Explaining the Sex Difference in Coronary Heart Disease Mortality Among Patients With Type 2 Diabetes Mellitus

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Background: Most studies suggest that diabetes is a stronger coronary heart disease (CHD) risk factor for women than men, but few have adjusted their results for classic CHD risk factors: age, hypertension, total cholesterol level, and smoking.

Objective: To establish an accurate estimate of the odds ratio for fatal and nonfatal CHD due to diabetes in both men and women.

Methods: We compared the summary odds ratio for CHD mortality and the absolute rates of CHD mortality in men and women with diabetes. We searched the MEDLINE and Cochrane Collaboration databases and bibliographies of relevant articles and consulted experts. Studies that included a nondiabetic control group and provided sex-specific adjusted results for CHD mortality, nonfatal myocardial infarction, and cardiovascular or all-cause mortality were included. Of 4578 articles identified, 232 contained primary data, and 182 were excluded. Two reviewers recorded data on study characteristics, quality, and outcomes from 50 studies.

Results: Sixteen studies met all inclusion criteria. In unadjusted and age-adjusted analyses, odds of CHD death were higher in women than men with diabetes. From 8 prospective studies, the multivariate-adjusted summary odds ratio for CHD mortality due to diabetes was 2.3 (95% confidence interval, 1.9-2.8) for men and 2.9 (95% confidence interval, 2.2-3.8) for women. There were no significant sex differences in the adjusted risk associated with diabetes for CHD mortality, nonfatal myocardial infarction, and cardiovascular or all-cause mortality. Absolute CHD death rates were higher for diabetic men than women in every age strata except the very oldest.

Conclusions: The excess relative risk of CHD mortality in women vs men with diabetes was absent after adjusting for classic CHD risk factors, but men had more CHD deaths attributable to diabetes than women.

Arch Intern Med. 2002;162:1737-1745

TYPE 2 diabetes mellitus is associated with an increased risk of coronary heart disease (CHD), cerebrovascular disease, and peripheral vascular disease. Estimates of CHD mortality in diabetic men have varied from 1- to 3-fold the rate in nondiabetic men, whereas estimates in diabetic women have ranged from 2- to 5-fold the rate in nondiabetic women. The variation in relative risk estimates of cardiovascular disease makes it difficult to evaluate the strength of diabetes as a risk factor for either sex. Two previous meta-analyses that included studies that did not adjust for major cardiac risk factors concluded that diabetes is a stronger risk factor for CHD mortality in women than men. However, it is unclear whether these reported sex differences in CHD risk are real or attributable to differences between men and women with diabetes with respect to other major risk factors for CHD.

We systematically reviewed the results from published studies and aimed to establish an accurate estimate of the odds ratio (OR) for fatal and nonfatal CHD due to diabetes in both men and women. We compared the sex-specific risk of CHD mortality, nonfatal myocardial infarction (NAMI), and cardiovascular or all-cause mortality between diabetic men and women. We also calculated absolute CHD death rates attributable to diabetes for each sex. Our main analyses included only studies that provided multivariate-adjusted comparisons to determine the independent association between diabetes and cardiovascular disease outcomes.
METHODS

DATA SOURCES

We performed a computerized search using MEDLINE and the Cochrane Collaboration database for all studies published from January 1966 through February 2000 using the keywords diabetes and cardiovascular disease, myocardial infarction, or ischemic heart disease. Additional studies were identified through review of bibliographies in relevant articles and consultation with experts. We limited our search to peer-reviewed articles. English language and non-English language articles were included. In the case of multiple publications from a single study, we used the most comprehensive or recent publication.

STUDY SELECTION

Studies were included if they met all of the following criteria: (1) the study population included both men and women and the outcomes were stratified by sex; (2) a control group of nondiabetic subjects was included (studies that used historical controls or standardized mortality ratios were excluded); (3) outcomes included CHD mortality, NFMI, and cardiovascular or all-cause mortality; (4) follow-up was at least 6 months; and (5) results were adjusted at least for age, hypertension, hypercholesterolemia, and smoking. In the event that results were not adjusted for these variables, we contacted the corresponding authors to request the results of adjusted analyses. We excluded studies that primarily followed up patients with prior myocardial infarction (MI). We planned to repeat the main comparisons in subgroups defined by race or ethnicity (white, black, Latino, Japanese American, and native American) and study design (prospective cohort or cross-sectional analyses).

