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The influence of sex on cardiovascular outcomes associated with diabetes among older black and white adults

Varsha G. Vimalananda, MD, MPH^{1,*}, Mary L. Biggs, PhD², James L. Rosenzweig, MD¹, Mercedes R. Carnethon, PhD³, James B. Meigs, MD, MPH⁴, Evan L. Thacker, PhD⁵, David S. Siscovick, MD, MPH⁶, and Kenneth J. Mukamal, MD, MPH⁴

¹Section of Endocrinology, Diabetes and Nutrition, Department of Medicine, Boston University School of Medicine, Boston, MA

²Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA

³Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL

⁴General Medicine Division, Department of Medicine, Harvard Medical School, Boston, MA

⁵Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL

⁶ Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle WA

Abstract

Aims—It is unknown whether sex differences in the association of diabetes with cardiovascular outcomes vary by race. We examined sex differences in the associations of diabetes with incident congestive heart failure (CHF) and coronary heart disease (CHD) between older black and white adults.

Methods—We analyzed data from the Cardiovascular Health Study (CHS), a prospective cohort study of community-dwelling individuals aged ≥ 65 from four U.S. counties. We included 4817 participants (476 black women, 279 black men, 2447 white women and 1625 white men). We estimated event rates and multivariate-adjusted hazard ratios for incident CHF, CHD, and all-cause mortality by Cox regression and competing risk analyses.

*Corresponding author: Varsha G. Vimalananda, MD, MPH Section of Endocrinology, Diabetes and Nutrition Boston University School of Medicine 88 East Newton Street, Evans 201 Boston MA 02118 Ph: (781) 687-3456 Fx: (781) 687-3106 varshav@bu.edu.

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Disclosures

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Results—Over a median follow-up of 12.5 years, diabetes was more strongly associated with CHF among black women (HR, 2.42 [95%CI, 1.70-3.40]) than black men (1.39 [0.83-2.34]); this finding did not reach statistical significance (P for interaction 0.08). Female sex conferred a higher risk for a composite outcome of CHF and CHD among black participants (2.44[1.82-3.26]) vs. (1.44[0.97-2.12]), P for interaction 0.03). There were no significant sex differences in the HRs associated with diabetes for CHF among whites, or for CHD or all-cause mortality among blacks or whites. The three-way interaction between sex, race, and diabetes on risk of cardiovascular outcomes was not significant ($P = 0.07$).

Conclusions—Overall, sex did not modify the cardiovascular risk associated with diabetes among older black or white adults. However, our results suggest that a possible sex interaction among older blacks merits further study.

Keywords

diabetes mellitus; sex-specific; ethnicity; African-American; epidemiology

Introduction

Sex has an important role in modifying the effect of diabetes on cardiovascular outcomes. The relative risk of fatal coronary heart disease (CHD) associated with diabetes is higher for white women than for white men [1]; indeed the lower rate of CHD in white premenopausal women is substantially eliminated among those with diabetes [2, 3]. Findings with respect to congestive heart failure (CHF) are mixed [4-8]. It is unclear whether the sex differences observed among white adults are also present among blacks. Blacks with diabetes are less likely to have myocardial infarctions compared to whites with diabetes [9], and such a difference in the effect of diabetes on cardiovascular outcomes by race may reduce or exaggerate the sex differences that are apparent among whites. Although the prevalence of diabetes is even higher among blacks compared to whites [10], no observational studies have evaluated the modifying effect of sex by race for different types of cardiovascular events [1, 4-8, 11-22]. Meta-analyses of sex differences in cardiovascular outcomes in diabetes have not evaluated the additional effect of race, in large part due to limited numbers of black study subjects [12, 23]

To address these questions, we conducted an analysis among participants of the Cardiovascular Health Study (CHS), an ongoing longitudinal study of older Americans that has large numbers of black participants. We assessed whether sex differences in the risks of CHF, CHD, and all-cause mortality among older adults with and without diabetes are similar between black and white adults. Because several studies have reported worse risk factor control among women [11, 23-26], we also examined whether any observed differences persisted after adjustment for lifestyle and cardiovascular disease risk factors.

