

# Impact of Diabetes on Coronary Artery Disease in Women and Men

## A meta-analysis of prospective studies

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**OBJECTIVE** — Women are at a much lower risk of coronary disease mortality than men are. It is widely believed that diabetes “erases” this female advantage, increasing the risk of heart disease much more in women than in men. In reality, the extent of this increased risk is controversial, with studies showing conflicting results and wide confidence intervals. Clarification of this issue has implications for the pathogenesis of coronary disease, and for public health efforts to reduce coronary disease in women.

**RESEARCH DESIGN AND METHODS** — We performed a meta-analysis to calculate a summary estimate of the relative risk of coronary death among women with diabetes as compared to those without. For comparison, we also calculated the analogous risk among men. All prospective cohort studies containing both men and women, and both patients with and without diabetes, were examined. Sixteen studies were identified; 10 had sufficient data for statistical analysis.

**RESULTS** — After combining studies that adjusted for other cardiac risk factors, the relative risk of coronary death from diabetes was 2.58 (95% CI 2.05–3.26) for women and 1.85 (1.47–2.33) for men. This difference is statistically significant ( $P = 0.045$ ). Other sensitivity analyses did not change these estimates appreciably.

**CONCLUSIONS** — The impact of diabetes on the risk of coronary death is significantly greater for women than men. Further research is required to explain this clinically meaningful difference between the sexes.

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Coronary artery disease is one of the leading causes of death among both men and women in the Western world (1). Nonetheless, women are at a much lower risk for heart disease mortality than men are. Data from the World Health Organization show that the ratio of coronary disease mortality in men to women is consistently close to 2, even though the prevalence of coronary disease varies widely between countries (2). One group of

women in whom this advantage is not as strong is women with diabetes.

It is widely held that women with diabetes are at especially high risk for coronary artery disease, relatively more so than men with diabetes (3). The extent of this increased risk is somewhat controversial. Some authors have stated that diabetes effectively eliminates “the female advantage” (4,5) over men, whereas other studies have shown no difference or only a minor differ-

ence in the risk conferred by diabetes on women as compared with men (6,8). One possible reason for this discrepancy is the small number of deaths occurring in each study, usually less than 20 among women with diabetes and sometimes less than 10. Such small numbers impair precise estimates of relative risk. An earlier meta-analysis (7) attempted to address this question, concluding that diabetes did reduce the sex differential in coronary heart disease (CHD) mortality. However, the analysis was limited to literature known to the author and did not include 3 recent large studies (8–10).

Clarifying this uncertainty is important, because it would have considerable implications with respect to the pathogenesis of coronary disease in both sexes. In addition, current public health efforts to reduce the incidence of coronary disease among women should be based on valid epidemiological data.

In this article, we describe a meta-analysis of all prospective cohort studies that examine the risk of coronary disease among women and men with diabetes. Our goal was to calculate a summary estimate of the relative risk of coronary disease among women with diabetes as compared with those without. In addition, we compared this estimate with the analogous risk among men.

## RESEARCH DESIGN AND METHODS

### Study selection

Using a priori inclusion and exclusion criteria (see below), 2 researchers independently conducted a comprehensive literature search using Medline (January 1966–January 1999) with the following medical subject headings: “diabetes mellitus,” “coronary disease,” “myocardial ischemia,” “atherosclerosis,” “angina pectoris,” “prospective studies,” “follow-up studies,” “cohort studies,” and “comparative study.” Personal files and bibliographies of all retrieved articles were used to identify further articles. All prospective cohort studies that examined the risk of coronary disease in both men and women,

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**Abbreviations:** CHD, coronary heart disease; NHANES I, National Health and Examination Survey I.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

both with and without diabetes, were included. Case-control and cross-sectional studies were excluded. Articles were also excluded if they were earlier reports or multiple reports of another publication, or if they were not in English.

There were no disagreements between the 2 researchers regarding inclusion or exclusion of articles.

Quality scoring of these nonexperimental studies was not attempted, since it is of unproven value (11,12). Instead, we performed sensitivity analyses to determine the effect of different study characteristics on the outcome (see below).

### Data abstraction

Two investigators using standardized forms independently abstracted data. Inconsistencies were resolved by reviewing the study in question and coming to an agreement.

