis to quantify any sex difference in all-cause mortality or cause-specific mortality that is associated with type 1 diabetes.[1,7] Evidence of any clinically meaningful sex difference would have ramifications for how affected patients are treated, and

See Online for appendix

for the development of cardiovascular risk prediction devices for this high-risk population.[1]

Methods

Search strategy and selection criteria

We did a systematic search of PubMed on Nov 26, 2014, using a combined text word and medical subject heading (MeSH) search strategy (appendix p 3). We scanned the reference lists of the reports that we found in our search to identify other potentially relevant studies. Studies were included if they had reported SMRs (or equivalents) or hazard ratios (HRs) for all-cause or cause-specific mortality for both men and women with type 1 diabetes compared with their counterparts without the disorder.

	Country	Baseline year(s)	Follow-up duration (years)	Participants (n)	% women	Mean age (years) at diagnosis	Case definition (age at diagnosis)	Deaths (n)	% deaths in women	Variables used to standardise SMR	Causes of death
Allegheny County Type 1 Diabetes Registry[20,21]	USA	1965–79	30	1075	48%	Men: 11·0 (SD 4·3), women: 10·8 (4·0)	Diabetes <18 years of age	279	51%	Age, sex, race	All-cause, cardiovascular disease, renal disease, cancer, accident/violence
Austrian IDDM registry[22]	Austria	1979–90	10	1185	48%	..	Diabetes <15 years of age	6	50%	Age	All-cause
British Diabetic Association Children's Register[23]	UK	1972–81	17	310	42%	..	Diabetes <2 years of age	7	71%	Age	All-cause
Canterbury Diabetes Registry[24]	New Zealand	1984	20	43	48%	15·7	Diabetes <30 years of age	115	43%	Age, sex	All-cause
Diabetes Incidence Study in Sweden[25]	Sweden	1983–99	17	4968	..	23·7	Doctor's classification	83	19%	Age, sex	All-cause
Diabetes UK Cohort Study[26–28]	UK	1972–93	28	27351	..	..	Diabetes <30 years of age	1320	40%	Age, sex, calendar year, country	All-cause, coronary heart disease, stroke, cardiovascular disease, renal, cancer, accident/violence
Dusseldorf University Hospital[29]	Germany	1978–94	10	3570	50%	..	Diabetes <31 years of age	251	41%	NA	All-cause
Estonian Childhood Diabetes Register[30]	Estonia	1980–89	10	518	48%	9·2	Diabetes <15 years of age	12	33%	Age	All-cause
Finnish Drug Reimbursement Register[31,32]	Finland	1965–99	41	17306	43%	..	Diabetes <30 years of age	1337	30%	Age, sex, calendar year	All-cause, coronary heart disease
GPRD*[12]	UK	1992	7	7479	..	..	Diabetes <30 years of age	508	..	NA	Stroke, coronary heart disease, cardiovascular disease
Japanese DERI Mortality Cohort[33,34]	Japan	1965–79	35	1408	60%	8·8 (SD 4·1)	Diabetes <18 years of age	137	..	Age, sex, calendar year	All-cause, cardiovascular disease, cancer, accident/suicide
Lainz Hospital, Vienna, Austria[35]	Austria	1983–84	20	648	47%	Men: 16·0 (SD 8·0), women: 14·9 (SD 7·7)	Diabetes <30 years of age	84	36%	NA	All-cause
Leicestershire Childhood Diabetes Cohort[36]	UK	1940–89	51	845	45%	10·4 (median)	Diabetes <17 years of age	44	34%	Age, sex, calendar year	All-cause
Lithuanian Childhood Diabetes Register[30]	Lithuania	1983–94	10	698	48%	9·1	Diabetes <15 years of age	25	52%	Age	All-cause
MigMed Database*[16]	Sweden	1987–2001	14	9239	39%	..	Diabetes <35 years of age	83	51%	Age	Stroke
National Diabetes Service Scheme[37]	Australia	1997–2010	11	86250	48%	21·1	Diabetes <30 years of age	6129	38%	Age, sex	All-cause
New Jersey 725 Study[38]	USA	1993–98	3	725	58%	..	Diabetes <30 years of age	131	54%	Age, sex	All-cause

(Table continues on next page)

