Chapter 4. Systematic Review of Diabetes as a Risk Factor for Coronary Heart Disease in Women

Introduction

Studies suggest that there may be a stronger association between type 2 diabetes and coronary heart disease (CHD) risk in women than in men. Estimates of coronary heart disease mortality in diabetic men have varied from 1 to 3-fold the rate in nondiabetic men,[1-10] while estimates in diabetic women have ranged from 2 to 5-fold the rate in nondiabetic women.[2, 5, 8, 10-12] Variations in study population, design, quality and findings make it difficult to evaluate the strength of diabetes as a risk factor for CHD in either sex. Two previous meta-analyses that included studies that did not adjust for major cardiovascular risk factors concluded that diabetes is a stronger risk factor for CHD mortality in women than in men.[13, 14] However, it is unclear whether these reported sex differences are real or attributable to differences in other major risk factors for CHD between diabetic men and women.

The goal of this systematic review is to establish an accurate estimate of CHD risk among women with type 2 diabetes and to compare the risk of CHD in diabetic women to that in diabetic men. Our main analyses will include only studies that provide multivariate-adjusted comparisons to determine the independent association between diabetes and coronary disease outcomes.

Methodology

Data Sources

We searched PubMed®, the Cochrane Database, and DARE for studies in English or other languages published from 1966 through January 2002 . We also reviewed bibliographies and asked peer reviewers (Appendix A) to identify additional articles. In the case of multiple publications from a single study, we used the most comprehensive or recent publication.

Search Terms

Search terms were developed in collaboration with a medical librarian and include the following:

Limits	publication dates 1966 to 2002, peer-reviewed articles
Predictor	diabetes
Outcomes	cardiovascular disease, myocardial infarction, ischemic heart disease

Inclusion Criteria

To be included, articles were required to fit the following criteria:

1) Include both men and women and provide an estimate of the CHD risk associated with diabetes in both sexes.
2) Followup of the cohort for at least six months.
2) Data on one of the following outcomes: total mortality, CHD mortality, cardiovascular disease (CVD) mortality or nonfatal myocardial infarction (MI).
3) Inclusion of primarily type 2 diabetic participants (defined by self-report, use of diabetic medication, medical record diagnosis, positive oral glucose tolerance test or an elevated fasting glucose).
4) Inclusion of multivariate adjustment for confounders, including at least age, hypertension, hypercholesterolemia and smoking.
5) Inclusion of a nondiabetic, concurrent control group.
6) Published between January 1, 1966 and January 1, 2002. Articles published outside this date range that were recommended by peer reviewers (Appendix A) were included.

Definition of Outcomes

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

Article Identification

An initial search using the terms listed above identified articles that potentially provided evidence. Two University of California, San Francisco (UCSF)-Stanford Evidence-based Practice Center (EPC) investigators reviewed the titles and excluded those that clearly did not provide data on humans or clearly did not address the question.

The abstracts of the remaining articles were reviewed independently by two UCSF-Stanford EPC physician investigators and coded using the categories listed below. Disagreements were discussed and consensus codes were entered into a database (Access, Microsoft Corporation).

RQ	Research question: the article clearly does not address the research question
R	Review – the study is a review that does not contain primary data
NH	No humans - the study clearly does not include data on humans
O	Outcome- the study clearly does not address the outcomes of interest
P	Predictor- the study clearly does not include type 2 diabetics
E_1	Eligible – the study may contain primary evidence regarding the research questions in women and will be reviewed in full-text

Articles coded E_1 were retrieved and the full text was reviewed independently by two UCSF-Stanford EPC physician investigators. Names of authors and titles of journals were obscured before articles were reviewed.

Obtaining Unpublished Results in Women

Some eligible studies included women in the study population, but did not report findings separately by gender. In these instances we twice attempted to contact the authors of these studies to obtain these data. We contacted the authors of 26 articles, requesting the required information.[4, 5, 8, 11, 15-36] Authors of seven studies[15-21] provided the data necessary to satisfy inclusion criteria. Some authors were unable to recreate their original analyses [4, 11, 22, 23] or did not have the necessary variables in the dataset,[24-26] and others did not provide the requested data.[5, 8, 27-36]

Quality Assessment

The full text of each eligible study was reviewed independently by two UCSF-Stanford physician investigators who completed a quality evaluation form (Appendix B). Most of the studies included in this systematic review are prospective cohort studies. The major quality issues with this study design are lack of information on potential confounders, inadequate duration of followup, non-blinded outcome adjudication and loss to followup.

