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Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies

Rachel Huxley, Federica Barzi, Mark Woodward

Abstract

Objective To estimate the relative risk for fatal coronary heart disease associated with diabetes in men and women.

Design Meta-analysis of prospective cohort studies.

Data sources Studies published between 1966 and March 2005, identified through Embase and Medline, using a combined text word and MESH heading search strategy, in addition to studies from the Asia Pacific Cohort Studies Collaboration.

Review methods Studies were eligible if they had reported estimates of the relative risk for fatal coronary heart disease comparing men and women with and without diabetes. Studies were excluded if the estimates were not adjusted at least for age.

Results 37 studies of type 2 diabetes and fatal coronary heart disease among a total of 447 064 patients were identified. The rate of fatal coronary heart disease was higher in patients with diabetes than in those without (5.4 v 1.6%). The overall summary relative risk for fatal coronary heart disease in patients with diabetes compared with no diabetes was significantly greater among women than it was among men: 3.50, 95% confidence interval 2.70 to 4.53 v 2.06, 1.81 to 2.34. After exclusion of the eight studies that had adjusted only for age, the difference in risk between the sexes was substantially reduced but still highly significant. The pooled ratio of the relative risks (women: men) from the 29 studies with multiple adjusted estimates was 1.46 (1.14 to 1.88).

Conclusions The relative risk for fatal coronary heart disease associated with diabetes is 50% higher in women than it is in men. This greater excess coronary risk may be explained by more adverse cardiovascular risk profiles among women with diabetes, combined with possible disparities in treatment that favour men.

Introduction

Type 2 diabetes has long been known as a risk factor for coronary heart disease and is conservatively estimated to increase the risk of a fatal event by twofold.^{1,2} The association between diabetes and coronary heart disease has been suggested to be stronger in women than in men, prompting the idea that diabetes eliminates, or substantially attenuates, the advantages of being female.³

Within the past decade three meta-analyses on this topic have produced conflicting results.⁴⁻⁶ Two concluded that women with diabetes were at increased risk of mortality from coronary heart disease compared with men, whereas the third found no difference. These discrepancies may have arisen from differences in the level of adjustment for other cardiovascular risk factors between included studies. For example, as lipid levels are directly

affected by diabetes, and to differing degrees in men and women,⁷ overadjustment for lipid variables may attenuate any real difference between the sexes in relation to diabetes and fatal coronary heart disease. Adjusting for age alone, however, fails to take into account potential differences in the levels of other cardiovascular risk factors (for example, blood pressure, body mass index) between men and women with diabetes, which could generate a spurious difference between the sexes in the relative risk of mortality due to coronary heart disease associated with diabetes.

The Asia Pacific Cohort Studies Collaboration comprises a large number of prospective cohort studies in the region and was established to provide reliable evidence about the effects of a variety of putative factors on the risk of cardiovascular disease among populations in this region.⁸ We sought to produce a reliable and unbiased comparison of the relative risk for fatal coronary heart disease associated with diabetes separately for men and women by updating the earlier reviews with published data from the Asia Pacific Cohort Studies Collaboration as well as any cohort studies published before March 2005.

Methods

We identified relevant studies through Embase and Medline using a combined text word and MESH heading search strategy of the terms “diabetes”, “gender”, “sex”, and “coronary heart disease”. We included eligible studies from the three previous reviews and we also scanned references to identify any other relevant studies, as recommended by the meta-analysis of observational studies in epidemiology guidelines.⁹

Data extraction

We included prospective cohort studies if by March 2005 they had published quantitative estimates and standard errors (or confidence limits) of the relative risk for fatal coronary heart disease associated with diabetes for both men and women. Studies were excluded if they provided only an estimate of effect, with no means by which to calculate the standard error; if the estimates were not adjusted at least for age; or if the study population had been derived from patients with a history of cardiovascular disease. We also excluded studies if they were carried out among single sex populations thereby preventing any internal comparison of the effects of diabetes between the sexes. We did not assess the methodological criteria of the studies owing to the questionable merit of quality scoring in meta-analyses of observational studies.^{10,11} Instead we investigated possible sources of heteroge-