	Country	Baseline year(s)	Follow-up duration (years)	Participants (n)	% women	Mean age (years) at diagnosis	Case definition (age at diagnosis)	Deaths (n)	% deaths in women	Variables used to standardise SMR	Causes of death
(Continued from previous page)											
Norwegian Childhood Diabetes Registry[10]	Norway	1973–82	30	1906	46%	..	Diabetes <15 years of age	103	27%	Age, sex, calendar year	All-cause, coronary heart disease, cardiovascular disease, renal disease, accident/ suicide
Piemonte Diabetes Register[39]	Italy	1991–99	9	1608	..	..	Diabetes <35 years of age	141	46%	..	All-cause, coronary heart disease, stroke, cardiovascular disease, cancer, accident/violence
South Tees Diabetes Mortality Study[40]	UK	1994–99	6	761	44%	..	Diabetes <35 years of age	54	43%	Age, sex, calendar year	All-cause, coronary heart disease, cardiovascular disease
Swedish National Diabetes Register*[17]	Sweden	1998	8	33 915	45%	..	Diabetes <30 years of age	2701	41%	NA	All-cause, cardiovascular disease
Taiwan NHIRD [41]	Taiwan	1999–2010	12	7225	52%	..	Type 1 diabetes registry	333	44%	Age, sex, calendar year	All-cause
Tasmanian IDDM prevalence cohort[42]	Australia	1984	9	480	45%	15·5 (8·3)	Diabetes <30 years of age	49	..	Age, sex	All-cause, cardiovascular disease
USVI Childhood Diabetes Registry Cohort[43]	United States Virgin Islands	1979–2005	20	103	52%	..	Type 1 diabetes registry	9	44%	Age, sex	All-cause
WESDR[44]	USA	1980	9	2972	52%	14·6 (7·6)	Diabetes <30 years of age	1004	50%	Age, sex	All-cause, coronary heart disease, stroke, renal, accident
WHO MSVDD[45]	Seven countries	1975–79	15	1139	..	Range: 35–54	Insulin use <1 year after diagnosis	328	42%	Age	All-cause

SMR=standardised mortality ratio. IDDM=Insulin Dependent Diabetes Registry. NA=not applicable (these studies reported hazard ratios instead of SMRs). GPRD=General Practice Research Database. DERI=Diabetes Epidemiology Research International. NHIRD=National Health Insurance Research Database. USVI=United States Virgin Islands. WESDR=Winsconsin Epidemiologic Study of Diabetic Retinopathy. MSVDD=Multinational Study of Vascular Disease in Diabetes. *Combined fatal and non-fatal outcomes.

Table: **Characteristics of included studies**

We excluded studies if they did not report such estimates for type 1 diabetes only but also included type 2 diabetes, or did not provide information about variability around the point estimate. When several articles from the same study had reported on the same endpoint, we included only the article that provided results for the longest duration of follow-up, which led to the exclusion of four articles (appendix p 2). The search strategy and items for data extraction were predefined and agreed upon by all authors. Variables that were extracted for each study were: name of first author, name of study, year of publication, data source, country of study, baseline study years, duration of follow-up, ascertainment of diabetes, subtype, study endpoints, sample size, number of observed and expected events, level of adjustment, measure of association, and method of standardisation of SMR. One author (SAEP) did the literature search and extracted the data. Uncertainties regarding the inclusion or exclusion of articles and data extraction were discussed by all authors and resolved by mutual consent. The meta-analysis was done in accordance with the MOOSE guidelines and the PRISMA statement.[13,14]

Outcomes

The primary endpoint for this study was all-cause mortality within the study period. Secondary endpoints were mortality or incident coronary heart disease, stroke, cardiovascular disease (a composite outcome that included coronary heart disease, stroke, and other cardiovascular diseases), renal disease, cancer, and the combined outcome of accident and suicide. Rather than report imprecise estimates, cause-specific outcomes for which fewer than 100 events were reported (when the data were aggregated from all relevant studies combined) were excluded from the analysis—namely, infectious disease and respiratory disease.

Statistical analysis

We extracted either sex-specific SMRs or HRs; see table) for people with diabetes type 1 versus those without type 1 diabetes and 95% CIs (or similar) for each study. We log-transformed these SMRs (or HRs) and computed their differences. We subsequently pooled the differences across studies using random-effects meta-analysis weighted by the inverse of the variances of the log SMRs, and then back-transformed the data to obtain the pooled women-to-men ratio of the SMR (rSMR).[15] We calculated the standard error of the log rSMR as the square root of the sum of the variance of the two sex-specific log SMRs for each of the studies. Three studies reported HRs for the association between type 1 diabetes and the combined outcome of fatal and non-fatal coronary heart disease and stroke.[12,16,17] We used the I^2 statistic to estimate the percentage of variability between studies caused by between-study heterogeneity.[18] Sex-specific SMRs were pooled similarly, except when the variances of sex-specific results differed substantially within studies, in which case the corresponding inverse variance weights from the pooled analysis of differences was used to preserve the (approximate) commutative association between the two pooling operations.

We did subgroup analyses by baseline year of data collection (before 1970, 1970–79, 1980–89, and after 1990); by region (Asia, Australia and New Zealand, the USA, and Europe); by duration of study follow-up (<10, 10–19, 20–29, and ≥30 years); by age by when study participants received a diagnosis of type 1 diabetes, which was categorised as either early onset only (<18 years of age) or both early and late onset (<35 years of age); whether the data were sourced from a registry or a cohort study; by categorising the studies into three groups according to whether the mortality rate in men was more than 10% higher than that in women, more than 0% but less than 10% higher than that in women, or less than in women; and by whether the studies were of high quality (at least six out of a maximum of eight points) versus low quality (fewer than six points) on the Newcastle–Ottawa Scale[19] (appendix p 4). We used funnel plots of the natural log of the women-to-men ratio of the SMR against its standard error to assess publication bias. Stata version 12.0 was used for all analyses. We judged p values less than 0·05 to be statistically significant.