To be categorized as *good quality*, articles were required to meet the following parameters:

- Prospective cohort design (vs. retrospective cohort or cross-sectional design)
- Type 2 diabetes defined by fasting plasma glucose or oral glucose-tolerance test (vs. other definitions of diabetes)
- Multivariate adjustment for potential confounders in addition to age, hypertension, hypercholesterolemia, and smoking
- At least 14 years of followup time (the median length of followup of all studies)
- Less than 10 percent loss to followup

Studies were considered to be of *fair quality* if they met the following parameters:

- Retrospective or cross-sectional study design
- Criteria other than fasting plasma glucose or oral glucose-tolerance test used to define diabetes
- Adjusted for age, hypertension, hypercholesterolemia, and smoking only
- Follow-up time of less than 14 years
- More than 10 percent loss to followup

Data Abstraction

Two UCSF-Stanford EPC physician investigators independently reviewed the full text of each eligible study and completed a data abstraction form (Appendix C). 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 UCSF-Stanford EPC physician investigators reviewed the 50 remaining manuscripts to determine study eligibility. Data were extracted on study quality, participant characteristics, length of followup, and outcomes (CHD mortality, nonfatal MI, and cardiovascular or all-cause mortality). Discrepancies between reviewers were resolved by consensus. For studies with multiple publications, only data from the most comprehensive or recent publication were used.

Data Management and Archive

We entered all identified titles and abstracts in an EndNote® (Niles Software, Inc) file that includes searchable key words as codes for eligibility. Information on all articles that were reviewed in full text was transferred from EndNote® (Niles Software, Inc) to a database (Access, Microsoft® Corporation) that allows us to categorize each article by reason for exclusion. Quality assessment data for each eligible study were also entered in the database (Access, Microsoft® Corporation), allowing us to categorize eligible articles by quality.

Abstracted data were entered into a database (EXCEL, Microsoft® Corporation) for preparation of evidence tables and calculation of summary estimates, confidence intervals and tests of heterogeneity.

The full-text articles that were retrieved, and the abstraction forms for each article are filed by topic and question in Dr. Grady's offices at the UCSF Mt. Zion Women's Health Clinical Research Center.

Data Analysis

The primary outcome of each study was expressed as the most adjusted odds ratio (and 95 percent confidence interval) for CHD events among persons with diabetes compared to those without diabetes. Summary estimates of odds ratio and 95 percent confidence

intervals were calculated using a general variance-based (confidence interval) method[37] that retains adjustment for confounding. We calculated summary odds ratios using both a fixed and random effects model.[38] Results were similar using both models and we report only summary odds ratios based on the random effects model. The significance level for all summary relative risks was set at 0.05. All estimates were assessed for heterogeneity using a Chi square test with the significance level set at 0.10.

Publication bias usually occurs if small studies with unremarkable findings (odds ratios for the association of diabetes and CHD risk around 1.0) are not published while small studies with markedly positive findings (high odds ratios) are published. We calculated the correlation between individual study weight (1/variance) and odds ratio using Kendall's Tau (a nonparametric correlation coefficient) to assess potential publication bias.

Summary estimates for men and women were compared using the Z-test, with a two-tailed five percent level of significance. The main comparisons were repeated in subgroups defined by race/ethnicity (white, black, Latino, Japanese American, and Native American) and by study design (prospective cohort and cross-sectional analyses). Sensitivity analyses were performed to assess the effects of study quality and degree of adjustment for confounding on the outcome.

Results

Results of Study Identification

Our searches identified 4,578 titles. Of the 233 articles that contained primary data, 50 were duplicative publications, 46 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. Eight studies did not provide data stratified by sex and used ineligible study designs,[39-46] seven were hospital-based studies with followup less than six months,[47-53] nine included only patients with prior MI.[54-62] Seven studies were excluded because the study population consisted of a single sex only.[63-69]

Of the 36 remaining studies, ten met all inclusion criteria.[12, 70-78] Twenty-two did not publish adequately adjusted risk estimates,[4, 5, 15-31, 33-35] two did not report 95 percent confidence intervals or p-values for adjusted results,[2, 8] and two provided only combined outcomes of nonfatal and fatal CHD.[11, 36] We contacted the authors of these 26 articles twice requesting the required information.[4, 5, 8, 11, 15-36] Authors of seven studies[15-21] provided the data necessary to satisfy inclusion criteria. Some authors were unable to recreate their original analyses [4, 11, 22, 23] or did not have the necessary variables in the dataset,[24-26] and others did not provide the requested data.[5, 8, 27-36]

Description of Eligible Studies

After receiving additional information from authors, 17 studies fulfilled all inclusion criteria (Evidence Table 9); 12 were prospective cohort studies[12, 15, 20, 70-78] and five were cross-sectional analyses.[16-19, 21] More than one publication provided data from the same cohort [70, 77] such that the meta-analysis includes adjusted findings from 14 distinct study populations.