Diabetes was defined by self-report, use of a diabetic medication, physician documentation in medical records, or fasting or 2-hour postchallenge glucose criteria. Most studies used the 1985 World Health Organization criteria for classification of diabetes. Most studies used age as a continuous variable in their multivariate analysis, but a few categorized age by 5- or 10-year increments. Most studies dichotomized smoking into current vs never or past use, whereas only 1 study considered number of cigarettes smoked per day as a continuous variable in their model. Total cholesterol level was considered a continuous variable by most studies, but some dichotomized the variable (by ≥240 mg/dL or >6.2 mmol/L cut points), whereas one study used quartiles of total cholesterol in their final model. Hypertension was managed more heterogeneously. Some studies used a combination of elevated systolic (≥140 mm Hg, >150 mm Hg, or >160 mm Hg) and diastolic (≥90 mm Hg or >95 mm Hg) blood pressures or an antihypertensive medication to define a dichotomous hypertension variable for the multivariable analysis. Other studies used a continuous systolic blood pressure measurement or categorized systolic blood pressure by increments of 5 or 10 mm Hg or used quartiles of systolic blood pressure for their model.

In all included studies, CHD mortality was defined by the International Classification of Diseases, Ninth Revision (ICD-9) codes 410 through 414 or by physician documentation of sudden cardiac death. Nonfatal myocardial infarction was defined by definite electrocardiographic criteria using the Minnesota code, enzyme levels consistent with MI, self-report (with or without Rose questionnaire criteria),

RESULTS

The MEDLINE and Cochrane Collaboration search located 4578 articles. Of the 234 articles that contained primary data, 50 were duplicative publications, 46 studies did not include a nondiabetic control group, 44 did not provide information about the outcomes of interest, and 26 did not perform analyses based on diabetes status. Another 9 did not provide data stratified by sex,19-27 7 were hospital-based studies with follow-up of less than 6 months,28-34 and 9 were studies of patients with prior MI.35-43 Another 7 studies were excluded since their study populations consisted of a single sex only.44-50

Of the 36 remaining studies, 10 studies met all of our inclusion criteria.13,22,51-58 Twenty-two did not publish fully adjusted risk estimates,5,6,9,78 2 did not report 95% CIs or P values for their adjusted results,5,9 and 2 provided only combined outcomes of nonfatal and fatal CHD.12,59 We contacted the corresponding authors of these 26 articles twice; authors of 6 studies54,65,72,74,75,77 provided the data necessary to satisfy inclusion criteria. Some authors were unable to recreate their original analyses,5,12,73,78 and some did not have the necessary variables in the data set,53,56,76 and others did not provide the requested data.5,6,9,50,59,62,71,79 We compared the crude summary estimates from 8 of these excluded studies that re-
or medical record documentation. We excluded outcomes that included both fatal and nonfatal coronary events aggregated in one estimate from the analysis. Cardiovascular mortality was defined by ICD-9 codes 389 through 439.

**DATA EXTRACTION AND SYNTHESIS**

One author reviewed titles and abstracts of articles retrieved from the search and excluded case reports, letters, comments, reviews, and reports without primary data. Two trained data abstractors (A.M.K. and Lily Chaput, MD) reviewed the 50 remaining manuscripts to determine study eligibility. Data were extracted on study quality, participant characteristics, length of follow-up, and outcomes (CHD mortality, NFMI, and cardiovascular or all-cause mortality). Discrepancies between reviewers were resolved by consensus.

We calculated summary estimates of the adjusted ORs and 95% confidence intervals (CIs) using a random-effects model with a general variance-based method that retains adjustment for confounding. We used an Excel-based (Microsoft Inc, Redmond, Wash) meta-analysis program developed by the University of California, San Francisco, for our analyses. We examined the heterogeneity of study findings using standard χ² analyses with a criterion for statistical significance of .10. Summary estimates for men and women were compared using the z test, with a 2-tailed level of significance of P = .05.