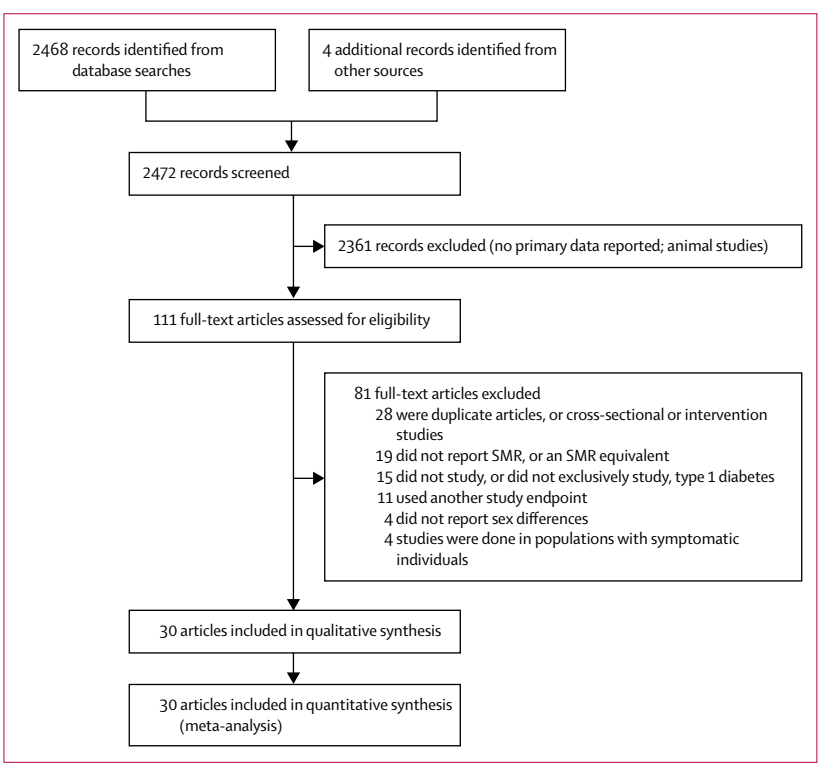

Figure 1: **Flowchart of the systematic review for the primary analysis**
SMR=standardised mortality ratio.

Role of the funding source

The funders of the study had no role in the acquisition, analysis, or interpretation of the data. SAEP and MW had full access to all the raw data. The corresponding author had final responsibility for the decision to submit for publication.

Results

Of the 2472 articles that were identified through the systematic search, 111 qualified for full-text evaluation (figure 1). Of these, 30 articles with information from 26 separate studies provided information about sex differences in the association between type 1 diabetes and all-cause mortality or cause-specific outcomes (table). The 26 included studies comprised 19 from type 1 diabetes registry studies, six from prospective cohort studies, and one from a General Practice research database (table).[10,12,16,17,20–45]

Data for 197 396 individuals and 14 682 deaths were available for the analysis of the sex-specific association between type 1 diabetes and all-cause mortality. Compared with unaffected individuals, the pooled SMR for all-cause mortality in people with type 1 diabetes was 5·80 (95% CI 4·89–6·89) in women, and 3·80 (3·42–4·23) in men (appendix p 6). Overall, the rSMR indicated a 37% significantly greater excess risk of all-cause mortality in women with type 1 diabetes compared with men (rSMR 1·37 [95% CI 1·21–1·56] p<0·0001), but with significant heterogeneity between the studies (I^2=86%, p<0·0001) (figure 2). There was no evidence of publication bias (appendix p 7).

Pooled estimates of the rSMR were broadly consistent across year of study baseline, with the exception of the very early studies (pre-1970) in which the estimate was slightly more extreme but still compatible with the overall summary estimate (p=0·20; figure 3). Similarly, regional estimates of the pooled rSMR were all compatible with the summary estimate (p=0·70). Duration of study follow-up also did not account for much of the between-study heterogeneity (p=0·68); a higher excess SMR in women than in men with type 1 diabetes was recorded across all

four groups with successively longer periods of follow-up (figure 3). Age by when an individual was documented as receiving a diagnosis of type 1 diabetes was also not an important source of between-study heterogeneity (p=0·12; figure 3). Pooled estimates derived from registry data versus cohort studies also did not differ significantly from each other, nor did they vary by study quality (figure 3). Differences in the background rate of mortality in women to mortality in men explained some of the heterogeneity in study findings: in studies where the mortality rate in men was more than 10% higher than women, the summary estimate of the rSMR was 1·13 (95% CI 0·97–1·33), compared with 1·59 (1·24–2·05) in studies in which the mortality rate in men was 0–10% higher than in women, and 2·43 (1·92–3·08) in studies in which the mortality rate in men was lower than in women (appendix p 8).

