Identification and Predictors for Cardiovascular Disease Risk Equivalents Among Adults With Diabetes

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Diabetes Care 2021;44:2411–2420 | https://doi.org/10.2337/dc21-0431

OBJECTIVE

We examined diabetes as a cardiovascular disease (CVD) risk equivalent based on diabetes severity and other CVD risk factors.

RESEARCH DESIGN AND METHODS

We pooled four U.S. cohorts (Atherosclerosis Risk in Communities [ARIC], Jackson Heart Study [JHS], Multi-Ethnic Study of Atherosclerosis [MESA], and Framingham Heart Study Offspring Cohort [FHS-Offspring]) and classified subjects into groups by baseline diabetes/CVD status (positive or negative). CVD risks of the diabetes mellitus (DM)+/CVD− group versus DM−/CVD+ group were examined by diabetes severity and in subgroups of other CVD risk factors. We developed an algorithm to identify subjects with CVD risk equivalent diabetes by comparing the relative CVD risk of being DM+/CVD− versus DM−/CVD+.

RESULTS

The pooled cohort included 27,730 subjects (mean age 58.5 years, 44.6% male). CVD rates per 1,000 person-years were 16.5, 33.4, 43.2, and 71.4 among those DM−/CVD−, DM+/CVD−, DM−/CVD+, and DM+/CVD+, respectively. Compared with those DM−/CVD+, CVD risks were similar or higher for those with HbA_{1c} ≥ 7%, diabetes duration ≥10 years, or diabetes medication use, while those with less severe diabetes had lower risks. Hazard ratios (95% CI) for DM+/CVD− vs. DM−/CVD+ were 0.96 (95% CI 0.86–1.07), 0.97 (0.88–1.07), 0.96 (0.82–1.13), 1.18 (0.98–1.41), 0.93 (0.85–1.02), and 1.00 (0.89–1.13) among women and those of White race, age <55 years, and with triglycerides ≥2.26 mmol/L, hs-CRP ≥2 mg/L, and estimated glomerular filtration rate <60 mL/min/1.73 m^2, respectively. In the DM+/CVD− group, 19.1% had CVD risk equivalent diabetes with a lower risk score but a higher observed CVD risk.

CONCLUSIONS

Diabetes is a CVD risk equivalent in one-fifth of CVD-free adults living with diabetes. High HbA_{1c}, long diabetes duration, and diabetes medication use were predictors of CVD risk equivalence. Diabetes is a CVD risk equivalent for women, white people, and those of younger age or with higher triglycerides or hs-CRP or reduced kidney function.

The concept of the "coronary heart disease (CHD) risk equivalent" was first introduced by Haffner et al. (1) In this landmark study, the investigators observed that the incidence of myocardial infarction (MI) for those with diabetes without prior MI (diabetes mellitus [DM]+/MI−) was as high as that of those who had a history

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Received 22 February 2021 and accepted 16 June 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.14807256.

of MI but no diabetes (DM−/MI+). They concluded that patients with diabetes had CHD risk comparable with the risk of those with established CHD and should be treated accordingly. Many subsequent studies evaluating whether diabetes is a CHD or cardiovascular disease (CVD) risk equivalent have shown mixed results (2–7). A meta-analysis of 13 cohort studies comprised of 45,108 subjects showed that those with diabetes had 43% lower risk for future CAD events (fatal or nonfatal MI) than those with a prior MI (5). A recent study of 1.6 million Kaiser Permanente Northern California patients aged 30–90 years found overall that those with diabetes but no history of CHD had a 39% lower 10-year CHD risk than those with CHD and no diabetes. However, in a subset of patients with duration of diabetes >10 years, diabetes was found to be a CHD risk equivalent (6).

Multiple factors likely contribute to whether diabetes is a risk equivalent, including follow-up length and duration of diabetes. Studies conducted primarily in White populations and those that did not adjust for other CVD risk factors/comorbidities also tended to be equivocal (2–4,7–9). In addition, contemporary diabetes populations differed from historical cohorts in various diagnostic criteria, treatment strategies, and diabetes severity, all of which influence whether diabetes is really a CHD risk equivalent. Last but not least, stroke, heart failure, and peripheral vascular disease (PVD) are also important complications of diabetes but often were not included in prior studies, presenting the question of what makes a "true" CVD equivalent. Addressing these gaps in the literature has important clinical implications, as intensified therapeutic intervention is warranted in those whose diabetes status confers the highest CVD risks.

