

## 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.<sup>1,2</sup> The association between diabetes and coronary heart disease has been suggested to be stronger in women than in men.<sup>3</sup>

Within the past decade three meta-analyses on this topic have produced conflicting results.<sup>4-6</sup> 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. Adjusting for age alone, however, fails to take into account potential differences in the levels of other cardiovascular risk factors 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, comprising a large number of prospective cohort studies, 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.<sup>7</sup> 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 and any cohort studies published before March 2005.

### Methods

We identified relevant studies through Embase and Medline (see [bmj.com](http://bmj.com) for search terms). We included eligible studies from the three previous reviews and we also scanned references to identify any other relevant studies.

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. (Exclusion criteria are on [bmj.com](http://bmj.com).) We investigated possible sources of heterogeneity by comparing the results for studies

George Institute for International Health, University of Sydney, PO Box M201, Sydney, NSW 2050, Australia

Rachel Huxley  
*senior epidemiologist*  
Federica Barzi  
*senior research fellow*  
Mark Woodward  
*professor of biostatistics*

Correspondence to:  
R Huxley  
[rhuxley@thegeorgeinstitute.org](mailto:rhuxley@thegeorgeinstitute.org)

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References for 49 excluded papers, additional figures, and details of studies contributing data are on [bmj.com](http://bmj.com)



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combined for particular characteristics and we examined the effect of duration of follow-up on estimates of effects by metaregression.<sup>8</sup>

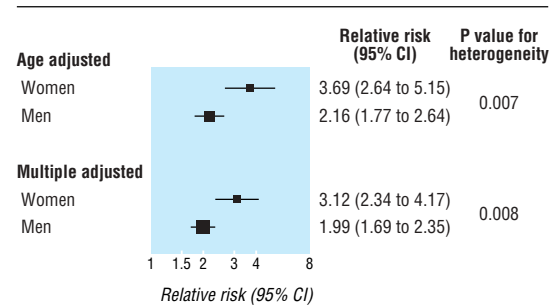
We obtained summary estimates by means of a random effects approach using inverse variance weighting.<sup>8</sup> Using the  $I^2$  statistic (95% CI), we estimated the percentage of variability across studies attributable to heterogeneity rather than to chance variation.<sup>8</sup> We estimated the 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 with only age adjusted estimates, and for studies with only multiple adjusted estimates. We assessed publication bias using a funnel plot. 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.

### Results

Our search strategy yielded 5621 articles, of which 306 included primary data. Of these we excluded 283 articles (see *bmj.com*). The remaining 23 eligible articles comprised 37 prospective cohort studies<sup>7 9-30</sup> with information on 447 064 patients (45% women). Seventeen of these studies were included in the earlier reviews (see *bmj.com*). The remaining 20 studies were identified for the purposes of this review (see *bmj.com*). 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.

In the 33 studies that reported the total number of deaths from coronary heart disease during follow-up, 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%); 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%.

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** 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

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 1). 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 1). 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 a much larger difference in levels of risk factors between women with and without diabetes compared with men with and without diabetes (table).

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 2). 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, and region of study. Metaregression indicated that the duration of study follow-up had no effect on the overall hazard ratios. The funnel plot showed no evidence of publication bias (see fig C on *bmj.com*).

### Discussion

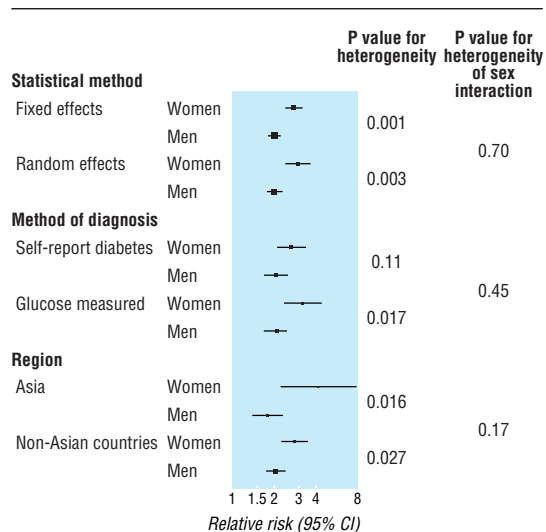
Diabetes poses a substantially greater increase in the risk of death from coronary heart disease among women than among men. Our finding is based on more than four times the amount of information

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 <sup>2</sup> )	0.69 (0.65 to 0.74)	1.98 (1.87 to 2.09)

\*Data from Asia Pacific Cohort Studies Collaboration.<sup>7</sup>

†Log transformed before analysis and subsequently transformed back.