For our analysis of type 1 diabetes and cause-specific events, we analysed data for fatal and non-fatal coronary heart disease. Information about 59 383 individuals and 1427 coronary heart disease events was available for inclusion in this analysis. The pooled SMR for coronary heart disease in women with type 1 diabetes versus those without the disease was 13·32 (95% CI 8·79–20·19) and the corresponding estimate in men was 5·62 (4·30–7·34) (appendix p 9). The overall pooled estimate of the rSMR suggested a 154% greater excess event rate in women than in men with type 1 diabetes (2·54 [95% CI 1·80–3·60], p<0·0001, I^2=67·86%; figure 4).

For our analysis of fatal and non-fatal stroke, we pooled overall data from 45 677 individuals and 371 stroke events. The combined SMR for stroke in women with type 1 diabetes versus those without was 5·70 (95% CI

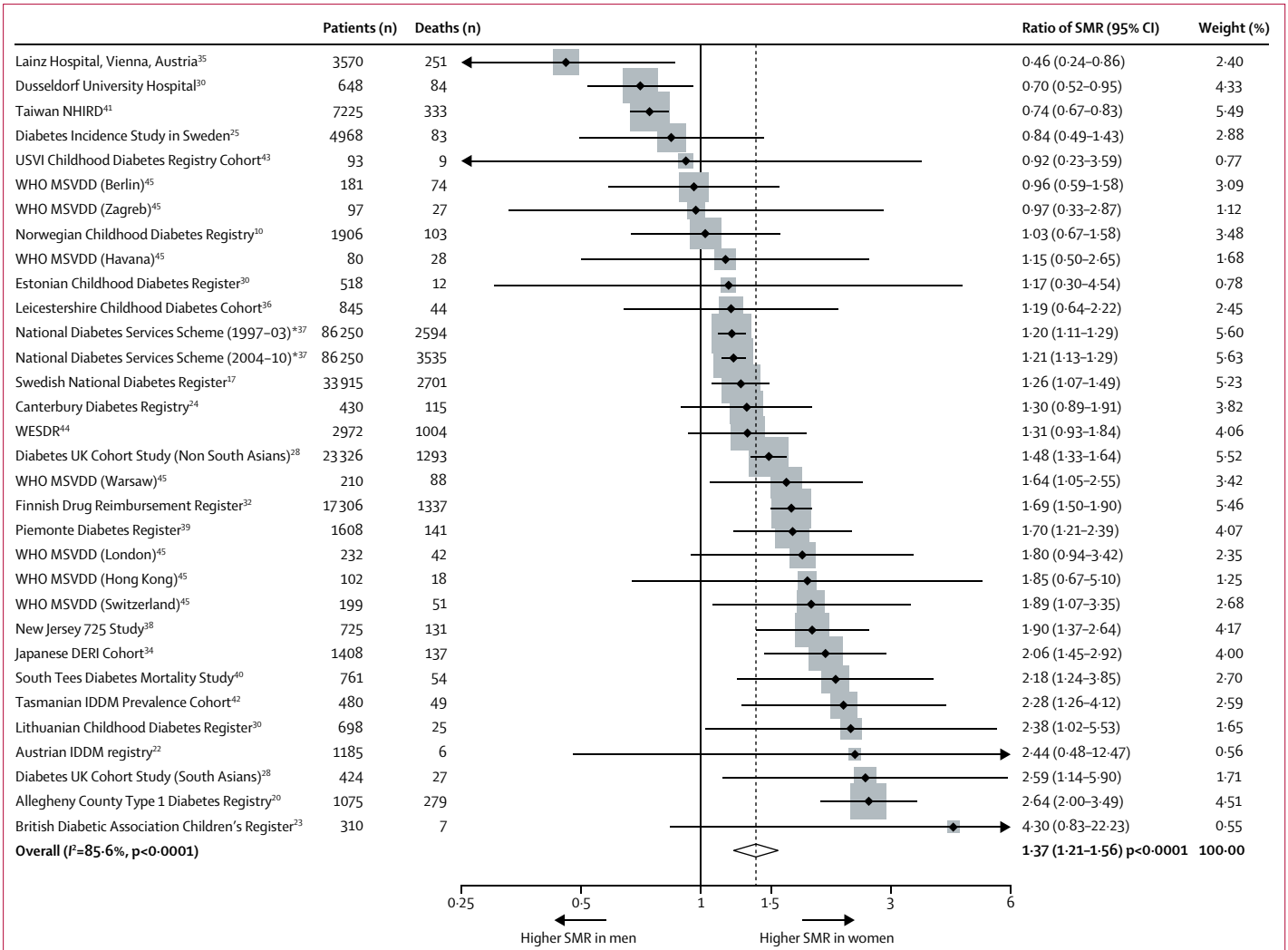

Figure 2: **Pooled women-to-men ratios of SMRs for all-cause-mortality, comparing people with type 1 diabetes versus those without the disorder**
Boxes represent individual point estimates from each study for the ratio of the SMR and the horizontal lines represent the 95% CIs around the point estimate. The diamond and vertical dotted line represents the pooled summary estimate and variance of the ratio of the SMR. *The sample size for the National Diabetes Services Scheme represents the total number of patients with type 1 diabetes who contributed to the National Diabetes Services Scheme 1997–2010.[37]