### Statistical analysis

Results are expressed as a relative risk of CHD death comparing diabetic with nondiabetic patients. For studies that considered CHD death and other end points (e.g., nonfatal myocardial infarction), CHD death was the end point used for this study. Of the 10 studies that were considered in the statistical analysis (see below), only 2 (8,13) examined a related or combined end point (e.g., fatal and nonfatal myocardial infarction) rather than CHD death per se. They were included in the analysis.

The relative risk estimates were obtained from the articles, along with their 95% CIs. If the CI was not stated, it was calculated from the original article. The relative risk from each article was plotted against study characteristics, including duration of the study, year of publication, percentage of patients with diabetes, mean age, percentage of smokers, and blood pressure. These graphical displays showed no clear relationship between the study outcomes and study characteristics (14). In addition, for each analysis, a  $\chi^2$  test of heterogeneity was performed, and no statistically significant differences were found ( $P \geq 0.25$  for all analyses) (15,16). Thus, we used the fixed-effects model to estimate an overall pooled relative risk.

When calculating an overall estimate of relative risk, the estimated relative risk from each study was treated as one stratum, and the estimates from each stratum were combined. Each stratum was weighted in proportion to the precision of that study's results, using the inverse of the variance of

the relative risk (17). In other words, larger studies contributed more to the summary estimate than did smaller studies.

Overall relative risks were compared between men and women using a z statistic,  $P < 0.05$  being significant. We also performed a Bonferroni correction of the  $P$  value to compensate for multiple comparisons (for 3 comparisons, the Bonferroni  $P$  value is 0.0170).

Some articles provided relative risk estimates that were adjusted for cardiac risk factors, whereas others calculated age-adjusted figures only. Those articles that adjusted for cardiac risk factors were considered in a separate analysis. If an article provided both age-adjusted and risk factor-adjusted relative risks, only the latter was considered. Some studies excluded patients with prior coronary disease and others did not, and these were considered in separate sensitivity analyses. One study excluded participants with prior coronary disease for the end point of myocardial infarction, but included them for the end point of CHD mortality (18). Hence different end points and relative risks from this study were considered in each analysis, including and excluding prior CHD.

For one specific analysis, relative risks from all of the studies were combined using a so-called "best data" approach, in which the highest quality data are abstracted from an article. This analysis allowed us to pool estimates from as many articles as possible. Specifically, for studies reporting age-adjusted and risk factor-adjusted relative risks, the latter was used in this analysis. For studies reporting analyses including and excluding participants with prior CHD, the estimates that excluded prior CHD were used. In no studies did a choice have to be made between choosing risk factor-adjusted data or data that excluded prior CHD for the "best-data" analysis.

Although data from the National Health and Nutrition Examination Survey I (NHANES I) have appeared in a number of publications, a specific article was used in the risk factor-adjusted analysis because only that article contained the required data (6). A later article on NHANES I gives only age-adjusted data (19). The Framingham Study was included using age-adjusted data (13); an earlier publication reported risk factor-adjusted data, but it was not possible to calculate a CI from the information provided (20).

Five studies were excluded from the statistical analysis because of insufficient

data (21–25). These studies did not calculate separate relative risks for the 2 sexes and did not provide enough data for them to be extracted. A cohort study of the Pima Indians reported no CHD events in participants without diabetes, and therefore could not report a relative risk (26).

**RESULTS** — Sixteen prospective cohort studies were eligible for this analysis (5,6,8–10,13,18,21–29); 5 studies, as described above, were excluded from further consideration because of missing data. Important characteristics of all of the studies are listed in Tables 1 and 2.

Of the 10 studies included in the analysis, all accepted a diagnosis of diabetes based on self-report from the participants. A common criterion for the diagnosis was if subjects had previously been diagnosed by a physician as having diabetes, or had a history of treatment with insulin or oral hypoglycemic agents. Five studies used random or fasting glucose parameters as alternative diagnostic criteria, but they did not report how often these criteria were used (8,10,13,27,28). The proportion of participants who actually had glucose measurements taken was reported in only one study (8). Determination of the outcome measures, such as CHD mortality, was from death certificates in many studies (5,6,18,10,29); in others, the death certificate information was supported by information from hospital records, interviews with families, or expert-panel review (8,9,13,28). In one study, the method by which the outcome measures were determined was not stated (27); however, a study of triglycerides and CHD mortality by the same authors, on the same cohort, and appearing in the same journal issue ascertained CHD mortality from death certificates (supported by autopsy reports and other information) (30).