Methods

Study population

Study participants were drawn from CHS, a prospective cohort study of cardiovascular disease risk factors among individuals aged ≥ 65 years at baseline. Individuals were recruited

from a random sample of Medicare-eligible residents in four U.S. communities (Sacramento County, CA; Washington County, MD; Forsyth County, NC; and Pittsburgh, PA). Between 1989 and 1990, 5201 participants (57% women) enrolled. In 1992-1993, an additional 687 black participants were recruited using similar methods. The final CHS cohort of 5888 included 931 (18%) black individuals. Individuals provided informed written consent before participating in the study. Institutional review board approval was obtained at each of the participating institutions and the coordinating center.

Participants underwent clinical exams yearly from 1989 through 1999, with annual phone contacts between exams. Phone contacts were twice per year thereafter and are ongoing to the present time. At baseline, the exams included standardized questionnaires, physical examination, anthropometric measurements, resting electrocardiography, and laboratory examinations. Detailed descriptions of CHS methods and procedures have been previously published [27]. For the present analysis, participants were excluded if they had prevalent CHF (n=156); prevalent CHD (n=703); prevalent atrial fibrillation (n=107); were not white or black (n=29); or if diabetes status at baseline was not determined (n=76). This resulted in a final sample of 4817 participants.

Ascertainment of cardiovascular events and mortality

Surveillance for incident events was done primarily during clinic exams and semiannual phone contacts. Unreported events were also identified during review of medical records for a reported event and through the use of Medicare hospitalization data. Proxies were interviewed when participants were unavailable. Deaths were identified through surveillance phone calls, scheduling calls for visits, and newspaper obituaries. Potential incident events and deaths were investigated by review of medical records and final classification was assigned by the CHS Events Subcommittee using standardized criteria. Details of the adjudication processes have been published previously [28].

Congestive heart failure—A classification of congestive heart failure required both a diagnosis from a physician and validation of this diagnosis by either (i) active treatment for CHF; (ii) characteristic X-ray; or (iii) characteristic echocardiography or contrast ventriculography findings. Active treatment for CHF was defined as a current prescription for both a diuretic and either digitalis or a vasodilator. Characteristic X-ray findings included cardiomegaly or pulmonary edema, while characteristic echocardiography or contrast ventriculography findings included a dilated ventricle and global or segmental wall-motion abnormalities with decreased systolic function.

Coronary heart disease—Coronary heart disease included non-fatal myocardial infarction (MI) and CHD death. Myocardial infarctions were classified on the basis of one of the following: an evolving diagnostic ECG pattern; a diagnostic ECG pattern and abnormal cardiac markers; or cardiac pain and abnormal cardiac markers and either an evolving ST-T pattern or an equivocal ECG pattern.

All-cause mortality—Deaths were confirmed by the Subcommittee through death certificates, autopsy reports, and medical records. Follow-up for vital status was completed for 100% of participants.

Ascertainment of diabetes and other covariates

Diabetes mellitus was defined as treatment with insulin or an oral hypoglycemic agent, fasting blood glucose (FBG) ≥ 7 mmol/L, or non-fasting glucose ≥ 11.1 mmol/L at baseline. Demographic, anthropomorphic, and clinical characteristics recorded at baseline were used as covariates. Age, race, education (years), physical activity (kilocalories/week), alcohol consumption (none, < 7 drinks weekly, ≥ 7 drinks weekly) and smoking status (never, former, current) were ascertained by self-report. Use of aspirin and medications for diabetes, hypertension, and dyslipidemia (yes/no) were assessed by the medication inventory method [29]. Clinical data included body-mass index (BMI, kg/m^2) and seated blood pressure (mmHg). Laboratory data included a fasting lipid profile and C-reactive protein (CRP, mg/L). Subclinical vascular disease was considered present (yes/no) if any of the following criteria were met: an ankle arm index of ≤ 0.9 , internal carotid wall thickness > 80 th percentile, common carotid wall thickness > 80 th percentile, carotid stenosis $> 25\%$, a major ECG abnormality, or positive responses to the Rose Questionnaire for angina or intermittent claudication [30].