**QUALITY ASSESSMENT AND SENSITIVITY ANALYSIS**

We also performed analyses based on study quality. A study was rated high quality if it had a prospective cohort design, used a fasting plasma glucose or oral glucose tolerance test to define diabetes, and adjusted for covariates in addition to the 4 specified for inclusion. Since the mean follow-up years from the pooled prospective cohort studies was 14 years, we also required that high-quality studies have at least 14 years of follow-up with a less than 10% loss to follow-up. Intermediate-quality studies were adjusted for age, hypertension, hypercholesterolemia, and smoking but were of shorter duration or were cross-sectional and did not use laboratory tests in defining diabetes. A third category of studies did not meet inclusion criteria for our meta-analysis because the analyses were not adjusted for age, hypertension, smoking, and total cholesterol level (termed unadjusted studies). We analyzed the available crude or age-adjusted ORs from these unadjusted studies as a part of our quality analysis. We performed a separate sensitivity analysis using age-adjusted and unadjusted estimates from our included studies that provided CHD mortality outcomes. If studies did not report unadjusted risk estimates, we used the crude rates of CHD mortality to calculate relative risk estimates and 95% CIs.

**ABSOLUTE RISK**

To ascertain the effect of diabetes on the absolute numbers of deaths from CHD (ICD-9 codes 410-414), we used the 1998 US Vital Statistics data for coronary death rates for each sex and all races/ethnicities stratified by age. We calculated the expected death rate among men and women by multiplying the observed death rate by the summary OR due to diabetes in men and women. We then calculated the excess death rate by subtracting these 2 estimates.

Although the summary ORs for CHD mortality from diabetes for women were somewhat higher than those for men overall and for every subgroup, the ORs were not statistically different. In analyses based on the unadjusted studies that were not included in the main meta-analysis, the summary OR for women was significantly higher than for men (10.4 vs 2.2; P = .02 for the comparison of ORs). Sensitivity analyses that included age-adjusted estimates for whites from the included studies found a statistically significant difference between estimates for men and women (2.1 vs 3.4; P = .05). The unadjusted risk estimates from the included studies were similar to the age-adjusted estimates (2.2 in men vs 3.2 in women), with a trend toward a statistically significant difference between the sexes. In analyses based on studies in white race and adjusted for major cardiovascular risk factors, the difference in relative risk between men and women was smaller and not statistically significant (2.2 vs 2.8; P = .20) (Figure 2).

Based on 4 population-based studies, the summary OR for NFMI due to diabetes was 1.6 (95% CI, 1.1-2.2) for men and 1.7 (95% CI, 1.3-2.3) for women, a difference that was not statistically significant (Table 4). The summary ORs for cardiovascular mortality due to diabetes were higher than for CHD mortality or NFMI for both sexes (3.2 in men vs 4.1 in women), but the difference was not statistically
Table 1. Characteristics of Studies of Coronary Heart Disease Risk in Diabetic vs Nondiabetic Subjects