Web references w1-w46, additional figures, and details of studies contributing data are on bmj.com

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neity by comparing the results for studies combined for particular characteristics (for example, method of diabetes diagnosis, country of origin). We examined the effect of duration of follow-up on estimates of effects by metaregression.¹²

Data analysis

We obtained summary estimates by means of a random effects approach using inverse variance weighting.¹² Using the I^2 statistic (95% CI), we estimated the percentage of variability across studies attributable to heterogeneity rather than to chance variation.¹² We estimated the women to men ratio of the relative risks for fatal coronary heart disease, comparing those with diabetes to those without, with 95% confidence intervals, both overall, for studies only with age adjusted estimates, and for studies only with multiple adjusted estimates. We assessed publication bias graphically using a funnel plot, plotting the natural log of the ratio of the relative risks against its standard error. We extracted differences in the mean (standard deviation) levels of systolic blood pressure, lipids, and body mass index in patients with and without diabetes from the Asia Pacific Cohort Studies Collaboration, weighted by their inverse variance and combined in a meta-analysis. All analyses were carried out using Stata version 8.

Results

Our search strategy yielded 5621 articles, of which 306 included primary data. Of these we excluded 234 articles either because there was no outcome of interest or because they reported duplicate data. A further 49 papers^{2 w1-48} were excluded for various reasons (fig 1). The remaining 23 articles were eligible for inclusion in our review. These comprised 37 prospective cohort studies^{s 13-34} with information on 447 064 patients (45% women). Seventeen of these studies were included in the earlier reviews (table 1). The remaining 20 studies, 13 of which were derived from a previous publication from the Asia Pacific Cohort Studies Collaboration (see bmj.com),^s were identified for the purposes of this review (table 2). All but six of the 37 studies reported the number of patients with a diagnosis of diabetes at baseline (24 714, 31% women). The duration of follow-up varied from between four to 36 years and the age range was between 15 and 98 years. Eleven of the 37 studies were from the United States, nine from Australia and New Zealand, nine from Asia, and eight from European countries.

Coronary heart disease event rates

In the 33 studies that reported the total number of deaths from coronary heart disease during follow-up, a total of 7570 of 420 630 (1.8%) people died. Twenty seven studies reported the number of fatal coronary heart disease events among participants by diabetes status (6335 of 333 400, 1.9%); of these, 1203 (41% women) had diabetes. The rate of fatal coronary heart disease was substantially higher in people with diabetes than in those without (5.4% v 1.6%). This difference was apparent in both sexes but more so among women (with and without diabetes 7.7 v 1.2%). The corresponding rates in men were 4.5% and 2.0%.

Summary estimate of relative risk for fatal coronary heart disease in patients with diabetes

The overall summary estimate of the relative risk for fatal coronary heart disease associated with diabetes was significantly greater in women than it was in men (relative risk 3.50, 95% confidence interval 2.70 to 4.53 v 2.06, 1.81 to 2.34; $P < 0.0001$: see figs A and B on bmj.com). We found significant heterogeneity