Statistical analysis

We categorized participants into 8 groups based on race (white, black), sex, and diabetes status and compared cardiovascular risk factors across the groups by computing means (SD) of continuous risk factors and proportions for categorical risk factors for each group. Cumulative event rates were obtained using the Kaplan-Meier method. In computing hazard ratios, we first compared black women with diabetes to those without diabetes. We then compared black men with diabetes to those without diabetes, and then formally tested whether an interaction by sex was present within race groups by evaluating the statistical significance of multiplicative interaction terms. This process was repeated for each outcome of CHF, CHD, and all-cause mortality. We then conducted the same series of analyses for white women and white men. We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CI) to compare the association of diabetes with each outcome. We first derived hazard ratios in a base model adjusted for age and clinical site. In a second model that explored the effect of lifestyle and obesity, we added education, smoking, alcohol consumption, physical activity, and BMI. In a third model, we added cardiovascular risk factors to the base model: HDL-C, LDL-C, systolic blood pressure, anti-hypertensive medication use, and CRP. A fourth model included the base model plus subclinical vascular disease. We assessed the validity of the proportional hazards assumption using Schoenfeld residuals and found no evidence of meaningful violations.

To explore whether the observed sex differences among blacks were due in part to differential non-CHD mortality in men and women, we also fit a model that accounted for death as a competing risk [31]. For this model, we used a composite of CHF and CHD as the endpoint after confirming similar sex interactions for both endpoints among black

participants. We also used this composite endpoint to assess the sex interaction among blacks in a standard (non-competing risks) analysis. We tested the three-way interaction between sex, race and diabetes using the composite endpoint.

To assess whether sex differences in cardiovascular risk associated with diabetes might be explained by heterogeneity in the duration or severity of disease among men and women, we conducted two sensitivity analyses. In CHS, baseline data on years with diabetes are available only for black participants enrolled in 1992-93. For this group we computed HRs stratified by the duration of diabetes (1-4, 5-15, >15 years). We used medication requirement as a proxy measure for severity of diabetes in both whites and blacks in a second sensitivity analysis. Medication use as a measure of severity has been shown to correlate with mortality in CHS [32], where insulin use was associated with a higher risk of death from sepsis, renal disease, and metabolic derangements compared to oral hypoglycemic agents. We therefore stratified diabetic individuals into categories representing descending intensities of treatment defined as: insulin use, oral hypoglycemic use alone, and no treatment.

The proportion of missing data was very low (<2% for any single variable) and missing covariate data was imputed using a single imputation [33]. All analyses were performed using Stata, Version 11.2.

Results

Of the 4817 participants, 755 (16%) were black and 2923 (61%) were women. Table 1 shows baseline characteristics of participants according to race, sex, and diabetes status. The mean age was similar across groups. Across sex and race groups, individuals with diabetes had a higher BMI, lower physical activity, higher systolic blood pressure, lower HDL-C, and higher CRP compared to those without diabetes. Except for HDL-C, each of these values was most extreme for black women with diabetes. Among blacks and whites, diabetes was associated with a greater absolute difference among women compared to men for BMI, systolic blood pressure, and HDL. Subclinical vascular disease was more prevalent among men.

Over a median follow-up of 12.5 years, there were 1342 incident cases of CHF, 1246 of CHD, and 3214 deaths. Kaplan-Meier curves for CHF and CHD are presented in Figure 1. Overall, the absolute risks for those with diabetes were higher than for those without diabetes. Men with diabetes generally had the highest rates of each outcome, with the exception of CHF, for which the highest rates were observed among black women with diabetes.