We aimed at evaluating CVD risk burden among adults with diabetes compared with those with no diabetes but prior CVD and identifying what factors, including diabetes severity indicators and other CVD risk factors, might influence CVD risk among those with diabetes but not prior CVD in comparisons with those with prior CVD and no diabetes in a large pooled, contemporary cohort of the U.S. population. Further, we developed an algorithm to define CVD risk equivalent diabetes and compared the CVD risk between those with CVD risk equivalent diabetes and those with non-CVD risk equivalent diabetes.

RESEARCH DESIGN AND METHODS

This project involved the use of de-identified data and was approved for expedited review by the institutional review board at University of California, Irvine (HS no. 2017-3984).

Study Sample

We pooled data from four U.S. prospective cohort studies with diverse ethnic, geographical, and temporal backgrounds: the Atherosclerosis Risk in Communities (ARIC) study, Multi-Ethnic Study of Atherosclerosis (MESA), Jackson Heart Study (JHS), and Framingham Heart Study Offspring Cohort (FHS-Offspring) (10–13). In brief, all four studies were National Institutes of Health–funded, cohort studies conducted in U.S. communities. A summary of each study can be found in Supplementary Table 1. Because hemoglobin A_{1c} (HbA_{1c}) is one of the current diabetes diagnosis criteria, our study used as baseline exams for each cohort where HbA_{1c} measures were first available instead of the original baseline (exam 2 [1990–1992] for ARIC, exam 2 [2002–2004] for MESA, exam 1 [2000–2002] for JHS, and exam 7 [1998–2001] for FHS-Offspring). Participants included in both JHS and ARIC were excluded from the JHS cohort, with the ARIC exam used instead as their baseline.

Diabetes was defined as at least one of the following before or at baseline: *1*) use of diabetes medication, *2*) self-report of diabetes, *3*) fasting blood glucose of ≥7.0 mmol/L (126 mg/dL), *4*) 2-h postchallenge glucose ≥11.1 mmol/L (200 mg/dL), or *5*) HbA_{1c} ≥6.5% (48 mmol/mol). Prevalent CVD at baseline is defined as having at least one of the below before the baseline exam: MI, cardiac revascularization, stroke, heart failure, or PVD. Subjects were then classified into four groups: no diabetes or prior CVD (diabetes mellitus [DM]−/CVD−), having diabetes and no prior CVD (DM+/CVD−), having no diabetes but prior CVD (DM−/CVD+), and having both diabetes and prior CVD (DM+/CVD+). Participants with DM+/CVD− were further classified by *1*) diabetes duration: newly diagnosed diabetes (diabetes duration <1 year or newly found diabetes based on HbA_{1c} or glucose criteria), diabetes duration <10 years, and diabetes duration 10+ years; *2*) HbA_{1c} levels: <7%, 7% to <9%, and ≥9% (and by <8% vs. ≥8% in sensitivity analysis); and *3*) diabetes medication use: yes versus no.

Baseline Risk Factors

We collected the following baseline information: age, sex, race/ethnicity, family history of premature CVD, smoking status, alcohol use, BMI, systolic blood pressure (SBP) and diastolic blood pressure, hs-CRP, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglycerides, total cholesterol, serum creatinine, atrial fibrillation, left ventricular hypertrophy, lipid-lowering medication, and antihypertensive treatment. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD equation (14). Ten-year CVD risk scores were calculated by the pooled cohort equation (PCE) (15). There was not ≥7% missing data for any variables, and missing data on risk factors were filled in with multiple imputation.

Follow-up and End Point Definitions

Our primary end point of interest was CVD, a composite end point including MI, cardiac revascularization, stroke, heart failure, PVD, and CVD death. Atherosclerotic CVD (ASCVD) events were examined as the secondary end point, including MI, stroke, and CVD death. Time to event was recorded as the time from our baseline exam to the first of the above events or time to death, loss to follow-up, or the last date of follow-up if no events occurred. The adjudication process for events involved a panel to review inpatient and outpatient records, follow-up visit data, and death records per study protocols previously published (Supplementary Table 1) (10–13). According to the designated baseline exam in the project, the maximum follow-up time was 26.9 years for ARIC, 13.8 years for MESA, 17.4 years for JHS, and 13.3 years for the FHS-Offspring cohort.