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Name or Location</th>
<th>Mean No. of Follow-up Years</th>
<th>Mean Age (Range), y</th>
<th>No. of Diabetic Subjects</th>
<th>No. of Nondiabetic Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Barrett-Connor et al, 51 1991*</td>
<td>Rancho Bernardo, Calif</td>
<td>14.4</td>
<td>63 (50-89)</td>
<td>207</td>
<td>127</td>
</tr>
<tr>
<td>Collins et al, 52 1996</td>
<td>Asian Indian, Fiji</td>
<td>11</td>
<td>20+</td>
<td>102</td>
<td>129</td>
</tr>
<tr>
<td>Fujimoto et al, 53 1987†</td>
<td>King County, Wash (men)</td>
<td>NA‡</td>
<td>62</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>Fujimoto et al, 54 1991†</td>
<td>King County (women)</td>
<td>NA</td>
<td>64</td>
<td>52</td>
<td>72</td>
</tr>
<tr>
<td>Jousilathti et al, 55 1999</td>
<td>WHO-MONICA§</td>
<td>7-12</td>
<td>25-64</td>
<td>262</td>
<td>254</td>
</tr>
<tr>
<td>Keil et al, 56 1993</td>
<td>Charleston Heart Study</td>
<td>30</td>
<td>50 (35-74)</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Kleinman et al, 57 1988</td>
<td>National Health and Nutrition Examination Survey I</td>
<td>57, 63</td>
<td>40-77</td>
<td>189</td>
<td>218</td>
</tr>
<tr>
<td>Lindeman et al, 58 1998</td>
<td>Bernalillo County, NM</td>
<td>NA</td>
<td>65</td>
<td>115</td>
<td>73</td>
</tr>
<tr>
<td>Lowe et al, 59 1997†</td>
<td>Chicago, Ill</td>
<td>22</td>
<td>45, 52</td>
<td>926</td>
<td>7975</td>
</tr>
<tr>
<td>Niskanen et al, 60 1998</td>
<td>Finland-Kuopio</td>
<td>15</td>
<td>55 (45-64)</td>
<td>70</td>
<td>62</td>
</tr>
<tr>
<td>Pan et al, 61 1996†</td>
<td>Gila River, Ariz</td>
<td>17</td>
<td>52 (34-79)</td>
<td>267</td>
<td>210</td>
</tr>
<tr>
<td>Rewers et al, 62 1992</td>
<td>San Luis Valley, Colo</td>
<td>24.5</td>
<td>25-74</td>
<td>186</td>
<td>521</td>
</tr>
<tr>
<td>Scheidt-Nave et al, 63 1999</td>
<td>Rancho Bernardo</td>
<td>14.4</td>
<td>50-89</td>
<td>159</td>
<td>157</td>
</tr>
<tr>
<td>Sievers et al, 64 1992</td>
<td>Gila River, Ariz</td>
<td>12.1</td>
<td>≥15</td>
<td>630</td>
<td>813</td>
</tr>
</tbody>
</table>

*Duplicate publication, but separate outcomes or subgroups reported in each article.
†Subjects were restricted to one sex, but complementary study reported second sex results.
‡NA indicates not applicable because it was a cross-sectional study.
§WHO-MONICA indicates World Health Organization–Monitoring of Trends and Determinants in Cardiovascular Disease.
(Values represent mean age for nondiabetic and diabetic subjects, respectively.)

Table 2. Adjusted Odds Ratios (95% Confidence Intervals) for Coronary Heart Disease (CHD) Mortality, Nonfatal Myocardial Infarction (NFMI), Cardiovascular Mortality, and All-Cause Mortality by Sex

<table>
<thead>
<tr>
<th>Source</th>
<th>Race/Ethnicity*</th>
<th>CHD Mortality</th>
<th>NFMI</th>
<th>Cardiovascular Mortality</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
</tbody>
</table>
| Barrett-Connor et al, 51 1991 | W | 1.9 (1.3-2.8) | 3.3 (2.0-5.6) | ... | ... | ... | ... | ... | ... | ...
| Scheidt-Nave et al, 52 1990 | W | ... | 1.3 (0.8-2.1) | 1.8 (1.0-3.0) | ... | ... | ... | ... | ...
| Collins et al, 53 1996 | I | 3.2 (1.3-2.0) | 20.7 (2.5-171) | ... | ... | ... | ... | ... | ... | ...
| Me | 1.6 (0.4-6.0) | 25.4 (12-24.3) | ... | ... | 1.4 (0.6-3.2) | 3.2 (1.3-7.8) | 1.3 (0.7-2.5) | 3.1 (1.4-6.6) | 1.3 (1.5-7.8) | ...
| Fujimoto et al, 54 1987† | JA | ... | 2.1 (1.3-3.3) | ... | ... | ... | ... | ... | ... | ...
| Fujimoto et al, 55 1991† | JA | ... | 1.2 (0.8-1.9) | ... | ... | ... | ... | ... | ... | ...
| Jousilathti et al, 56 1999 | W | 2.4 (1.6-3.4) | 4.3 (2.4-7.6) | ... | ... | ... | ... | ... | ... | ...
| Keil et al, 57 1993 | B | 0.8 (0.5-2.4) | 1.3 (0.4-4.5) | ... | ... | ... | ... | ... | ... | ...
| W | 2.5 (0.8-17.7) | 2.0 (0.9-4.5) | ... | ... | ... | ... | ... | ... | ...
| Kleinman et al, 58 1988 | W | 2.8 (2.0-3.8) | 2.5 (1.6-3.8) | ... | ... | ... | ... | ... | ... | ...
| Lindeman et al, 59 1998 | W | ... | 3.4 (1.2-5.5) | 3.6 (1.3-10) | ... | ... | ... | ... | ...
| Lindeman et al, 60 1998† | L | ... | 1.7 (0.9-3.3) | 1.4 (0.5-3.7) | ... | ... | ... | ... | ...
| Collins et al, 61 1997 | W | ... | 2.5 (2.1-3.0) | ... | ... | 1.9 (1.6-2.2) | ... | ... | ...
| Pan et al, 62 1986 | B | ... | 1.6 (0.6-3.3) | ... | ... | 1.8 (1.0-3.3) | ... | ... | ...
| W | 3.8 (1.7-8.4) | 4.7 (1.9-11.9) | ... | ... | ... | ... | ... | ...
| Niskanen et al, 63 1998 | W | ... | 7.7 (2.8-21) | 13.3 (3.0-59) | 5.4 (1.7-14.7) | 5.2 (1.8-15) | ...
| Rewers et al, 64 1992† | W | ... | 1.7 (1.0-2.8) | 2.7 (1.5-4.7) | ... | ... | ... | ...
| Sievers et al, 65 1992† | L | ... | 0.9 (0.5-1.4) | 1.4 (0.9-2.1) | ... | ... | ... | ...
| Vilbergson et al, 66 1998 | W | 5.3 (2.2-13) | 6.3 (0.8-50) | ... | ... | 1.8 (1.4-2.4) | 1.9 (1.3-2.1) | ...
| Wei et al, 67 1998 | M | ... | 3.2 (1.4-7.1) | 8.5 (2.8-25) | 2.1 (1.3-3.5) | 3.2 (1.9-5.4) | ...