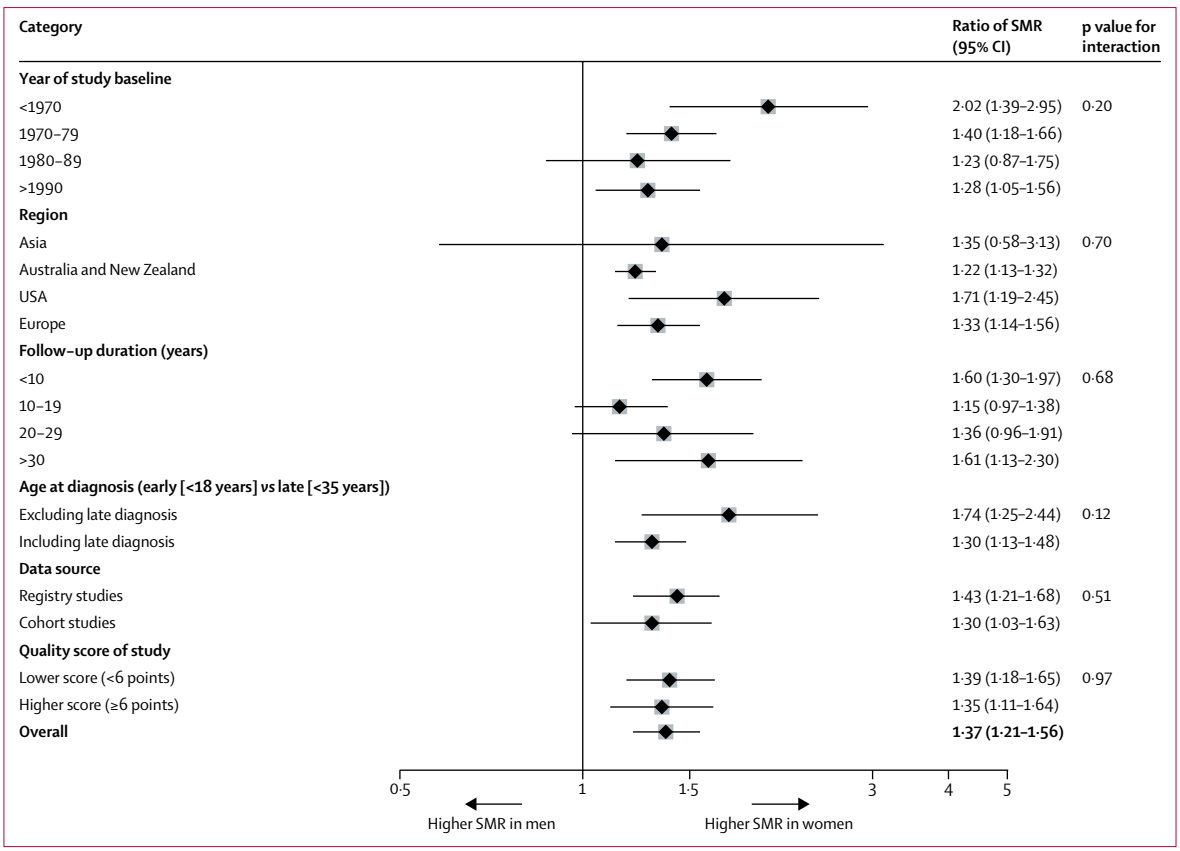

Figure 3: **Forest plot showing the results of the subgroup analyses**
Plotted points are the pooled women:men SMR for each variable and the horizontal lines represent the 95% CIs. SMR=standardised mortality ratio.

1·80–18·07) and the corresponding estimate in men was 4·89 (1·86–12·87) (appendix p 10). The overall pooled estimate of the rSMR indicated a 37% greater excess event rate in women than in men with type 1 diabetes (1·37 [95% CI 1·03–1·81], p=0·0308) with no significant between-study heterogeneity (figure 4).

For cardiovascular disease mortality, when we combined data from 75 983 individuals and 2166 events, the pooled SMR for cardiovascular disease in people with type 1 diabetes versus those without was 11·30 (95% CI 6·87–18·59) in women versus 5·68 (3·82–8·44) in men (appendix p 11). Overall the rSMR was 1·86 (1·62–2·15, p<0·0001, I^2=2·39%; figure 4).