The duration of the 10 studies ranged from 4 to 36 years. The participants were generally between 40 and 70 years of age, although 2 studies specifically examined adults older than 60 or 65 (10,18). In the majority of the studies, the age at onset and the duration of diabetes in the participants were not reported. One study reported that 96% of its participants were diagnosed with diabetes after the age of 30 (8). Another reported an average duration of diabetes of 13–14 years, with the average age of those with diabetes being  $\sim 63$  (28). One large study reported a mean duration of diabetes of  $\sim 8$  years, with the mean age of the diabetic participants being  $\sim 62$  (6).

Table 1—Prospective cohort studies included in the analysis

Study	Excludes prior CHD	Age (years)	Outcome measure	Duration of study (years)	Adjusted relative risk, diabetic to nondiabetic female (95% CI)	Adjusted relative risk, diabetic to nondiabetic male (95% CI)	Other variables adjusted for
Pan et al. (5)	Y	35–64	CHD death (ICD 410–414)	9	4.72 (1.77–12.6)	3.79 (1.63–8.78)	Age, cholesterol, sBP, #cig/day, ECG, education
Kleinman et al. (6)	Y	40–77	IHD death (ICD 410–414)	9	2.59 (1.59–4.22)	2.37 (1.55–3.62)	Age, smoking, sBP, cholesterol, BMI
Folsom et al. (8)	Y	45–64	incident CHD (definite, probable, silent MI, definite CHD death)	4–7	2.04 (1.21–3.44)	1.81 (1.24–2.64)	Age, race, smoking, ethanol, education, sports, hormone replacement, BMI, waist-to-hip ratio, total and HDL cholesterol, TG, sBP, and others
Fraser et al. (9)	Y	>25	“definite” MI, “definite” fatal CHD (which was ICD 410–414)	6	MI 2.34 (1.22–4.49); fatal CHD 1.82 (1.12–2.97)	MI 2.08 (1.10–3.93); fatal CHD 1.57 (0.85–2.89)	Age, hypertension, smoking, physical activity, BMI
Simons et al. (10)	N	>60	CHD (ICD 410–414)	5.2	Initial CHD: 1.41 (1.003–1.99)	Initial CHD: 1.53 (0.86–2.73)	Age
Kannel and Wilson (13)	N	35–64	multiple end points e.g. CHD, CVD	36	CHD 3.7 (1.85–7.29)	CHD 1.5 (1.16–1.93)	Age
Seeman et al. (18)	Y (subgroup); complete data used for CHD mortality	>65	MI (in those free of baseline CHD), ICD 410–414 in entire cohort	6	CHD mortality 4.47 (1.85–10.79); MI 3.20 (1.46–7.01)	CHD mortality 1.55 (0.68–3.50); MI 1.75 (0.97–3.16)	Age, exertional chest pain, sBP, dBP, use of antihypertensive medications, smoking, BMI
Heyden et al. (27)	Y	Unclear	IHD death	4.5	2.8 (0.61–12.87)	1.0 (0.31–3.27)	Age, sBP, cholesterol, TG, BMI, smoking
Barrett-Connor et al. (28)	N	40–79	IHD death (ICD 410–414)	14	Age adjusted 3.27 (1.96–5.48); risk-factor adjusted 3.32 (1.98–5.59)	Age-adjusted 1.83 (1.24–2.70); risk-factor adjusted 1.89 (1.28–2.80)	Age, cholesterol, sBP, BMI, smoking, use of “sex hormones”
Butler et al. (29)	Y	>40	CHD death (ICD 410–414.9)	12–20	3.0 (1.68–5.36)	3.0 (1.70–5.30)	Age

Data are from the 10 studies included in the statistical analysis. BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; ICD, International Classification of Diseases; IHD, ischemic heart disease; MI, myocardial infarction; TG, triglycerides.

Most studies did not report the proportion of patients with diabetes on insulin, oral agents, or diet alone. Two studies reported on subsets of their diabetic patients, in which more than 80% were on oral agents or no drug treatment (6,28). In another study, 82% of all of the diabetic participants were on oral agents or no drug therapy (10). The high average age of the participants and the lack of insulin use suggest that most of the patients in the 10 studies have type 2 diabetes.