**Fig 2** Sensitivity analyses on basis of statistical method, method of diagnosis, and region

available for previous reviews, making possible reliable quantitative estimates of the association between diabetes and risk for coronary heart disease between the sexes.

Several mechanisms could explain why diabetes has a greater adverse affect in women than in men. Diabetes may induce a more unfavourable cardiovascular risk profile among women.<sup>31,32</sup> 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 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 men with diabetes.

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.

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, as information on menopausal status and

hormone replacement therapy use was not available 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.<sup>33</sup>

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### What is already known on this topic

People with type 2 diabetes are at 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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## Neurotropic viruses and cerebral palsy: population based case-control study

Catherine S Gibson, Alastair H MacLennan, Paul N Goldwater, Eric A Haan, Kevin Priest, Gustaaf A Dekker, for the South Australian Cerebral Palsy Research Group

Editorial by  
Alberman and  
Peckham

University of  
Adelaide, Women's  
and Children's  
Hospital, 1st Floor  
Queen Victoria  
Building, 72 King  
William Road,  
Adelaide, SA 5006,  
Australia

Catherine S Gibson  
postdoctoral research  
fellow, Department of  
Obstetrics and  
Gynaecology  
Alastair H  
MacLennan  
professor, Department  
of Obstetrics and  
Gynaecology  
Gustaaf A Dekker  
professor, Department  
of Obstetrics and  
Gynaecology  
Paul N Goldwater  
senior consultant  
clinical microbiologist,  
Department of  
Microbiology and  
Infectious Diseases  
Eric A Haan  
clinical geneticist,  
Department of  
Genetic Medicine

Epidemiology  
Branch,  
Department of  
Health, Adelaide,  
SA 5000  
Kevin Priest  
epidemiologist

Correspondence to:  
C S Gibson  
catherine.s.gibson@  
adelaide.edu.au

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### Abstract

**Objective** To investigate the association between cerebral palsy and direct evidence for perinatal exposure to neurotropic viruses.

**Design** Population based case-control study.

**Setting** Adelaide Women's and Children's Hospital Research Laboratory.

**Participants and main outcome measures** Newborn screening cards of 443 white case patients with cerebral palsy and 883 white controls were tested for viral nucleic acids from enteroviruses and herpes viruses by using polymerase chain reaction. Herpes group A viruses included herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpes virus 8 (HHV-8); herpes group B viruses included varicella zoster virus (VZV) and human herpes viruses 6 and 7 (HHV-6 and HHV-7).

**Results** The prevalence of viral nucleic acids in the control population was high: 39.8% of controls tested positive, and the prevalence was highest in preterm babies. The detection of herpes group B viral nucleic acids increased the risk of developing cerebral palsy (odds ratio 1.68, 95% confidence interval 1.09 to 2.59).

**Conclusions** Perinatal exposure to neurotropic viruses is associated with preterm delivery and cerebral palsy.

### Introduction

Intrauterine infection is postulated to be an important contributor to the development of cerebral palsy.<sup>1-3</sup> The herpes viruses (including cytomegalovirus (CMV), herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), and enteroviruses can all cross the placenta and infect the fetus. These viruses are potentially neurotropic. The likelihood of maternal infection resulting in infection of the fetus varies according to

the specific virus, whether the infection is primary or recurrent, and the gestational age of the fetus at the time of infection. Once the infection has crossed the placenta into the fetal circulation, the potential for neuronal damage is there, directly and also by the fetal inflammatory response.

Some viruses can persist for months or years after the initial infection. These viruses may have effects as long as 30 years after the original infection.

We investigated associations between potentially neurotropic viruses and cerebral palsy in a white Australian population. Our hypothesis was that evidence of perinatal viral infection may be associated with the development of cerebral palsy.

### Methods

#### Selection of patients and controls

The study population comprised all children with cerebral palsy born in 1986-99 in South Australia to white mothers (n=443), ascertained by South Australia's cerebral palsy register. The controls were 883 babies born to white mothers from 1986 to 1999.<sup>4</sup> We identified newborn screening cards for each case and control. We selected four potential controls from screening cards filed (by date of receipt) before (n=2) and after (n=2) the cards of cases. The date of birth of each control was within a few days of the case, the hospital from which we took the screening cards was of the same category (metropolitan teaching, metropolitan private, or country), and we took samples on roughly the same day of life as for the cases. The control population included a higher proportion of preterm infants than the general population, as many of the cases of cerebral palsy were born preterm and had been

**P+** A table showing prevalences of neurotropic viruses in a population of newborns diagnosed with cerebral palsy is on [bmj.com](http://bmj.com)

**ELPS** This is the abridged version of an article that was posted on [bmj.com](http://bmj.com) on 6 January 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38668.616806.3A>