Associations of diabetes with CHF, CHD, and mortality among black women and men

CHF: Black women and men with diabetes experienced greater rates of CHF compared to those without diabetes (Table 2). Black women with diabetes had a higher rate of CHF than did black men (46.3 per 1000 person-years vs. 31.9 per 1000 person-years). In addition, the HR associated with diabetes for CHF tended to be greater for women (2.42, 95% CI 1.70-3.43) compared to men, in whom there was a modest and statistically non-significant

relationship between diabetes status and incident CHF (1.39, 95%CI 0.83-2.34), although a formal test of interaction was not statistically significant (P for interaction = 0.08). Adjustment for multiple risk factors attenuated the HR to a greater degree in black women than men.

CHD: HRs for the association of diabetes and CHD followed the pattern seen for CHF and were numerically but not significantly higher among women (2.38, 95%CI 1.59-3.57) compared to men (1.54, 95%CI 0.96-2.49, P for interaction = 0.17).

All-cause mortality: The association of death with diabetes was similar among black women and men (P for interaction = 0.57).

Composite: The sex interaction among blacks was statistically significant for the composite of CHD and CHF, with higher HRs associated with diabetes among women as compared to men (2.44, 95%CI 1.82-3.26 vs. 1.44, 95%CI 0.97-2.12, P for interaction = 0.03). Findings were similar in the competing risks model (women: sub-hazard ratio=2.47, 95%CI 1.86-3.28 vs. men: sub-hazard ratio=1.38, 95%CI 0.91-2.08; P for interaction = 0.02). A formal test that sex modified the risk of cardiovascular events associated with diabetes more among blacks than whites was not statistically significant (Table 3; P for three-way interaction 0.07).

Associations of diabetes with CHF, CHD, and mortality among white women and men

CHF: The rate of CHF was higher among white women and men with diabetes compared to their non-diabetic counterparts (Table 3). The hazard ratio (HR) for CHF associated with diabetes was very similar for white women (2.10, 95% confidence interval (CI) 1.68-2.63) and white men (2.07, 95% CI 1.67-2.56, P for interaction = 0.91) (Figure 1). Adjustment for multiple risk factors attenuated the HR to a similar degree in women and men.

CHD: The HR for CHD associated with diabetes was similar among white women (HR 2.13, 95%CI 1.68-2.70) compared to white men (HR 1.83, 95%CI 1.48-2.27), the interaction was not statistically significant (P = 0.35), and multiple risk factor adjustment had a similar impact for both sexes.

All-cause mortality: The HR of death related to diabetes was also similar for white women and men (P for interaction = 0.77).

Sensitivity Analyses

In a sensitivity analysis, we stratified blacks enrolled in 1992-1993 by sex and duration of diabetes at baseline (no diabetes, 1-4 years, 5-15 years, and >15 years). The age-adjusted mean duration of diabetes was longer in men by 2.0 years (P = 0.48). For each outcome, women had approximately 2-fold higher HRs than did men at every category of diabetes duration.

We next stratified whites and blacks by medication use as a proxy for disease severity. We found that white women had HRs for CHD, CHF, and mortality associated with diabetes that were similar to those of men for untreated diabetes and diabetes treated with oral

hypoglycemic agents, but higher HRs for diabetes treated with insulin, particularly for CHF (4.29, 95%CI 2.42-7.62 vs. 2.58, 95%CI 1.51-4.41). By contrast, black women had higher HRs of CHD and CHF regardless of medication use, including for insulin-treated diabetes (HR for CHF=3.16 for women, 95% 1.67-5.96 vs. 1.54 for men, 95%CI 0.61-3.86).

Discussion

Data from prospective studies are sparse regarding how the influence of sex on cardiovascular outcomes in diabetes may differ by race. The question has been difficult to address because prospective studies have included relatively small numbers of black participants. To address this issue, we have used data from the Cardiovascular Health Study, which has the strengths of being large, current, prospective, adjudicated, and with a long-term follow up period in a population which includes over 750 black older adults. We found that sex differences for individual outcomes did not reach statistical significance in either race group, nor did we observe an overall difference between black and white individuals in the influence of sex on cardiovascular outcomes associated with diabetes. However, while white women and men with diabetes generally had similar HRs for CHF, black women had higher relative and absolute risks of CHF associated with diabetes compared to black men. This finding nearly reached statistical significance. The HRs for incident CHD among blacks followed a similar pattern to that for CHF, and we observed a statistically significant interaction by sex for the composite outcome of CHF and CHD among blacks, with women at higher risk. The trend towards higher relative risk in black women as compared to black men was also observed in sensitivity analyses of duration and severity of diabetes.