Follow-up in all but one of the included studies was reported as 78% (27) or higher, with many studies reporting follow-up of greater than 90%. Percentage of follow-up in the Framingham Study was not reported in the article used for the

analysis (13), but was described as “complete” in a later article (31). The number of participants in each study ranged from 502 (27) to 27,658 (9). The second-largest study had ~19,000 participants (5), and the next largest had 13,000 (8). One study had ~7,200 patients (6), and another had ~5,200 (13). The remaining studies had between 1,800 and 3,000 patients (10,18,28,29). In total, the 10 studies include more than 75,000 patients.

Using the “best data” approach (described earlier), the pooled relative risk of CHD death in diabetic women compared with nondiabetic women was 2.54 (95% CI 2.08–3.09). The analogous statistic in men was 1.76 (1.51–2.05),  $P = 0.004$  for the comparison between the relative risks.

When all of the studies that adjusted the risk of CHD for other risk factors were considered together, the pooled relative risks of CHD death from diabetes were 2.58 (2.05–3.26) for women and 1.85 (1.47–2.33) for men (Fig. 1A and B),  $P = 0.045$ .

The analysis was repeated with only those studies that excluded patients with prior CHD. The pooled relative risks were 2.37 (1.83–3.07) for women and 1.85 (1.43–2.39) for men,  $P = 0.183$ .

**CONCLUSIONS** — It has long been held that the impact of diabetes on the coronary risk of women far exceeds its impact on men. Some authors have even asserted that diabetes “erases the female advantage”

Table 2—Prospective cohort studies that were excluded

Study	Excludes prior CHD	Age (years)	Outcome measure	Duration of study (years)	Adjusted relative risk, diabetic to nondiabetic female (95% CI)	Adjusted relative risk, diabetic to nondiabetic male (95% CI)	Other variables adjusted for
Kuller and Tonascia (21)	N	40–80	arteriosclerotic heart disease death	12–13	NA	NA	Unclear
Welborn and Wearne (22)	Y	“Adults”	CHD incidence and death (ICD 410–414)	6-year incidence, 12-year mortality study	NA	NA	Age, BP, cholesterol, uric acid, % ideal weight, insulin
Jensen et al. (23)	Y	20–60+ Unclear	acute MI	7	NA	NA	Age, family history, earlobe crease, smoking, income, alcohol, BMI, cholesterol, TG, antihypertensives, sBP
Fujishima et al. (24)	Y	40–79	CHD (acute/silent MI, sudden cardiac death)	5	NA	NA	Age, sBP, ECG, BMI, TC, HDL cholesterol, smoking, alcohol
Aronow et al. (25)	N	62–103	“coronary events”: nonfatal/fatal MI, ventricular fibrillation associated with CAD, sudden cardiac death	3.4	NA	NA	Age, previous CHD, sBP, dBP, hypertension, TC, HDL cholesterol, TC/HDL ratio, TG, obesity
Nelson et al. (26)	N	>5	CHD death (ICD 410–411.8, 412–414.9, 798.1)	9	No events in nondiabetics	No events in nondiabetics	Age

Data are from the 6 studies that were excluded from the statistical analysis. BP, blood pressure; CVD, cardiovascular disease; ICD, International Classification of Diseases; IHD, ischemic heart disease; MI, myocardial infarction; NA, not available; TC, total cholesterol; TG, triglycerides.

(3,32). In reality, estimates of this increased risk have varied widely and have had little precision (Table 1). To add to the confusion, in some quarters, the argument that diabetes makes women equivalent to men with respect to their risk of CHD death seems to be based on a comparison of diabetic women to nondiabetic men (5,6). Kleinman et al. (6) make the point that this would be analogous to asserting that hypertension erases the female advantage for coronary disease, if one compares hypertensive women to men without hypertension.

If diabetes truly does eliminate the female advantage, the evidence should come from a comparison of diabetic women to diabetic men. In other words, the data should demonstrate that diabetes imposes a greater risk of coronary artery disease death on women than it does on men.

Our analysis suggests that the relative risk of CHD death from diabetes is indeed greater for women than for men. Depending on the analysis, the relative risk for women is ~2.5, versus a relative risk of about 1.85 for men.