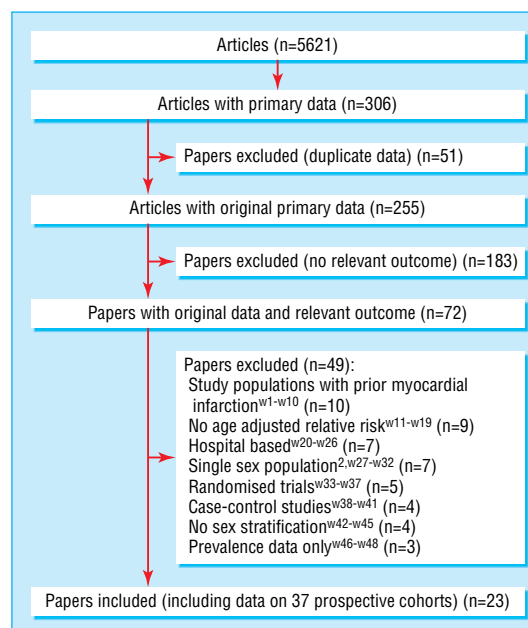


Fig 1 Flow chart of search strategy

across all studies (men: $I^2 = 43%$, 95% confidence interval 16% to 61%; women: 74%, 65% to 81%) that was substantially attenuated after exclusion of the eight studies with only age adjusted coefficients (26%, -18% to 53% and 35%, 15% to 59%). Exclusion of these eight studies reduced the relative risk of fatal coronary heart disease in women with diabetes but not men (2.95, 2.39 to 3.65 v 2.02, 1.76 to 2.31; $P = 0.003$ for sex difference).

To further examine the effect of adjustment we considered the 22 studies that had provided both age and multiple adjusted coefficients (fig 2). All but two of these studies, in addition to adjusting for systolic blood pressure and total cholesterol, had adjusted for smoking. Adjustment resulted in a larger attenuation of the relative risk of fatal coronary heart disease among women than among men (fig 2). This greater attenuation in the relative risk among women with diabetes may be due in part to both the significantly higher levels of other cardiovascular risk factors compared with their male equivalents and the much larger difference in levels of risk factors between women with and without diabetes, compared with men with and without diabetes (table 3).

Ratio of relative risks for fatal coronary heart disease among men and women with diabetes

The pooled ratio of relative risks for diabetes from all 37 studies was 1.70 (1.27 to 2.27). Excluding the eight pairs of age adjusted relative risks, the ratio of relative risks was reduced to 1.46 (1.14 to 1.88). Thus the best evidence available suggests that the relative risk of fatal coronary heart disease associated with diabetes is about 50% higher in women than it is in men.

Sensitivity analyses

We carried out sensitivity analyses on the 29 studies for which multiple adjusted coefficients were available for both sexes (fig 3). We found no difference in the ratio of the relative risks for diabetes between men and women with diabetes according to fixed effects or random effects models, method of diabetes diagnosis (self report v glucose measured), and region of study (Asia v non-Asian countries). Metaregression indicated that the duration of study follow-up had no effect on the overall hazard ratios. Visual examination of the funnel plot showed no evidence

Table 1 Characteristics of studies of coronary heart disease risk in individuals with and without diabetes that contributed to earlier reviews

Reference	Cohort, country	Study size (No with diabetes)	Age range (years)	Duration of study (years)	No of fatal coronary heart disease events (No in patients with diabetes)	Variables adjusted for in analyses
Butler 1985 ¹³	Tecumseh, United States	921 men (43); 937 women (70)	>40	12-20	161 (19); 88 (17)	Age
Pan 1986 ¹⁴	Chicago Heart Association detection project in industry, United States	11 220 men (377); 8030 women (170)	35-64	9	286 (44); 47 (6)	Age, smoking, systolic blood pressure, total cholesterol, electrocardiography, education
Kleinman 1988 ¹⁵	National health and nutrition examination survey I, United States	3340 men (189); 4041 women (218)	40-77	9	321 (44); 160 (25)	Age, smoking, systolic blood pressure, total cholesterol, body mass index
Heyden 1990 ¹⁶	Georgia, United States	1284 men; 1420 women	25-74	4.5	524	Age, smoking, systolic blood pressure, total cholesterol, triglycerides, body mass index
Barrett-Connor 1991 ¹⁷	Rancho Bernardo California, United States	1100 men (207); 1351 women (127)	40-79	14	127 (36); 77 (19)	Age, smoking, systolic blood pressure, total cholesterol, body mass index, hormone replacement therapy
Fraser 1992 ¹⁸	California seventh day adventists, United States	10 376 men (374); 17 282 women (812)	>25	6	136 (13); 166 (20)	Age, smoking, hypertension, body mass index, exercise
Sievers 1992 ¹⁹	Arizona, United States	2463 men (536); 2668 women (730)	>15	12.1	24 (1); 12 (0)	Age, smoking, hypertension, hypercholesterolaemia
Seeman 1993 ²⁰	Connecticut, United States	1169 men (156); 1643 women (230)	>65	6	102 (18); 125 (29)	Age, smoking, systolic blood pressure, body mass index
Keil 1993 ²¹	Charleston heart (white people), United States	653 men, 741 women	35-74	30	237	Age, smoking, hypertension, hypercholesterolaemia
Keil 1993 ²¹	Charleston heart (black people), United States	333 men, 454 women	35-74	30	123	Age, smoking, systolic blood pressure, total cholesterol, body mass index, education
Kannel 1995 ²²	Framingham study, United States	5209	30-62	36	NA	Age
Simons 1996 ²³	Dubbo, Australia	1155 men (106); 1472 women (101)	>60	5.2	223 (36); 200 (34)	Age
Collins 1996 ²⁴	Fiji	472 men (79); 582 women (87)	≥20	11	NA	Age, smoking, hypertension, total cholesterol
Collins 1996 ²⁴	Fiji	605 men (23); 654 women (42)	—	11	NA	Age, smoking, systolic blood pressure, total cholesterol, body mass index, survey area
Folsom 1997 ²⁵	Atherosclerosis risk in communities study	13 446	45-64	4-7	Men, 209 (43); women, 96 (33)	Age, smoking, systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, triglycerides, body mass index
Vilbergsson 1998 ²⁶	Reykjavik study, Iceland	9139 men (267); 9773 women (210)	34-79	17	(92)	Age, smoking, systolic blood pressure, total cholesterol, triglycerides, body mass index
Jousilahti 1999 ²⁷	Multinational monitoring of trends and determinants in cardiovascular disease, Finland	7090 men (262); 7696 women (254)	25-64	7-12	231; 63	Age, smoking, systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, body mass index