For renal disease mortality, data from 30 332 individuals and 142 renal events were pooled. The summary SMR for mortality from renal disease in people with type 1 diabetes versus those without was 69·77 (95% CI 54·39–89·51) in women and 48·36 (37·78–61·89) in men (appendix p 12). The overall pooled summary estimate of the rSMR suggested a 44% excess risk of renal mortality in women compared with men with type 1 diabetes (1·44 [1·02–2·05]; p=0·0404), with no evidence of between-study heterogeneity (figure 4).

In our analysis of cancer mortality, for which we combined data from 31 018 individuals and 119 cancer events, type 1 diabetes was not associated with an increased risk of mortality from cancer in either women or men. The pooled SMR in people with type 1 diabetes versus those without the disorder was 1·00 (95% CI 0·73–1·36) in women and 0·80 (0·61–1·05) in men (appendix p 13). The overall pooled summary estimate of the rSMR showed no evidence of a significant difference between the sexes (1·23 [95% CI 0·79–1·98], p=0·32) or of significant between-study heterogeneity (I^2=0%; figure 4).

In our analysis of mortality from accident and suicide, data from 36 320 individuals and 260 accident and suicide events contributed to the analysis. Compared with unaffected individuals, those with type 1 diabetes had a higher SMR relating to this outcome: in women the SMR was 2·53 (95% CI 1·65–3·89) and in men 1·80 (1·32–2·47) (appendix p 14). Overall, there was no significant evidence of a sex difference in mortality from accident and suicide in individuals with type 1 diabetes: pooled rSMR 1·34 (0·97–1·84; p=0·073), with no evidence of between-study heterogeneity (I^2=0%; figure 4).

Discussion

The main aim of this meta-analysis, which included data from more than 200 000 men and women and

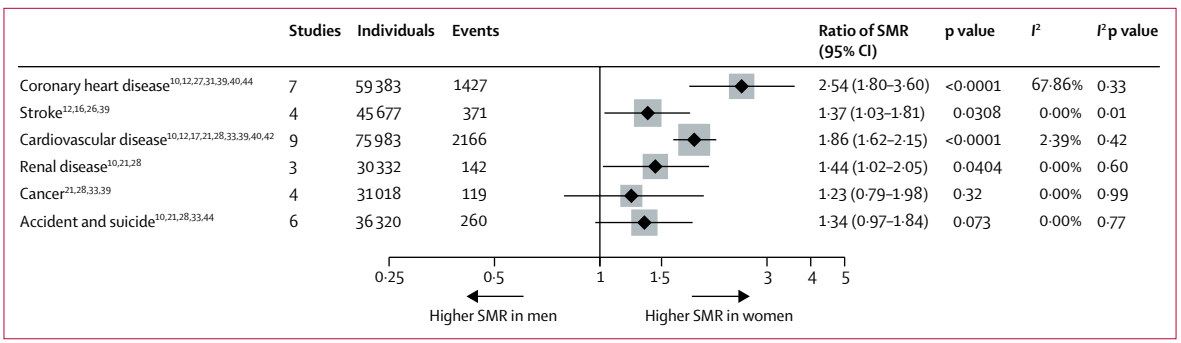

Figure 4: **Pooled women-to-men ratios of SMRs for incident coronary heart disease and stroke, and for mortality from cardiovascular disease, renal disease, cancer, and accident and suicide**

Two studies[12,17] reported the sex-specific age-adjusted hazard ratio (and variance) for coronary heart disease, stroke, and cardiovascular disease events in patients with type 1 diabetes compared with individuals who were free from previous cardiovascular disease; therefore the ratios of the hazard ratios (women:men) were obtained and included in the summary estimate. SMR=standardised mortality ratio.

information about more than 15 000 deaths, was not to estimate the excess mortality associated with type 1 diabetes per se—although we have provided such estimates in the appendix—but rather to establish whether or not sex differences in outcomes are present when women and men from the same study are compared. We have shown that a significant and clinically meaningful sex difference exists in the excess risk of mortality (in particular vascular mortality conferred by type 1 diabetes to the detriment of women)—in individuals with type 1 diabetes the excess risk of all-cause mortality was 37% higher in women than in men. For macrovascular outcomes (including cardiovascular and renal diseases) the excess risk of mortality in women compared with men was even more extreme. Mortality rates from neoplastic causes or from accident and suicide were similar in both women and men.