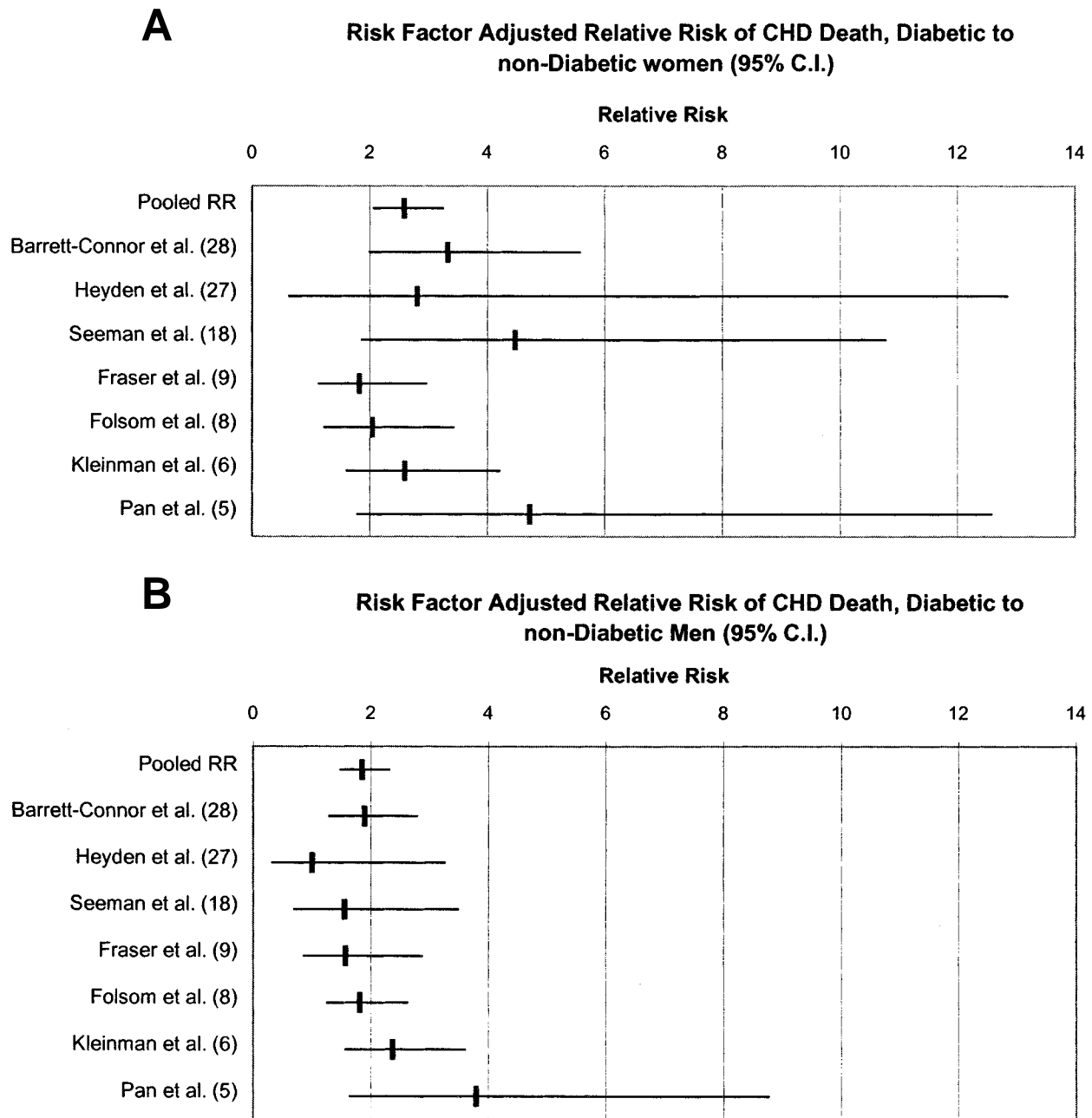
This difference was statistically significant in most analyses and is fairly robust to

change; it is still present after adjustment for other cardiac risk factors and persists (although diminished) after exclusion of patients with prior coronary events. Bonferroni correction changes the statistical significance of some of the analyses, but the trend is quite clear. Our results are in agreement with an earlier meta-analysis that found a relatively greater risk of CHD mortality from diabetes in women as compared to men (7). That meta-analysis was limited to literature known to the author and did not include 3 recent cohort studies (8–10). It also involved a somewhat different analysis than ours, calculating the relative risk for CHD mortality of men to women, in both diabetic and nondiabetic subjects. In contrast, we have determined the relative risk for each sex separately.