NA=not available.

of publication bias (see fig C on bmj.com), which was confirmed by the Egger test.

Discussion

Diabetes poses a substantially greater increase in the risk of death from coronary heart disease among women than among men. Our finding is based on more than four times the amount of information available for previous reviews, making possible reliable quantitative estimates of the association between diabetes and risk for coronary heart disease between the sexes. Our findings are compatible with recent results from INTERHEART, a large case-control study of more than 15 000 cases of acute myocardial infarction, which concluded that diabetes was a more significant coronary risk among women than it was among men (odds ratio 4.3, 95% confidence interval 3.5 to 5.2 *v* 2.7, 2.7 to 3.0).³⁵

Several mechanisms could explain why diabetes has a greater adverse affect in women than in men. As supported by our analyses, diabetes may induce a more unfavourable cardiovascular risk profile among women.^{36 37} We found that women with

diabetes not only have significantly higher levels of blood pressure and lipids than men with diabetes but that the difference in the levels among people with and without diabetes was significantly greater in women than it was in men. This would potentially explain why, after adjustment, the attenuation of the relative risk was considerably greater among women with diabetes than it was among their male equivalents, suggesting that the sex difference in coronary heart disease risk is mediated in large part by differences in the levels of cardiovascular risk factors.

Alternatively, the greater coronary risk associated with diabetes seen in women may reflect a treatment bias that favours men. Recent studies found that men with diabetes or established cardiovascular disease are more likely to receive aspirin, statins, or antihypertensive drugs than are women. For example, one study found that only 35% of women with diabetes or cardiovascular disease were prescribed a statin compared with 45% of men with similar medical histories.³⁸ Similar findings were reported from the United Kingdom prospective diabetes study,³⁹ where women with diabetes were significantly less likely to use aspirin compared with men. In two recent studies from the United

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Table 2 Characteristics of studies from Asia Pacific Cohort Studies Collaboration and other studies not included in previous reviews of coronary heart disease risk in people with and without diabetes