The recorded excess relative risk in women might be an artefact of the data driven by the (generally) higher absolute mortality rates in men than in women in the background population. If this is the case, then the relative effect of diabetes on mortality would be more extreme in women than in men in populations in which the absolute mortality rate is higher in men than in women, but should converge when the mortality rates are similar between the sexes. However, our present findings show strong evidence to the contrary; high mortality rate ratios (indicating a greater excess risk in women than men) were recorded in the studies in which there was little sex difference in background mortality rates and in those in which the background mortality rates were higher in women than in men. As in a previous meta-analysis of sex differences in associations between risk factors and disease, we presented the results in terms of relative rather than absolute risk differences because risk is represented as a ratio rather than as a difference.[46,47] Consequently, to compare risks and relative risks through their ratios is both consistent and logical. Moreover, an averaged pooled mortality risk difference (ie, mortality associated with type 1 diabetes minus that associated with no diabetes, for either sex), and the difference in these differences between sexes would be of little clinical relevance. By contrast, the current findings of the pooled sex-specific SMRs and their ratio are reasonable approximations of individual outcomes across a wide range of settings.

The specificity of the observed sex difference for vascular-related outcomes in patients with type 1 diabetes adds to the accumulating evidence suggesting a greater adverse effect of hyperglycaemia and diabetes on vascular risk in women than in men.[46,47] Previous studies have reported increased rates of coronary artery calcification and other indices of endothelial dysfunction[48,49] in women than in men with type 1 diabetes[50] and more extensive atherosclerotic lesions associated with hyperglycaemia in women than in men.[51] We speculate that the excess vascular mortality recorded in women compared with men with type 1 diabetes might be due to women having an overall greater cumulative lifetime exposure to hyperglycaemia because of poorer glycaemic control compared with men.[47] Previous studies of individuals with type 1 diabetes have shown notable sex differences in the control of blood glucose and HbA_{1c} levels; young girls and women are more likely to be in persistent poor glycaemic control than are young boys and men,[52,53] despite higher use of insulin pumps in girls and women.[54] This sex disparity in glycaemic control has been attributed to a greater impairment of insulin sensitivity during puberty in young women with type 1 diabetes,[55,56] and an increased propensity towards eating disorders and underdosing with insulin in women affected by type 1 diabetes compared with similarly affected men.[57] Alternatively, the excess vascular risk associated with type 1 diabetes in women might be a manifestation of the well-reported disturbances in the hypothalamus–pituitary–ovarian axis that are associated with diabetes, including delayed age of menarche, menstrual irregularities, and precocious menopause.[58]

A key strength of this meta-analysis is its size and the ability to study the sex-specific associations for several cause-specific outcomes, which are potentially more informative than all-cause mortality with respect to understanding the underlying mechanisms involved. The inclusion of only those studies that provided sex-specific estimates for men and women within the same study avoided any bias that would have been introduced if we had included estimates for men and women derived from different studies. The limitations of this study are inherent to the use of published data and include the absence of standardisation with respect to method of case ascertainment, study design and duration, endpoint definition, and the degree of adjustment for confounding across studies: most studies standardised by age, and some standardised by race and year of study baseline. In the present analysis, we used region as a proxy for ethnic origin because we did not have access to the individual participant data. However, the absence of any signal or statistical evidence of a regional interaction (figure 3) suggests that even if such an analysis were possible, the association is unlikely to have differed materially across ethnic groups. Despite doing a range of sensitivity analyses, we were also unable to explain most of the heterogeneity between the studies for the primary outcome of all-cause mortality (although different background mortality rates and patterns of mortality explained some of the variation), so these findings remain speculative until confirmed by future studies.

The inherent inability of observational studies to fully capture the effects of confounders (both measured and unmeasured) means that some residual confounding is likely in the current estimates. Crucially, however, the confounding is likely to have been non-differentially distributed between women and men from the same study and therefore we assume that it would have had only a negligible effect on the associations reported in this Article. Finally, since we only compared women and men from within the same study, any bias that was introduced by the use of general population rates to estimate the expected number of deaths (a procedure that necessitates the unlikely assumption that all individuals in the general population are free from type 1 diabetes to calculate the SMR is likely to have affected women and men similarly.[59]

A recent joint statement issued by the American Heart Association and the American Diabetes Association relating specifically to type 1 diabetes and cardiovascular diseases concluded that further research into racial and ethnic differences and improved cardiovascular risk-prediction methods in this patient group was needed.[1] In view of our findings, we argue that this statement should be extended to include sex. Ultimately, an increased understanding and appreciation of sex differences in the effect of type 1 diabetes on vascular-related disease is likely to have profound clinical implications for how women with type 1 diabetes are treated and managed throughout their life course.

Contributors
RRH conceived the study, interpreted the data, and drafted and critically revised the report. SAEP did the search, analysed and interpreted the data, and critically revised the report. GDM critically revised the report. MW participated in data collection, oversaw the data analysis, interpreted the data, and critically revised the report.

Declaration of interests
We declare no competing interests.

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Excess deaths in women with type 1 diabetes: time to act

Women die, on average, at an older age than men. For more than 40 years we have known that this usual so-called female protection is lost in women with diabetes treated with insulin.[1] Thus, in absolute terms, mortality rates are highest in men with type 1 diabetes,[2] but the within-sex excess mortality in type 1 diabetes is higher in women than in similarly affected men.