Previous studies have provided conflicting data on sex differences in CHF incidence among those with diabetes [4-8]. In a predominantly white population, the Framingham Heart Study reported over 30 years ago that CHF was five times more common among women with diabetes than those without diabetes, while it was only two times more common among diabetic compared to non-diabetic men [4]. Other authors have reported a higher risk of CHD associated with diabetes among women than among men [1]. We did not find such a difference by gender in risk of CHF or CHD among white adults, perhaps related to the older age of CHS participants and a higher baseline risk due to age alone that would obscure the sex differences observed in younger individuals. The few contemporary studies that specifically addressed CHF incidence in diabetic individuals by sex have not reported a difference, although these more recent studies have not necessarily investigated sex differences in CHF as a primary outcome and often had relatively short follow-up periods [15, 16, 18].

There is little prior work against which to compare our findings about the impact of diabetes on CHF and CHD risk among black women and men. Similarly, little is known about how differences in the associations of sex and diabetes with risk of adverse outcomes differ by race. Few if any previous studies have been designed to detect sex differences within race groups. One study reported a secondary analysis of the sex/race interaction on cardiovascular outcomes in diabetes and did not identify sex differences by race, but this investigation was conducted in a younger HMO population [9]. In an older population, we report a similar lack of overall effect modification by sex. However, we noted a trend

towards higher risks of CHF and CHD in women versus men among blacks that was absent among whites.

Why female sex might confer a high risk specifically among diabetic black older adults is uncertain, although it is in keeping with the trend toward disproportionate effects of diabetes among women and blacks previously noted. We do not currently have robust data to support a biologic basis for increased CHF or CHD risk among older black women with diabetes by virtue of their particular combination of race and sex [34], although pathophysiological explanations have been proposed for the greater effect of diabetes in women generally. Numerous studies suggest that black women are less likely than other sex/race groups to have adequate risk factor control and treatment for cardiovascular disease [26, 35-37]. In CHS, black women had the highest blood pressures, LDL-C levels, and BMI, and the lowest physical activity levels of any sex/race group. This pattern of risk factors is consistent with a nationally representative multi-ethnic sample of older adults from NHANES III [38]. The trend towards excess risk of CHF and CHD among black women compared to men in CHS persisted after adjustment. However, a single measurement of any risk factor may not adequately adjust for the effects of that characteristic over a lifetime. There is also the potential for contributions from other factors related to lifestyle, clinical characteristics, and/or treatment.

Strengths of this study include the rigorously defined and adjudicated outcomes, the standardized and comprehensive ascertainment of cardiovascular risk factors, and the long follow-up period, which now approaches twenty years. In addition, we conducted a competing risks analysis to explore whether non-CHD death among black men might explain the sex differences we observed. The Cardiovascular Health Study (CHS) is a population-based study with a high response rate despite recruitment from Medicare lists (i.e. the cohort was not comprised of volunteers). The study population is therefore highly representative of the community-dwelling older adults in those and similar communities. There are also limitations to our study. We lacked complete data on diabetes duration and severity. We did, however, conduct and report the results of two sensitivity analyses that explore the role of these factors. A second limitation is statistical power. Though CHS has enrolled one of the largest observational cohorts of black study participants, the number of participants was small in certain categories and we found wide confidence intervals in some analyses among blacks. Similarly, because power to conduct tests of interaction is lower than that for main effects, we confirmed significant interactions only for a composite outcome of CHF and CHD, although the direction was similar for both endpoints separately. In addition, CHS is a study of cardiovascular disease risk factors in older adults, so survival bias could be present if attrition prior to enrollment were differential with respect to sex, race, diabetes, and prognosis.