Reference	Country	Study size (No with diabetes)	Age range (years)	Duration of study (years)	No of fatal coronary heart disease events (No with diabetes)	Variables adjusted for in analyses
Tanno 1977*	Japan	919 men (62); 1048 women (79)	39-65	16.4 (15.3)	18 (2); 6 (1)	Age, smoking, systolic blood pressure, total cholesterol
Perth 1978*	Australia	5123 men (98); 4599 women (95)	20-90	14.4 (12.8)	136 (10); 51 (3)	Age, smoking, systolic blood pressure, total cholesterol
Singapore heart 1982*	Singapore	1168 men (152); 1123 women (113)	20-89	14.6 (12.3)	21 (9); 8 (2)	Age, smoking, systolic blood pressure, total cholesterol
Akabane 1985*	Japan	812 men (27); 1020 women (18)	40-69	11.0 (11.1)	5 (1); 2 (1)	Age, smoking, systolic blood pressure, total cholesterol
Newcastle 1988*	Australia	1713 men (80); 1690 women (39)	21-77	4.5 (6.0)	32 (3); 10 (1)	Age, smoking, systolic blood pressure, total cholesterol
CVDFACTS 1988*	Taiwan	2461 men (77); 3079 women (67)	20-92	6.0 (6.4)	6 (1); 6 (1)	Age, smoking, systolic blood pressure, total cholesterol
ANHF 1989*	Australia	4500 men (96); 4610 women (66)	20-70	8.3 (8.2)	58 (4); 19 (1)	Age, smoking, systolic blood pressure, total cholesterol
Melbourne 1990*	Australia	16 905 men (1206); 24 235 women (1015)	27-75	8.5 (8.6)	242 (38); 81 (13)	Age, smoking, systolic blood pressure, total cholesterol
Fletcher challenge 1992*	New Zealand	7369 men (181); 2856 women (84)	20-89	5.8 (5.7)	80 (13); 32 (5)	Age, smoking, systolic blood pressure, total cholesterol
KMIC 1992*	South Korea	106 736 men (10 736); 53 497 women (1513)	35-59	4.0 (4.0)	89 (19); 5 (1)	Age, smoking, systolic blood pressure, total cholesterol
ALSA 1992*	Australia	600 men (58); 554 women (27)	65-98	4.7 (4.9)	40 (6); 20 (1)	Age, smoking, systolic blood pressure, total cholesterol
Singapore NHS92 1992*	Singapore	1593 men (155); 1710 women (165)	20-70	6.2 (6.2)	17 (8); 5 (3)	Age, smoking, systolic blood pressure, total cholesterol
Kuusisto 1994 ²⁸	Finland	470 men (74); 828 women (155)	65-74	3.5	75 (39)	Age
Laakso 1995 ²⁹	Finland	1219 men (581); 1213 women (478)	45-64	7.2	122 (97); 63 (61)	Age
Qvist 1996 ³⁰	Sweden	2546 men (96); 2760 women (75)	45-74	10	189 (20); 75 women (18)	Age
Busselton 1996*	Australia	2709 men (109); 2948 women (89)	20-94	20.5 (20.2)	306 (14); 234 (16)	Age, smoking, systolic blood pressure, total cholesterol
Tunstall-Pedoe 1997 ³¹	Scotland	5754 men (86); 5875 women (88)	40-59	6-9	404 (NA); 177 (NA)	Age
Nilsson 1998 ³²	Sweden	18825 men (420); 19 454 women (356)	25-74	16	Men, 1050 (94); women, 470 (87)	Age
Imazu 2002 ³³	Japan	400 men (78); 517 women (91)	60	10-18	29 (12); 14 (9)	Age, smoking, hypertension, total cholesterol, triglycerides, body mass index, uric acid
Juutilainen 2004 ³⁴	Finland	1012 men (429); 1119 women (406)	45-64	13	Men, 138 (101); women, 96 (90)	Age, smoking, total cholesterol, high density lipoprotein cholesterol, triglycerides, body mass index

NA=not available.

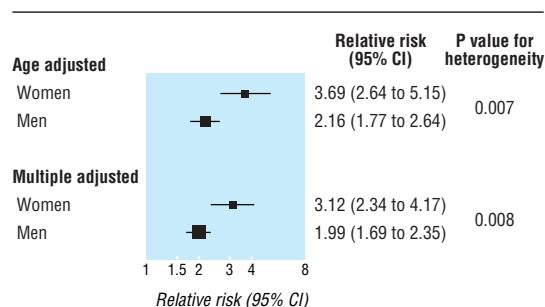
*Cohort study from Asia Pacific Cohort Studies Collaboration⁸; see bmj.com.

