Journal of Diabetes and Its Complications 28 (2014) 316–322

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

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

Varsha G. Vimalananda [a,*], Mary L. Biggs [b], James L. Rosenzweig [a], Mercedes R. Carnethon [c], James B. Meigs [d], Evan L. Thacker [e], David S. Siscovick [f], Kenneth J. Mukamal [d]

[a] Section of Endocrinology, Diabetes and Nutrition, Department of Medicine, Boston University School of Medicine, Boston, MA, USA
[b] Department of Biostatistics, School of Public Health, University of Washington, Seattle, WA, USA
[c] Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
[d] General Medicine Division, Department of Medicine, Harvard Medical School, Boston, MA, USA
[e] Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, USA
[f] Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle, WA, USA

ARTICLE INFO

Article history:
Received 5 November 2013
Received in revised form 17 December 2013
Accepted 18 December 2013
Available online 26 December 2013

Keywords:
Diabetes mellitus
Sex-specific
Ethnicity
African-American
Epidemiology

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 US 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.
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.

Published by Elsevier Inc.

1. 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 (Natarajan, Liao, Cao, et al., 2003); indeed the lower rate of CHD in white premenopausal women is substantially eliminated among those with diabetes (Kautzky-Willer, Kamyar, Gerhat, et al., 2010; Pan, Cedres, Liu, et al., 1986). Findings with respect to congestive heart failure (CHF) are mixed (Iribarren, Karter, Go, et al., 2001; Kannel, Hjortland, & Castelli, 1974; Kuller, Velentgas, Barzilay, et al., 2000; Nichols, Hillier, Erbey, et al., 2001; Nichols, Gullion, Koro, et al., 2004). 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 (Karter, Ferrara, Liu, et al., 2002), and such a

Disclosures: The authors have no conflicts of interest to disclose.

☆ Funding: This research was supported by National Heart, Lung, and Blood Institute (NHLBI) contracts HHSN268201200036C, N01-HC-85239, N01-HC-85079 through N01-HC-85086; N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133; and NHLBI grants HL094555 and HL080295, with additional contribution from NINDS. Additional support was provided through AG-023629, AG-15928, AG-20098, and AG-027058 from the National Institute on Aging (NIA). Dr. Meigs is supported by K24 DK080140. See also http://www.chs-nhlbi.org/pi.htm. These data were presented at the American Diabetes Association 72nd Scientific Sessions; Philadelphia, PA, June 2012.

* Corresponding author at: Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, 88 East Newton Street, Evans 201, Boston MA 02118, USA. Tel.: +1 781 687 3456; fax: +1 781 687 3106.
E-mail address: varshav@bu.edu (V.G. Vimalananda).

1056-8727/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.jdiacomp.2013.12.004

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 (Centers for Disease Control, Prevention, 2011), no observational studies have evaluated the modifying effect of sex by race for different types of cardiovascular events (Bertoni, Hundley, Massing, et al., 2004 Mar; Carnethon, Biggs, Barzilay, et al., 2010; Fried, Kronmal, Newman, et al., 1998; Gottdiener, Arnold, Aurigemma, et al., 2000; Gregg, Gu, Cheng, et al., 2007; He, Ogden, Bazzano, et al., 2001; Ho, Paultre, & Mosca, 2005; Huxley, Barzi, & Woodward, 2006; Iribarren et al., 2001; Jousilahti, Vartiainen, Tuomilehto, et al., 1999; Juutilainen, Kortelainen, Lehto, et al., 2004; Kannel et al., 1974; Kuller et al., 2000; Natarajan et al., 2003; Nichols et al., 2001, 2004; Psaty, Furberg, Kuller, et al., 1999; Wexler, Grant, Meigs, et al., 2005). 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 (Huxley et al., 2006; Kanaya, Grady, & Barrett-Connor, 2002)

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 (Ferrara, Mangione, Kim, et al., 2008; Gouni-Berthold, Berthold, Mantzoros, et al., 2008; Kanaya et al., 2002; Wexler et al., 2005; Winston, Barr, Carrasquillo, et al., 2009), we also examined whether any observed differences persisted after adjustment for lifestyle and cardiovascular disease risk factors.

2. Methods

2.1. 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 US 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 (Fried, Borhani, Enright, et al., 1991). 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.

2.2. 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 (Ives, Fitzpatrick, Bild, et al., 1995).

2.3. 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.

2.4. 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.

2.5. 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.

2.6. 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 (Psaty, Lee, Savage, et al., 1992). Clinical data included body mass index (BMI, kg/m^2) and seated blood pressure (mm Hg). 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 >80th percentile, common carotid wall thickness >80th percentile, carotid stenosis >25%, a major ECG abnormality, or positive responses to the Rose Questionnaire for angina or intermittent claudication (Kuller, Borhani, Furberg, et al., 1994).

2.7. Statistical analysis

We categorized participants into eight 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