In summary, we did not find overall effect modification by sex on cardiovascular outcomes in diabetes in older blacks and whites. However, even with limited power, we observed a trend towards higher risks of both CHF and CHD among black women as compared to men. Given these findings and the well-documented and particularly high rates of poorly controlled risk factors among black women, the possibility that effect modification by sex may exist even into older age among black adults requires further study.

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Figure 1.

Cumulative incidence of CHF and CHD among women and men with and without diabetes, by race.

Table 1

Characteristics of CHS participants at baseline by race, sex, and diabetes status.*

	Black				White			
	Women Diabetes		Men Diabetes		Women Diabetes		Men Diabetes	
	No (n=365)	Yes (n=111)	No (n=207)	Yes (n=72)	No (n=2,196)	Yes (n=251)	No (n=1,368)	Yes (n=247)
Age, years	73.1 ± 5.8	72.9 ± 5.3	72.5 ± 5.6	72.2 ± 4.9	72.2 ± 5.3	72.5 ± 5.9	72.6 ± 5.5	72.7 ± 5.7
Education, years	11.3 ± 3.7	10.9 ± 3.7	11.3 ± 4.1	11.3 ± 4.0	12.5 ± 2.8	11.5 ± 2.8	12.7 ± 3.3	12.0 ± 3.2
BMI, kg/m ²	28.7 ± 5.8	31.6 ± 5.6	26.4 ± 4.0	28.0 ± 4.3	26.0 ± 4.8	28.6 ± 5.1	26.1 ± 3.5	27.9 ± 4.2
Physical activity, kcal/wk	1047.4 ± 1512.0	765.4 ± 1014.4	1285.7 ± 1549.8	1192.0 ± 1590.9	1793.8 ± 2086.1	1373.0 ± 1717.6	2158.5 ± 2275.6	2075.3 ± 2429.6
Systolic BP, mmHg	141.6 ± 23.3	147.8 ± 23.6	138.7 ± 20.3	139.5 ± 21.7	134.8 ± 21.5	140.5 ± 19.7	135.0 ± 20.7	140.6 ± 22.5
Diastolic BP, mm Hg	74.6 ± 10.8	75.0 ± 12.2	77.2 ± 11.2	73.6 ± 12.2	69.1 ± 10.8	68.5 ± 11.4	71.8 ± 11.0	72.7 ± 12.3
Total cholesterol, mmol/L	5.5 ± 1.0	5.5 ± 1.2	5.0 ± 0.9	5.2 ± 1.1	5.9 ± 1.0	5.8 ± 1.1	5.3 ± 0.9	5.0 ± 0.9
HDL Cholesterol, mmol/L	1.6 ± 0.4	1.4 ± 0.3	1.4 ± 0.4	1.2 ± 0.3	1.6 ± 0.4	1.3 ± 0.3	1.3 ± 0.3	1.1 ± 0.3
LDL cholesterol, mmol/L	3.4 ± 0.9	3.5 ± 1.1	3.2 ± 0.8	3.3 ± 0.9	3.5 ± 0.9	3.5 ± 1.1	3.2 ± 0.9	2.9 ± 0.9
C-reactive protein, mg/L	4.4 ± 6.0	7.1 ± 9.2	3.8 ± 6.8	4.1 ± 3.8	3.0 ± 4.4	4.8 ± 7.3	3.1 ± 5.8	4.6 ± 10.2
HTN medication use, %	63.6	70.3	46.9	61.1	38.7	61.8	34.1	52.6
Lipid-lowering medication, %	5.5	12.6	3.9	4.2	5.3	6.4	3.2	5.7
Aspirin use >2 days in 2 weeks, %	26.3	32.4	29.0	31.9	29.1	30.0	32.8	38.1
Oral hypoglycemics, %	0	49.5	0	37.5	0	34.7	0	38.5
Insulin, %	0	21.6	0	20.8	0	10.0	0	13.8
Alcohol consumption, %								
None	68.2	83.8	46.4	62.5	49.3	70.9	35.7	59.1
<7 drinks/wk	29.3	13.5	38.2	29.2	38.6	23.1	41.5	29.1
7+ drinks/wk	2.5	2.7	15.5	8.3	12.1	6.0	22.8	11.7
Smoking status, %								
Never	56.4	61.3	26.6	37.5	56.9	56.6	32.5	34.8
Former	28.8	28.8	49.8	45.8	30.4	31.1	57.1	56.3
Current	14.8	9.9	23.7	16.7	12.7	12.4	10.4	8.9
Subclinical vascular disease, %	62.2	77.5	71.5	80.6	56.3	73.3	65.9	79.4