Statistical Analysis

Continuous variables were compared among DM/CVD groups using ANOVA. To get a normal distribution, we used log transformation for variables with

skewness >1. The χ^2 test was used for comparison of categorical variables. Cox proportional hazards regression model was used to calculate the hazard ratios (HRs) for DM−/CVD+ (overall and by diabetes duration, HbA_{1c}, or diabetes medication use groups) versus DM−/CVD+ group with *1*) no adjustment, *2*) adjustment for age, sex, and race, and *3*) adjustment for all risk factors. Subgroup analysis comparing the HRs of DM+/CVD− versus DM−/CVD+ was done by age (<55 years, 55 to <65 years, ≥65 years), sex, race (White, Black, other races), cohorts (ARIC vs. other cohorts), family history of CVD, current smoking status, hypertension, triglycerides dyslipidemia (≥2.26 mmol/L vs. <2.26 mmol/L), HDL-C dyslipidemia (<1.0 mmol/L for men or <1.3 mmol/L for women vs. ≥1.0 mmol/L for men or ≥1.3 mmol/L for women), obesity (BMI ≥30 kg/m^2 vs. <30 kg/m^2), high hs-CRP (≥2 mg/L vs. < 2 mg/L), and chronic kidney disease (eGFR ≥90 mL/min/1.73 m^2, 60–89 mL/min/1.73 m^2, <60 mL/min/1.73 m^2).

To define CVD risk equivalent diabetes in the DM+/CVD− group, we calculated the HR (or relative risk) of being DM+/CVD− versus DM−/CVD+ on the same subject and then compared the HR with 1. In the Cox models, the DM/CVD variable was dummy coded using those with DM−/CVD+ as the reference group. β-Coefficients were defined as β_1 for DM+/CVD− variable and β_{1X} for statistically significant interaction of DM+/CVD− variable and other variables X in the model. For any subject from the DM+/CVD− group, the HR of being DM+/CVD− versus DM−/CVD+ was calculated from the following equation, where X is the subject's actual CVD risk factor value(s), meds is medications, and HbA1c′ is the 6.5% if subject's HbA_{1c} was ≥6.5% or actual HbA_{1c} value if subject's HbA_{1c} was <6.5%:

$$HR = e^{(\beta_1 + \sum \beta_{1X} * X + \beta_{\text{HbA1c}} * \text{HbA1c} + \beta_{\text{DM duration}} * \text{DM duration} + \beta_{\text{DM meds}} * \text{DM meds}) - (\beta_{\text{HbA1c}} * \text{HbA1c}')}$$

If the HR was ≥1, the subject was considered to have CVD risk equivalent diabetes; otherwise, the subject was classified as having non-CVD risk equivalent diabetes. We further compared the risk factor profile and event risks between the two subgroups among those with DM+/CVD−.

Statistical analysis was done with SAS (version 9.4; SAS Institute, Cary, NC). A two-sided *P* value <0.05 (and *P* value <0.1 for interaction test) was considered statistically significant.

RESULTS

In a total of 27,730 study subjects, 14,331 (51.7%) were from ARIC (baseline 1990–1992) and 13,399 (48.3%) were from the other four cohorts (baseline 1998–2004). Among all subjects, 3,751 (13.5%) were DM+/CVD−, 2,463 (8.9%) were DM−/CVD+, and 1,119 (4.0%) were DM+/CVD+. At baseline, those with DM+/CVD−, DM−/CVD+, and DM+/CVD+ were of older age and had higher hs-CRP, and a higher proportion were men or had family history of CVD. SBP was slightly higher among those with diabetes and LDL-C was higher among those with prior CVD. Compared with subjects with DM+/CVD−, those with DM−/CVD+ were slightly older, with a greater proportion being men, White race, smokers, alcohol consumers, and those with a family history of CVD, left ventricular hypertrophy, atrial fibrillation, higher LDL-C, and serum creatinine. However, they had lower SBP, BMI, and triglycerides and higher HDL-C. Lipid-lowering medication use was similar between the two groups (Table 1).