*W indicates white; B, black; I, East Indian; Me, Melanesian; JA, Japanese American; L, Latino; P, Pima Indian; M, multiple races; and ellipses, not applicable.
†Multivariate results received via personal communication with author.
There was also little difference between the summary ORs for all-cause mortality due to diabetes between men and women (2.1 vs 1.9). There was heterogeneity among the findings of the individual studies for these 3 outcomes that could not be easily eliminated in subgroup analyses. Only the unadjusted studies showed significantly higher summary ORs in women than men for these 3 outcomes as well (data not shown).

Despite summarizing estimates from 13 distinct study populations, we lacked power to perform subgroup analyses by race/ethnicity for cardiovascular mortality and all-cause mortality and were unable to derive meaningful summary estimates for CHD mortality in African Americans, Japanese Americans, or native Americans. We were able to derive summary estimates for NFMI for Latinos only from 2 cross-sectional analyses. Diabetes did not significantly increase risk of NFMI for Latino men (OR, 1.2; 95% CI, 0.6-2.4) or for Latina women (OR, 1.4; 95% CI, 0.9-2.1). The summary estimates for Latino men and women were lower than those for non-Latino whites (men: OR, 1.7; 95% CI, 1.1-2.6; women: OR, 2.8; 95% CI, 1.7-4.4).

Table 3. Summary Odds Ratios (95% Confidence Intervals) for Coronary Heart Disease Mortality by Sex (Diabetes vs No Diabetes)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Summary Odds Ratio (95% Confidence Interval)</th>
<th>P Value*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 8)</td>
<td>Men: 2.33 (1.91-2.85) Women: 2.92 (2.22-3.84)</td>
<td>.19</td>
<td>13, 22, 51-54, 56, 77</td>
</tr>
<tr>
<td>White race (n = 6)</td>
<td>Men: 2.22 (1.79-2.75) Women: 2.79 (2.11-3.69)</td>
<td>.20</td>
<td>13, 22, 51, 53, 54, 56</td>
</tr>
<tr>
<td>Quality of studies†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (n = 2)</td>
<td>Men: 1.96 (1.56-2.47) Women: 2.54 (1.73-3.72)</td>
<td>.26</td>
<td>13, 51</td>
</tr>
<tr>
<td>Intermediate (n = 4)</td>
<td>Men: 2.42 (1.71-3.42) Women: 3.07 (1.97-4.80)</td>
<td>.41</td>
<td>22, 53, 54, 56</td>
</tr>
<tr>
<td>Unadjusted (n = 2)</td>
<td>Men: 2.17 (0.76-6.20) Women: 10.37 (4.69-22.9)</td>
<td>.02</td>
<td>70, 71</td>
</tr>
<tr>
<td>Sensitivity analysis‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age adjusted only (n = 4)</td>
<td>Men: 2.07 (1.39-3.08) Women: 3.42 (2.55-4.59)</td>
<td>.05</td>
<td>13, 51, 53, 56</td>
</tr>
<tr>
<td>Unadjusted only (n = 3)</td>
<td>Men: 2.16 (1.56-2.98) Women: 3.22 (2.39-3.43)</td>
<td>.08</td>
<td>51, 53, 54</td>
</tr>
</tbody>
</table>