* Values shown are mean ± SD unless otherwise noted

Table 2

Associations of diabetes with coronary heart disease, congestive heart failure, and all-cause mortality among black participants in the Cardiovascular Health Study, by sex.

	Women		Men		<i>P</i> interaction
	Diabetes		Diabetes		
	No (n=365)	Yes (n=111)	No (n=207)	Yes (n=72)	
Congestive heart failure					
No. events	89	49	49	20	
Rate per 1000 person-years	20.8	46.3	24.2	31.9	
Model 1 ¹ HR (95% CI)	1.00 (Ref.)	2.42 (1.70-3.43)	1.00 (Ref.)	1.39 (0.83-2.34)	0.08
Model 2 ² HR (95% CI)	1.00 (Ref.)	2.04 (1.42-2.92)	1.00 (Ref.)	1.14 (0.68-1.93)	0.07
Model 3 ³ HR (95% CI)	1.00 (Ref.)	2.15 (1.49-3.09)	1.00 (Ref.)	1.24 (0.74-2.10)	0.09
Model 4 ⁴ HR (95% CI)	1.00 (Ref.)	2.25 (1.59-3.21)	1.00 (Ref.)	1.36 (0.81-2.29)	0.12
Coronary heart disease					
No. events	65	37	53	25	
Rate per 1000 person-years	14.7	31.9	25.8	38.5	
Model 1 ¹ HR (95% CI)	1.00 (Ref.)	2.38 (1.59-3.57)	1.00 (Ref.)	1.54 (0.96-2.49)	0.17
Model 2 ² HR (95% CI)	1.00 (Ref.)	2.43 (1.60-3.70)	1.00 (Ref.)	1.51 (0.93-2.45)	0.14
Model 3 ³ HR (95% CI)	1.00 (Ref.)	2.06 (1.35-3.14)	1.00 (Ref.)	1.46 (0.90-2.36)	0.28
Model 4 ⁴ HR (95% CI)	1.00 (Ref.)	2.15 (1.43-3.23)	1.00 (Ref.)	1.48 (0.92-2.39)	0.24
All-cause mortality					
No. events	199	78	141	59	
Rate per 1000 person-years	42.7	64.6	63.5	85.8	
Model 1 ¹ HR (95% CI)	1.00 (Ref.)	1.68 (1.29-2.19)	1.00 (Ref.)	1.44 (1.06-1.95)	0.45
Model 2 ² HR (95% CI)	1.00 (Ref.)	1.71 (1.30-2.24)	1.00 (Ref.)	1.42 (1.04-1.93)	0.37
Model 3 ³ HR (95% CI)	1.00 (Ref.)	1.57 (1.20-2.06)	1.00 (Ref.)	1.42 (1.04-1.94)	0.62
Model 4 ⁴ HR (95% CI)	1.00 (Ref.)	1.60 (1.23-2.09)	1.00 (Ref.)	1.40 (1.03-1.89)	0.50

	Women		Men		<i>p</i> interaction
	Diabetes		Diabetes		
	No (n=365)	Yes (n=111)	No (n=207)	Yes (n=72)	
	Composite outcome (CHF and CHD)				
No. events	127	71	85	36	
Rate per 1000 person-years	30.3	68.8	43.7	59.8	
Cox model HR (95% CI) ¹	1.00 (Ref.)	2.44 (1.82-3.26)	1.00 (Ref.)	1.44 (0.97-2.12)	0.03
Competing risks model SHR ^{1,5} (95% CI)	1.00 (Ref.)	2.47 (1.86-3.28)	1.00 (Ref.)	1.38 (0.91-2.08)	0.02