During a median follow-up of 14.0 years, there were 5,163 (25.3%), 1,576 (42.0%), 1,396 (56.7%), and 768 (68.6%) CVD events and 2,332 (11.4%), 863 (23.0%), 883 (35.9%), and 553 (49.4%) ASCVD events that occurred among those DM−/CVD−, DM+/CVD−, DM−/CVD+, and DM+/CVD+, respectively. Corresponding CVD event rates per 1,000 person-years were 16.5, 33.4, 43.2, and 71.4 (see Supplementary Fig. 1 for ASCVD events and Supplementary Fig. 2 for event rates by study). We examined the HRs for CVD events by DM/CVD status at three levels of covariate adjustment (Fig. 1). The unadjusted HRs for DM+/CVD−, DM−/CVD+, and DM+/CVD+ versus DM−/CVD− were 2.22 (95% CI 2.10–2.35), 2.93 (95% CI 2.76–3.11), and 5.13 (95% CI 4.75–5.53), respectively. With full adjustment of non-diabetes-specific CVD risk factors, the HRs for all three groups were attenuated to a different extent. Regardless of levels of adjustment, there was stepwise increase of CVD risk among those DM−/CVD−, DM+/CVD−, DM−/CVD+, and DM+/CVD+ (see Supplementary Table 2 for ASCVD events).

We classified those DM+/CVD− according to diabetes severity indicated by HbA_{1c} level, diabetes duration, or medication use and examined their CVD risk compared with that in the DM−/CVD+ group (event rates shown in Supplementary Fig. 3). Overall, those DM+/CVD− had a 14% lower CVD risk and 24% lower ASCVD risk than those DM−/CVD+ independent of other CVD risk factors (HR 0.86 [95% CI 0.80–0.93] for CVD and 0.76 [95% CI 0.69–0.84] for ASCVD) (Table 2). Among DM+/CVD− subjects, having a diabetes duration of ≥10 years was associated with 20% higher CVD risk than that for the DM−/CVD+ group, while newly diagnosed diabetes was associated with a 31% lower CVD risk. Those with HbA_{1c} of 7% to <9% had CVD risks comparable with that among the DM−/CVD+ group, while those with HbA_{1c} ≥9% had a 34% higher CVD risk. DM+/CVD− subjects on diabetes medication use had similar CVD risk as the DM−/CVD+ group [HR (95% CI) 1.05 (0.96–1.15)], while those not on diabetes medication had 26% lower CVD risk [HR (95% CI) 0.73 (0.67–0.80)] (Supplementary Table 3). Sensitivity analysis of HbA_{1c} categories showed that in comparisons with the DM−/CVD+ group, the HRs for CVD events were 0.77 (95% CI 0.71–0.83) for those DM+/CVD− with HbA_{1c} <8% and 1.23 (95% CI 1.10–1.37) with HbA_{1c} ≥8%; HRs for ASCVD were 0.65 (95% CI 0.58–0.72) and 1.16 (95% CI 1.01–1.34), respectively.

In subgroup analysis, we examined the HRs of DM+/CVD− versus DM−/CVD+ according to other CVD risk factors. Women, those of White race, those aged <55 years, and those with triglycerides ≥2.26 mmol/L, hs-CRP ≥2 mg/L, or eGFR <60 mL/min/1.73 m^2 with DM+/CVD− tended to have similar CVD risks as their counterparts with DM−/CVD+ (HRs close to 1 with nonsignificant *P* values), while men, those of non-White race, those aged ≥55 years, and those with triglycerides <2.26 mmol/L, hs-CRP <2 mg/L, or eGFR >60 mL/min/1.73 m^2 with DM+/CVD− had lower CVD risk than those with DM−/CVD+. Similar patterns in HRs in comparisons of the above subgroups were also observed for ASCVD events, except for race groups (Supplementary Table 4). Unadjusted CVD/