Followup time in the 12 prospective cohort studies ranged from 5 to 32 years (mean approximately 14 years). Most of the studies enrolled middle-aged participants; one study enrolled only subjects older than 65.[19] The 14 study populations included 6,235 diabetic participants (48 percent women) and 71,306 nondiabetic control subjects (52 percent women). In 7 of the 17 studies,[12, 15, 16, 18, 19, 71, 79] all diabetics were type 2; the remainder of the studies included a few type 1 diabetics, but the majority were type 2.[20, 21, 70, 72, 144, 73-78]

Summary of Results

Evidence Table 10 presents the multivariate-adjusted odds ratios (OR) by gender and ethnicity for CHD mortality, nonfatal MI, and all-cause mortality for each included study. Most of the studies show a higher OR for CHD mortality and for nonfatal MI due to diabetes among women compared to men. Outcomes for cardiovascular and all-cause mortality are mixed with approximately half of the studies showing a higher odds ratio for women than men.

CHD Mortality

The overall summary OR for CHD mortality due to diabetes was 2.3 (95% CI, 1.9 - 2.8) for men and 2.9 (95% CI, 2.2 - 3.8) for women for all race/ethnic groups combined (Evidence Table 11). Although the overall summary OR for CHD mortality from diabetes for women was somewhat higher than for men, the summary estimates were not statistically different (p=0.19 for the comparison of ORs). In sensitivity analyses that included only studies of whites, a trend to statistically significant differences between the summary odds ratios for men and women was observed only when outcomes were inadequately adjusted for potential confounders (Evidence Table 12). For example, based on the results of studies that provided age-adjusted estimates, the summary OR was higher in women compared to men (3.42 vs. 2.07; p-value for difference = .05).

Most studies that reported CHD mortality were performed in white subjects, limiting subgroup analyses by race to whites. Summary estimates for CHD mortality from eligible studies for white men and women were similar to those for all ethnicities combined 2.2 (95% CI, 1.8-2.7) for men and 2.8 (95% CI, 2.1–3.7) for women.

Nonfatal Myocardial Infarction and All-Cause Mortality

The summary OR for nonfatal MI 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 (p=.68 for comparison of ORs in men and women) (Evidence Table 11).

The summary OR for all-cause mortality due to diabetes was 2.1 (95% CI, 1.7-2.7) for men and 1.9 (95% CI, 1.7-2.3) for women, a difference that was not statistically significant (p=.50 for comparison of ORs in men and women) (Evidence Table 11).

Despite summarizing estimates from 14 distinct study populations, we lacked power to perform subgroup analyses by race/ethnicity for CHD mortality and total mortality. We were able to derive summary estimates for nonfatal MI for Latinos only from two cross-sectional analyses.[18, 19] Diabetes did not significantly increase risk of nonfatal myocardial infarction for Latino men (summary OR 1.2; 95% CI, 0.6-2.4) or for Latina women (1.4; 95% CI, 0.9-2.1). The summary estimates for Latino men and women were lower than those for non-Latino whites (OR 1.7; 95% CI 1.1-2.6 for men and 2.8; 95% CI 1.7-4.4 for women).

Assessments for Heterogeneity and Publication Bias

There was no heterogeneity in the findings of the individual studies for CHD death, nonfatal MI and total mortality in women. There was no hetereogeneity in the findings of the studies for CHD mortality in men, but there was significant heterogeneity of the findings among men for nonfatal MI and total mortality (Evidence Table 11) that was not explained in subgroup analyses.

There was no evidence of publication bias in any of the summary odds ratios.

Conclusions

Using estimates adjusted for age, hypertension, hypercholesterolemia and smoking, summary ORs for CHD mortality and nonfatal MI due to diabetes were higher among women than men, but ORs for all-cause mortality were slightly higher in men than women. All of the differences were modest and not statistically significant.