¹ Adjusted for age and clinical site

² Adjusted for age, clinical site, education, smoking, alcohol consumption, BMI, and physical activity

³ Adjusted for age, clinical site, HDL cholesterol, LDL cholesterol, systolic blood pressure, anti-hypertensive medication use, and C-reactive protein

⁴ Adjusted for age, clinical site, and subclinical vascular disease

⁵ SHR= sub-hazard ratio, accounts for death as a competing risk

Table 3

Associations of diabetes with coronary heart disease, congestive heart failure, and all-cause mortality among white participants in the Cardiovascular Health Study, by sex.

	Women				Men			
	Diabetes		Diabetes		Diabetes		Diabetes	
	No (n=2,196)	Yes (n=251)	No (n=1,368)	Yes (n=247)	No (n=1,368)	Yes (n=247)	No (n=1,368)	Yes (n=247)
Congestive heart failure								
No. events	535	90	405	105				
Rate per 1000 person-years	18.6	36.0	26.0	49.7				
Model 1 ¹ HR (95% CI)	1.00 (Ref.)	2.10 (1.68-2.63)	1.00 (Ref.)	2.07 (1.67-2.56)				0.91
Model 2 ² HR (95% CI)	1.00 (Ref.)	1.84 (1.47-2.32)	1.00 (Ref.)	1.86 (1.49-2.31)				0.97
Model 3 ³ HR (95% CI)	1.00 (Ref.)	1.70 (1.35-2.14)	1.00 (Ref.)	1.74 (1.39-2.16)				0.89
Model 4 ⁴ HR (95% CI)	1.00 (Ref.)	1.97 (1.58-2.47)	1.00 (Ref.)	1.98 (1.60-2.46)				0.97
Coronary heart disease								
No. events	449	82	431	104				
Rate per 1000 person-years	15.3	30.1	28.1	47.9				
Model 1 ¹ HR (95% CI)	1.00 (Ref.)	2.13 (1.68-2.70)	1.00 (Ref.)	1.83 (1.48-2.27)				0.35
Model 2 ² HR (95% CI)	1.00 (Ref.)	1.99 (1.57-2.53)	1.00 (Ref.)	1.70 (1.37-2.11)				0.33
Model 3 ³ HR (95% CI)	1.00 (Ref.)	1.77 (1.39-2.25)	1.00 (Ref.)	1.61 (1.29-2.00)				0.57
Model 4 ⁴ HR (95% CI)	1.00 (Ref.)	1.96 (1.54-2.48)	1.00 (Ref.)	1.73 (1.39-2.14)				0.45
All-cause mortality								
No. events	1322	203	993	219				
Rate per 1000 person-years	42.8	69.6	58.2	88.9				
Model 1 ¹ HR (95% CI)	1.00 (Ref.)	1.81 (1.56-2.10)	1.00 (Ref.)	1.76 (1.52-2.04)				0.77
Model 2 ² HR (95% CI)	1.00 (Ref.)	1.82 (1.57-2.12)	1.00 (Ref.)	1.72 (1.48-1.99)				0.57
Model 3 ³ HR (95% CI)	1.00 (Ref.)	1.68 (1.44-1.95)	1.00 (Ref.)	1.64 (1.41-1.90)				0.84
Model 4 ⁴ HR (95% CI)	1.00 (Ref.)	1.71 (1.47-1.98)	1.00 (Ref.)	1.69 (1.46-1.96)				0.92

- ¹Model 1 is adjusted for age and clinical site
- ²Model 2 is adjusted for age, clinical site, education, smoking, alcohol consumption, BMI, and physical activity
- ³Model 3 is adjusted for age, clinical site, HDL cholesterol, LDL cholesterol, systolic blood pressure, anti-hypertensive medication use, and C-reactive protein
- ⁴Model 4 is adjusted for age, clinical site, and subclinical vascular disease