Table 1—Baseline characteristics by baseline DM/CVD status

	DM−/CVD−	DM+/CVD−	DM−/CVD+	DM+/CVD+	
N	20,397	3,751	2,463	1,119	$P_{a,b}$
Age, years	57.5 ± 9.5	59.9 ± 9.1	62.3 ± 10.4	64 ± 9.3	<0.0001
Male sex	8,922 (43.7)	1,721 (45.9)	1,186 (48.2)	539 (48.2)	0.079
Race/ethnicity					<0.0001
White	12,663 (62.1)	1,678 (44.7)	1,732 (70.3)	595 (53.2)	
Black	6,094 (29.9)	1,641 (43.7)	704 (28.6)	504 (45.0)	
Other races	1,640 (8.0)	432 (11.5)	27 (1.1)	20 (1.8)	
Education level					0.0001
Less than high school	2,933 (14.4)	962 (25.6)	632 (25.7)	397 (35.5)	
High school graduate	5,456 (26.7)	1,009 (26.9)	791 (32.1)	311 (27.8)	
Above high school	4,963 (24.3)	857 (22.8)	408 (16.6)	190 (17.0)	
Smoking status					<0.0001
Never	8,498 (41.7)	1,601 (42.7)	804 (32.6)	380 (34.0)	
Prior	8,337 (40.9)	1,565 (41.7)	1,046 (42.5)	515 (46.0)	
Current	3562 (17.5)	585 (15.6)	613 (24.9)	224 (20.0)	<0.0001
Alcohol use	11,832 (58.0)	1,601 (42.7)	1,258 (51.1)	391 (34.9)	<0.0001
Family history of CVD	8,573 (42.0)	1,643 (43.8)	1,371 (55.7)	616 (55.0)	<0.0001
SBP, mmHg	121.8 ± 18.6	129.6 ± 19.8	124.6 ± 19.7	130.8 ± 21.0	<0.0001
DBP, mmHg	72.6 ± 10.1	73.1 ± 10.4	72.3 ± 10.7	71.6 ± 10.6	0.001
BMI, kg/m^2	28.0 ± 5.6	31.4 ± 6.5	28.4 ± 6.1	31.4 ± 7.5	<0.0001
HbA_{1c}, %	5.4 ± 0.4	7.3 ± 1.8	5.5 ± 0.4	7.7 ± 2.0	<0.0001
HbA_{1c}, mmol/mol	36.0 ± 4.4	56.0 ± 19.7	37.0 ± 4.4	61.0 ± 21.9	<0.0001
Fasting glucose, mmol/L	5.4 ± 0.7	8.7 ± 3.7	5.6 ± 0.7	9.3 ± 4.1	<0.0001
Total cholesterol, mmol/L	5.2 ± 1.0	5.2 ± 1.1	5.3 ± 1.0	5.4 ± 1.3	<0.0001
LDL-C, mmol/L	3.3 ± 0.9	3.2 ± 1.0	3.4 ± 1.0	3.4 ± 1.1	<0.0001
HDL-C, mmol/L	1.4 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	1.1 ± 0.4	<0.0001
Triglycerides, mmol/L	1.4 ± 0.8	1.8 ± 1.4	1.5 ± 0.9	2.0 ± 1.4	<0.0001
hs-CRP, mg/L	4.0 ± 6.8	5.8 ± 10.5	5.4 ± 7.9	7.5 ± 10.6	0.136
Serum creatinine, μmol/L	92.1 ± 24.5	94.7 ± 43.6	102.4 ± 56.3	108.6 ± 68.4	<0.0001
eGFR, mL/min/1.73 m^2	69.5 ± 16.0	71.5 ± 18.8	62.8 ± 15.6	63.7 ± 19.1	<0.0001
Left ventricle hypertrophy	593 (2.9)	152 (4.1)	163 (6.6)	130 (11.6)	<0.0001
Atrial fibrillation	99 (0.5)	18 (0.5)	89 (3.6)	61 (5.5)	<0.0001
Lipid-lowering medication	1,947 (9.5)	700 (18.7)	483 (19.6)	293 (26.2)	0.352
Hypertension medication	5,913 (29.0)	2,146 (57.2)	1,498 (60.8)	898 (80.3)	0.005
Diabetes medication	—	1,778 (47.4)	—	584 (52.2)	—
Diabetes duration, years	—	5.3 ± 7.6	—	9.8 ± 10.5	—

Continuous variables are presented as mean ± SD, and categorical variables are presented as *n* (%). [a]*P* values specifically compare the difference between DM+/CVD− and DM−/CVD+ by *t* test and χ^2 test. [b]*P* values for compare the difference among all four groups (ANOVA or χ^2 test) were all <0.001.