*P value for comparison of odds ratio estimates between men and women.
†See the “Methods” section for quality rating of studies. Unadjusted studies were not included in the overall summary estimates. Estimates are for white race only.
‡Estimates are for white race only. Unadjusted estimates calculated from crude rates of the included studies.
§P value for heterogeneity <.10.
to diabetes was higher among men than women at all ages except those older than 85 years.

A previous meta-analysis included 25 prospective, population-based studies that provided crude data to examine sex differences in relative risk of CHD mortality and MI associated with type 2 diabetes mellitus. The risk of fatal CHD was increased for diabetic women, suggesting women’s natural protection from CHD is reduced in the presence of diabetes. However, many of the large cohort studies included in this meta-analysis did not control for the main established risk factors for coronary disease. A more recent meta-analysis that included 10 studies found that women with diabetes were at significantly higher risk of CHD mortality compared with men (2.58 vs 1.85, P = .04). This meta-analysis included studies that adjusted only for age, reported combined end points for CHD mortality and NFMI, and followed up subjects with prior CHD. In a subgroup analysis excluding studies of patients with existing CHD, there was no significant difference between summary ORs for diabetic men and women for CHD mortality (1.9 in men vs 2.4 in women, P = .18). These results are consistent with our findings.

The difference in relative risk for CHD mortality between men and women was progressively attenuated with adjustment for age and other major cardiovascular risk factors. Possible explanations for this phenomenon may be that diabetic women compared with nondiabetic women may have a more severe degree of risk factor abnormalities than diabetic men compared with nondiabetic men or the unfavorable cardiac risk factors may have a bigger impact on women than men. Other explanations could be that risk factors in women are managed less aggressively in men or that women are more likely to have more than one risk factor. Adjustment for other cardiovascular risk factors that were not included in most of the studies in our analysis (high-density lipoprotein cholesterol, triglyceride levels, exercise, body mass index) or more specific adjustment using continuous measures of risk rather than risk categories might eliminate the remaining disparity between men and women. These data suggest that most of the observed difference in risk between men and women for CHD mortality from diabetes is mediated by traditional cardiac risk factors that are modifiable.

Four large, widely quoted prospective cohort studies did not meet criteria for inclusion in our meta-analysis. These 4 studies had conflicting results; 1 showed a higher diabetes-associated relative risk for CHD mortality in men compared with women. 

Table 4. Summary Odds Ratios (95% Confidence Intervals) for Nonfatal Myocardial Infarction, Cardiovascular Mortality, and All-Cause Mortality

Table 5 presents the death rates from coronary disease by sex and age in the US population in 1998 and uses the overall summary OR for CHD mortality (2.3 for men and 2.9 for women) to calculate the expected coronary death rate and excess death rate among diabetic men and women. Even though the summary OR for coronary death due to diabetes is slightly higher in women, the higher absolute coronary death rate in men results in higher excess deaths due to diabetes in men at all ages except for the very oldest (>85 years).

Table 5. US Death Rates per 100 000 Population From Coronary Heart Disease by Sex and Age

Table 6. Summary Odds Ratios (95% Confidence Intervals) for Nonfatal Myocardial Infarction, Cardiovascular Mortality, and All-Cause Mortality

COMMENT

Using estimates adjusted for age, hypertension, total cholesterol level, and smoking, summary ORs for CHD mortality, NFMI, and cardiovascular mortality due to diabetes were higher among women than men, but differences were modest and not statistically significant. The summary OR for CHD mortality from the 8 prospective cohort studies was 2.3 for men with diabetes and 2.9 for women with diabetes. Differences in ORs can be misleading because CHD mortality rates are higher in men than women of the same age. Although the odds for CHD mortality were slightly higher for women than for men with diabetes, the number of excess deaths attributable
increased relative risk among women, and the 2 remaining studies found no difference between the sexes. It is unlikely that the addition of the results of these 4 studies would have changed our summary estimates significantly.