Two prior meta-analyses have addressed the question of whether there is a sex-specific difference in risk for coronary outcomes related to diabetes.[13, 14] The first meta-analysis included the results of 25 prospective, population-based studies that provided unadjusted data to examine gender differences in relative risk of CHD mortality and myocardial infarction associated with type 2 diabetes.[13] The risk of CHD death was higher for diabetic women compared to men. However, many of the cohort studies included in this meta-analysis did not control for established risk factors for coronary disease. The second and more recent meta-analysis included the results of 10 studies and found that women

with diabetes were at significantly higher risk of CHD mortality compared with men (2.58 vs. 1.85, p=.045 for the comparison of ORs)[14]. This meta-analysis included studies that adjusted only for age and included subjects with prior coronary disease. In a subgroup analysis excluding studies of patients with existing coronary disease, there was no significant difference between summary ORs for CHD death between men and women (1.9 in men vs. 2.4 in women, p=0.18). A third systematic review based on this evidence report was recently published.[80]

These results of the two prior systematic reviews are consistent with our findings, except that we found no statistically significant differences between summary ORs for CHD for men and women. This disparity is likely due to the fact that the prior reviews included studies in which outcomes were unadjusted, while our inclusion critieria required adjustment for major CHD risk factors. Our subgroup analyses suggest that the difference in relative risk for CHD mortality between men and women is attenuated with adjustment for major cardiovascular risk factors. This may be due to the fact that diabetic women have more risk factors or more severe risk factor abnormalities compared to nondiabetic women than do diabetic men compared to nondiabetic men.[81] Alternatively, cardiac risk factors may have a stronger impact on CHD risk in women than in men or risk factors may be managed less aggressively in women than in men.[82, 83] Adjustment for additional risk factors that were not included in most of the analyses in studies in our meta-analysis, (HDL cholesterol, triglycerides, 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 for CHD due to diabetes in men and women is mediated by traditional cardiac risk factors that are likely modifiable.

Four large prospective cohort studies did not meet criteria for inclusion in our meta-analysis.[4, 8, 11, 36] These four studies had conflicting results; one showed a higher diabetes-associated relative risk for CHD mortality in men compared to women,[36] another showed a higher relative risk among women,[4] and the two remaining studies found no difference between the sexes.[8, 11] It is unlikely that the addition of the results of these four studies would have changed our summary estimates significantly. The results of one large prospective cohort study in the United States was not included, since participants were all women.[66] In a sensitivity analysis, we added the results of this study to our summary estimate for CHD mortality in white women. The resulting summary OR for CHD mortality was 2.83 (95% CI, 2.27-3.53), very similar to the summary estimate restricted to the results of studies that included both men and women (OR = 2.79; 95% CI, 2.11-3.69).

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 myocardial infarction.[84] Based on the results of the present review, diabetes independently increases the risk of fatal CHD in both men and women without pre-existing CHD by 2- to 3-fold. The fact that the summary OR for CHD mortality is

attenuated more with adjustment for major risk factors in women than in men diabetics suggests that women with diabetes might benefit more from aggressive risk factor management than diabetic men.

As with any systematic review, we are limited to the variables measured and endpoints reported in each eligible study. We required that outcomes be adjusted for major CHD risk factors, but these variables were defined differently in the studies. Likewise, there were differences in definition of outcomes among studies. Some studies differentiated patients with impaired glucose tolerance from those with frank diabetes, while others included those with impaired glucose tolerance with nondiabetic subjects. Some studies did not completely distinguish participants with type 1 diabetes from those with type 2. These errors of misclassification may have caused us to underestimate summary ORs. Lastly, we were unable to analyze results based on race/ethnicity for most of the outcomes due to the absence of studies meeting our inclusion criteria in nonwhite populations.

The advantage of the present systematic review is that it is restricted to the findings of studies controlled for age, hypertension, hypercholesterolemia, and smoking. The most accurate adjusted summary odds ratio for coronary heart disease mortality due to diabetes for all race/ethnic groups combined is 2.3 for men and 2.9 for women. The difference in odds ratios between men and women is modest and not statistically significant.

Future Research

Future prospective studies should present sex- and ethnicity-specific fatal and nonfatal coronary disease endpoints before and after adjustment with established CHD 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 coronary outcomes among ethnic minority groups with diabetes.

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