ASCVD event rates by subgroups showed consistent results (Supplementary Figs. 4–9). Given that the baseline exam of ARIC was ∼10 years earlier than those of the other four cohorts, we investigated the potential cohort effect in sensitivity analysis. In ARIC ($N = 14,331$), the HR for DM+/CVD− subjects for CVD was 1.08 (95% CI 0.99–1.19, $P = 0.09$) in comparisons with DM−/CVD+ group, while in the pooled non-ARIC cohort ($N = 13,399$), the corresponding HR was 0.46 (95% CI 0.40–0.53, $P < 0.0001$). The subgroup analysis by other risk factors is presented in Supplementary Table 5. We also examined the HRs of DM+/CVD− versus DM−/CVD+ in the combined age, sex, and race groups (Supplementary Fig. 10) and show a linear trend of HRs by age in women but not in men.

We developed an algorithm to define CVD risk equivalent diabetes in the DM+/CVD− group (Supplementary Table 6). We showed how this is applied with an individual example of a 60-year-old White man. He has triglycerides of 2.03 mmol/L, hs-CRP 2.0 mg/L, eGFR 68 mL/min/1.73 m^2, HbA_{1c} 8.0% with diabetes medication, and diabetes duration 3 years. Based on his risk profile, his CVD risk is 12% lower for DM+/CVD− versus DM−/CVD+; therefore, he had non–CVD risk equivalent diabetes.

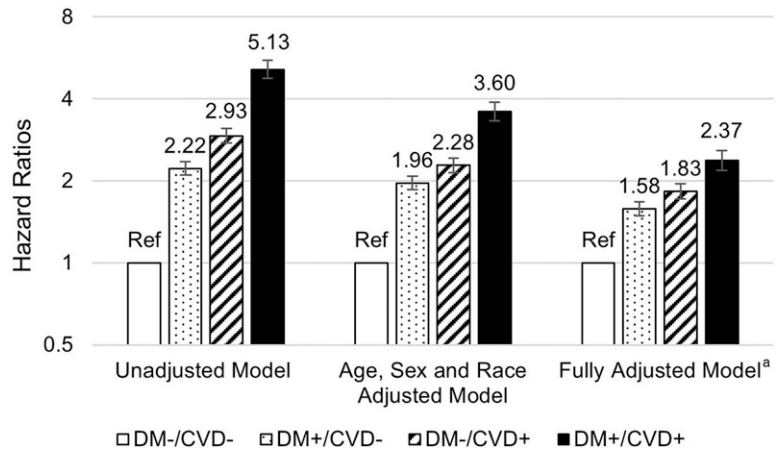

Figure 1—HRs of DM/CVD groups (with DM−/CVD− as reference). Stepwise increase of CVD risk among those DM−/CVD−, DM+/CVD−, DM−/CVD+, and DM+/CVD+ was consistently seen at different levels of covariate adjustment; with full adjustment for non-diabetes-specific CVD risk factors, the HRs for the DM+/CVD−, DM−/CVD+, and DM+/CVD+ groups compared with DM−/CVD− were attenuated. [a]Fully adjusted model: Adjustment for age, sex, race, family history of CVD, education, smoking, alcohol use, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, lipid-lowering medication, and hypertension medication. All HR *P* values <0.0001.