It is now recommended that cardiovascular risk factors be treated as aggressively in diabetic patients without a history of CHD as in nondiabetic patients with a prior MI. Based on the present meta-analysis, diabetes independently increases the risk of fatal CHD in both men and women without preexisting CHD by 2- to 3-fold. Since dyslipidemia and hypertension often cluster with type 2 diabetes mellitus and there is an additive effect for each of these risk factors, diabetic patients are at high risk of CHD death and should be treated more aggressively than persons at low risk. The larger effect of adjusting for major risk factors in women vs men suggests that women with diabetes might benefit more from blood pressure and cholesterol-lowering treatment than diabetic men.

As with any meta-analysis, we are limited to the variables measured and end points reported in each study. We insisted that the outcomes be adjusted for major risk factors to study the association between diabetes and CHD, but these variables were defined differently in the studies. For example, some studies used categorical levels of elevated systolic blood pressure as evidence of hypertension, whereas others included the use of an antihypertensive medication as evidence. Likewise, there were differences in definition of outcomes among studies. Most studies used predefined electrocardiographic criteria to determine MI, but some used history of revascularization by coronary artery bypass surgery or angioplasty or patient history of MI for this outcome. Some studies differentiated patients with impaired glucose tolerance from those with frank diabetes, whereas others included the impaired glucose tolerance group with nondiabetic subjects. Most studies did not completely distinguish participants with type 1 diabetes mellitus from those with type 2. However, most of these errors of misclassification would be expected to occur similarly for men and women and should not explain the lack of sex difference in relative risk. Because most patients with type 2 diabetes mellitus have their conditions diagnosed years after disease onset, length of follow-up in cohort studies was used as a rough proxy for duration of diabetes. We found no significant sex difference for any outcome among the adjusted prospective studies with 14 or more years of follow-up. Lastly, we were unable to analyze results based on race/ethnicity for most of the outcomes owing to lack of studies meeting our inclusion criteria in nonwhite populations.

The advantage of the present meta-analysis is that it is restricted to the findings of studies controlled for age, hypertension, hypercholesterolemia, and smoking. The most accurate adjusted summary OR for CHD mortality due to diabetes for all race/ethnic groups combined is 2.3 for men and 2.9 for women. The difference in risk between the men and women is modest and not statistically significant. Most reports of a greatly elevated relative risk in women with diabetes did not control for major CHD risk factors. The present meta-analysis offers further evidence that much of the previously reported excess risk of coronary outcomes in diabetic women is mediated by well-established modifiable cardiac risk factors. Future prospective studies should present sex-specific fatal and nonfatal cardiovascular disease end points before and after adjustment for risk factors. Analyzing the effect of specific risk factors separately and in combination will help to clarify their role in the cardiovascular protection observed in women without diabetes. In addition, much remains to be learned about cardiovascular outcomes among ethnic minority groups with diabetes.

Accepted for publication November 19, 2001.

This study was supported in part by a grant from the Department of Health and Human Services (Dr Kanaya) (Faculty Development in General Internal Medicine 1D08PE50109-01). We thank the following authors, assistants, and statisticians for their help in providing us with additional data from their studies: Leo Niskanen, MD, Wilfred Fujimoto, MD, Jane Shofer, MS, Edward J. Boyko, MD, MPH, Donna L. Leonetti, PhD, Marion Rewers, MD, Susan Shetterly, MS, Richard Hannan, MD, DrPH, William deGrauw, MD, Hans Bor, BS, Robert Lindeman, MD, C. Lillian Yau, MS, Maurice Sievers, MD, Robert Nelson, MD, PhD, Desmond Williams, MD, and Christine Hoehner, MPH. We are indebted to Lily Chaput, MD, for data abstraction and review and Eric Vittinghoff, PhD, for statistical expertise.

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