What is the reason for this persistent and significant difference between women and men? Most studies have demonstrated that this gap is not accounted for by other conventional risk factors. One approach is that the excess risk of CHD death in diabetic women is due either to a higher incidence of CHD in diabetic women than in diabetic men, or to a greater mortality from it (or

some combination of them). The argument concerning mortality has been addressed in at least 2 recent studies, the findings of which are contradictory. Liao et al. (33) found that among patients with angiographically confirmed coronary disease, diabetes conferred a substantially higher risk of death to women than to men. In contrast, a registry study by Miettinen et al. (34) found that the relative risk of CHD mortality after myocardial infarction was fairly similar for diabetic women and men. Although these studies are not directly comparable, they illustrate that differential mortality from CHD in diabetes remains controversial.

Another popular theory to explain the sex difference relates to HDL. Walden et al. (35) suggested that HDL cholesterol levels are lower in diabetic women than in diabetic men. In fact, it has also been postulated that the inverse association between CHD and HDL levels is stronger in women than in men. Gordon et al. (36) showed that for each milligram-per-decimeter increase in HDL, there was an ~2% decrease in CHD risk in men, but a 3% decrease in women. In this context, it is interesting to reexamine the studies listed in Table 1. Only one arti-



**Figure 1**—Risk factor–adjusted relative risk of coronary heart disease death, diabetic to nondiabetic women (A) and risk factor–adjusted relative risk of coronary heart disease death, diabetic to nondiabetic men (B). Taller vertical lines represent relative risk, with surrounding 95% CIs.

cle (8) adjusted for HDL cholesterol levels, and it showed no significant difference in relative risk between women and men.

There are many other theories proposed to account for the excess risk from diabetes in women. These include differences in coagulation (37), in the patterns of obesity between men and women (38), and a possible role for hyperinsulinemia (39). The discussion of these theories and others is beyond the scope of this article;

suffice it to say that the underlying basis for the sex difference in risk from diabetes remains, for the most part, speculative.

Because of the nature of the studies we examined, this overview has some limitations. Compared to meta-analyses of randomized controlled trials, there is greater potential for bias and heterogeneity between studies. The sources of heterogeneity include the criteria for the diagnosis of diabetes, the outcomes studied, and

the comorbidities for which adjustments were made. The populations from which these studies recruited participants may have significant and unrecognized differences that might confound any attempts to combine them. It is important to acknowledge that heterogeneity may exist, even if tests of heterogeneity are not statistically significant. We believe that our careful and rational approach to analyzing the data reduces the potential impact of hetero-

geneity and allows us to draw useful conclusions from our work.

Another weakness inherent to this overview is the use of death certificates for measuring CHD mortality. The use of death certificates is notoriously inaccurate (39), and a certain percentage of deaths may be misclassified. If CHD is underdiagnosed in women relative to men (40), a greater percentage of deaths in women with diabetes might be misclassified (as non-CHD-related) than in men with diabetes. This is one way in which the relative risk of CHD death conferred by diabetes in women might in fact be underestimated.

In the studies included in this overview, diabetes was usually defined by self-report, which would tend to underestimate the prevalence of diabetes. This bias could lead to overestimation of the relative risk of coronary events, because patients with known diabetes are likely to have had it longer or to have more severe disease. A large population survey has suggested that women aged 45–64 years are 50% more likely than men to have undiagnosed diabetes (41). This age-group (45–64 years of age) is in fact the one represented in the majority of the studies considered here. The consequence of this “underdiagnosis” in women could be that the overestimation of relative risk stemming from the self-report of diabetes might affect men more than women. In other words, the difference in relative risk of coronary death from diabetes between women and men might be even greater than we have calculated.

Although we have shown that the relative risk of CHD death from diabetes is higher in women than men, it is important to remember that the absolute risk imposed by diabetes is higher in men. Kleinman et al. (6) showed that the age-adjusted death rate in women with diabetes was virtually identical to the rate in men without diabetes (~10 per 1,000 person-years). Nonetheless, the death rate in men with diabetes was almost 3 times higher. The reasons for this higher absolute mortality in men are unclear (38).

In conclusion, the relative risk of CHD death conferred by diabetes is significantly higher in women than in men. The differential impact of diabetes on the coronary risk of men and women may have important implications for the pathogenesis of atherosclerosis. Further research is required to explain this significant difference in relative risk.

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