In a meta-analysis in *The Lancet Diabetes & Endocrinology* that included 26 studies and 214 114 individuals, Rachel Huxley and colleagues[3] quantify the ratio of excess mortality of women with type 1 diabetes compared with men with the same disorder. The results show that in patients with type 1 diabetes, women have a higher excess all-cause mortality than men (ratio of standardised mortality ratio 1·37 [95% CI 1·21–1·56]), and higher excess mortality from stroke (1·37 [1·03–1·81]), coronary heart disease (2·54 [1·80–3·60]), cardiovascular disease (1·86 [1·62–2·15]), and renal disease (1·44 [1·02–2·05]).

The cohorts included in Huxley and colleagues' meta-analysis are very heterogeneous, since they include a mixture of carefully defined cohorts or registries, along with a General Practice (GP) research database. Monogenic diabetes would probably have been present in a small proportion of patients across the registries. However, GP databases in particular often misclassify the type of diabetes, such as classifying insulin-treated type 2 diabetes as type 1 diabetes.[4] 13 cohorts based the type 1 diabetes diagnosis upon an age that could have included patients with type 2 diabetes. However, inclusion of patients without type 1 diabetes is unlikely to have affected the findings because no evidence currently exists for sex differences in misclassification.

The mechanisms underlying the higher all-cause and cardiovascular standardised mortality ratios in women than in men are still unclear. Mechanisms that differentially affect women could include an increased effect of the same degree of hyperglycaemia, a higher degree of hyperglycaemia, differences independent of hyperglycaemia, or a combination of these factors. Differences in premature vascular calcification and endothelial dysfunction, along with lipid changes and greater central adiposity in women with type 1 diabetes compared with those without the disease, have been implicated in the higher excess cardiovascular disease mortality rate reported in women.[1,3] These features seem to be downstream effects from the absolute insulin deficiency that is the hallmark of type 1 diabetes. Brittle diabetes could explain some of the excess mortality in girls and women: this type of diabetes has an especially high all-cause mortality rate, and is more common in female than male patients.[5] Poor glycaemic control and difficulties with insulin management are more frequent in patients with some clinical conditions that are more prevalent among girls and women (eg, eating disorders).[3] Achievement of HbA_{1c} targets does seem to be more difficult in women than in men, at least early in the course of the disease,[6] although whether differences between the sexes are behavioural, physiological, or both remains unclear. Indeed, glycaemic control improves in many women who are motivated and have access to close attention during pre-pregnancy or antenatal care, which is likely to generate improved confidence and self-management skills in the long term. In fact, overall, HbA_{1c} is only about 0·1% higher in female than male patients with type 1 diabetes at all ages[7,8] and this difference is unlikely to be sufficient to explain their excess mortality.

Although type 1 diabetes complications or their severity can be limited by tight glycaemic control, the excess all-cause mortality at all ages, in both sexes, persists. A major problem in type 1 diabetes is that cardiovascular disease benefits do not accrue for almost two decades of tight glucose control.[9] In the Diabetes Control and Complications Trial (DCCT) and the follow-on Epidemiology of Diabetes Interventions and Complications study, cardiovascular disease and death were 57% lower in patients within the intensive control group than the standard care control group, 8 years after the end of the trial. During this post-trial period, glycaemic control was similar in both groups. This finding has been interpreted as so-called "metabolic memory"—ie, physical changes have occurred that are not reversed by improving glycaemic control. However, as with smoking, this process is continuous, indicating that the earlier glycaemic control is optimised, the better.

Huxley and colleagues rightly suggest that the sex difference in excess mortality in those with type 1 diabetes should stimulate some kind of action.

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However, this action should not be sex based: health and funding systems should systematically support improvements in glycaemic control from diagnosis, for all patients with type 1 diabetes, through tailored therapy as implemented in the DCCT, including mental health support and personalised strategies that help avoid hypoglycaemia.[9] Sex differences in management of cardiovascular disease and its risk factors[6,8] also need to be rectified. A process for reporting rates of cardiovascular disease risk factor treatment, goal achievement, and intervention by sex, as well as overall, would help to systematically introduce strategies to address under-treatment where it exists.

A key question is how the risk of excess mortality in women can be reduced further—a particular challenge given that the reasons for excess mortality in type 1 diabetes are still unclear. For example, should women with mildly raised HbA_{1c} concentrations (eg, higher than 7%) be commenced on statins or angiotensin-converting enzyme inhibitors as young adults (with appropriate contraception, taking into account their teratogenic effects)? Should blood pressure be treated at a lower threshold in younger women (eg, <130/80 mm Hg if aged <40 years)?

Achievement of a reduction in the high type 1 diabetes mortality rates will need additional expenditure on the care of patients with the disorder, many of the benefits from which might not be seen for up to 20 years. The additional investment in the services and equipment to improve glycaemic control must start now.

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