States, women with diabetes were also less likely to be treated with aspirin and lipid lowering agents or to achieve recommended levels of blood pressure or low density lipoprotein cholesterol than were men.^{40 41} Therefore more aggressive treatment of risk factors for coronary heart disease in

men with diabetes may explain a large component of the excess risk associated with diabetes in women.

Limitations of study

As with previous reviews, the lack of individual patient data precluded further exploration of the effect of adjustment as well as the role of treatment differences on the association of diabetes with coronary risk among men and women. Moreover, informa-

**Fig 2** Overall summary estimates of relative risks and 95% confidence intervals for fatal coronary heart disease in men and women with and without diabetes in 22 studies that reported both age and multiple adjusted coefficients**Table 3** Mean baseline risk factor levels and differences among men and women with and without diabetes

Risk factor	Difference (diabetes–no diabetes) (95% CI)	
	Men*	Women*
Systolic blood pressure (mm Hg)	7.8 (7.5 to 8.1)	12.5 (12.0 to 13.0)
Total cholesterol (mmol/l)	0.24 (0.22 to 0.26)	0.46 (0.43 to 0.49)
Triglycerides† (mmol/l)	1.53 (1.41 to 1.66)	2.01 (1.88 to 2.14)
High density lipoprotein cholesterol (mmol/l)	-0.076 (-0.1 to -0.05)	-0.13 (-0.16 to -0.1)
Body mass index (kg/m ²)	0.69 (0.65 to 0.74)	1.98 (1.87 to 2.09)

*Data from Asia Pacific Cohort Studies Collaboration.⁸

†Log transformed before analysis and subsequently transformed back.

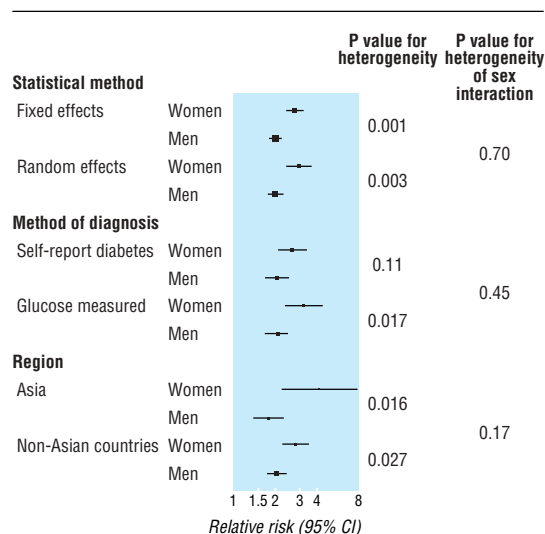


Fig 3 Sensitivity analyses on basis of statistical method, method of diagnosis, and region

tion on menopausal status and hormone replacement therapy use was not available for the present analyses, therefore we could not exclude their potential confounding effect. Finally, as we did not have information on the duration of diabetes we were unable to confirm a previous study's finding that there is a difference between the sexes in the effect of duration of diabetes on fatal coronary heart disease.⁴²

Conclusion

The excess risk of coronary death associated with diabetes is substantially higher in women than it is in men. This may be a consequence of diabetes inducing a more adverse cardiovascular risk profile in women, combined with a reduced likelihood of women receiving standard treatment and attaining recommended levels of other coronary heart disease risk factors. More aggressive treatment and better control of other coronary heart disease risk factor levels in women with diabetes is likely to substantially reduce the excess coronary heart disease mortality seen in this subgroup.

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Competing interests: None declared.

Ethical approval: Not required.

What is already known on this topic

People with type 2 diabetes are at a much greater risk of fatal coronary heart disease than those without diabetes

It is unclear whether the adverse effects of diabetes are greater for women than they are for men

What this study adds

The risk of death from coronary heart disease associated with type 2 diabetes is about 50% greater in women than it is in men

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