Among the 3,751 subjects DM+/CVD, 715 (19.1%) were found to have CVD risk equivalent diabetes according to the above definition. Baseline risk factors of those with CVD risk equivalent diabetes versus non-CVD risk equivalent diabetes were compared (Supplementary Table 7). Those with CVD risk equivalent diabetes were significantly younger, and more were women and had higher HbA_{1c} and longer diabetes duration, with more frequent diabetes medication use. They also had higher triglycerides, higher hs-CRP, and lower eGFR by definition. We calculated the PCE for 10-year ASCVD risk in the two groups and found the CVD risk equivalent diabetes group had a mean PCE risk of 19.3%, while the non–CVD risk equivalent diabetes group had a mean PCE risk of 21.6% ($P = 0.0002$). Observed event rates per 1,000 person-years were 53.8 vs. 29.2 for CVD and 27.7 vs. 14.1 for ASCVD among those with CVD risk equivalent diabetes versus non–CVD risk equivalent diabetes, respectively. Compared with those DM−/CVD−, those with non–CVD risk equivalent diabetes had an HR of 1.36 (95% CI 1.28–1.46, $P < 0.0001$) for CVD events and 1.57 (95% CI 1.43–1.72, $P < 0.0001$) for ASCVD events, while those with CVD risk equivalent diabetes had an HR of 2.54 (95% CI 2.29–2.81, $P < 0.0001$) for CVD events and 3.00 (95% CI 2.62–3.43, $P < 0.0001$) for ASCVD events with adjustment for age, sex, race, and other non-DM-specific risk factors.

CONCLUSIONS

To our knowledge, this is the first comprehensive investigation to examine both diabetes severity and other CVD risk factors as to their impact on CVD risk equivalency status. Our study is also unique in defining CVD risk equivalent diabetes based on an individual's specific diabetes and CVD risk profile. We also included a whole spectrum of CVD events, including heart failure and PVD, within our primary end point, which is important given the predominance of these conditions as first CVD manifestations in those with diabetes (16).

In our pooled study of four large U.S. community-based cohorts, we found that there is a stepwise increase of CVD risk among those DM−/CVD, DM+/CVD, DM−/CVD+, and DM+/CVD+. Diabetes without prior CVD is not a CVD risk equivalent condition, with an average of 14% lower CVD risk and 24% lower ASCVD risk for those DM+/CVD− than the risk for those DM−/CVD+. Among those DM+/CVD−, high HbA_{1c}, long diabetes duration, and current diabetes medication use were found to be CVD risk equivalents for both CVD and ASCVD events. In addition, those DM+/CVD− had CVD risk similar to that of

Table 2—HRs for CVD events in comparisons of diabetes severity groups with DM−/CVD+ group

	Unadjusted HRs (95% CI)	Age-, sex-, and race-adjusted HRs (95% CI)	Fully adjusted HRs (95% CI)
Overall DM+/CVD− vs. DM−/CVD+ group	0.76 (0.71–0.82)‡	0.86 (0.80–0.93)‡	0.86 (0.80–0.93)†
Diabetes duration groups vs. DM−/CVD+ group			
Newly diagnosed diabetes	0.59 (0.53–0.66)‡	0.69 (0.62–0.77)‡	0.69 (0.62–0.77)‡
Duration 1 to <10 years	0.78 (0.71–0.85)‡	0.88 (0.80–0.96)*	0.88 (0.80–0.96)*
Duration 10+ years	1.11 (0.98–1.25)	1.18 (1.05–1.33)*	1.20 (1.06–1.35)*
HbA_{1c} groups vs. DM−/CVD+ group			
HbA_{1c} <7%	0.62 (0.57–0.68)‡	0.71 (0.65–0.77)‡	0.72 (0.66–0.79)‡
HbA_{1c} 7% to <9%	0.86 (0.78–0.96)*	0.98 (0.88–1.09)	0.95 (0.86–1.06)
HbA_{1c} ≥9%	1.12 (0.99–1.26)	1.36 (1.20–1.53)‡	1.34 (1.18–1.52)‡
Diabetes medication use groups vs. DM−/CVD+ group			
Not on diabetes medication	0.62 (0.57–0.68)‡	0.73 (0.67–0.80)‡	0.74 (0.68–0.81)‡
On diabetes medication	0.98 (0.90–1.08)	1.07 (0.98–1.17)	1.05 (0.96–1.15)

Fully adjusted HRs: adjustment for age, sex, race, family history of CVD, education, smoking, alcohol use, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, lipid-lowering medication, hypertension medication, and other two DM/CVD groups. *$P < 0.01$, †$P < 0.001$, ‡$P < 0.0001$.

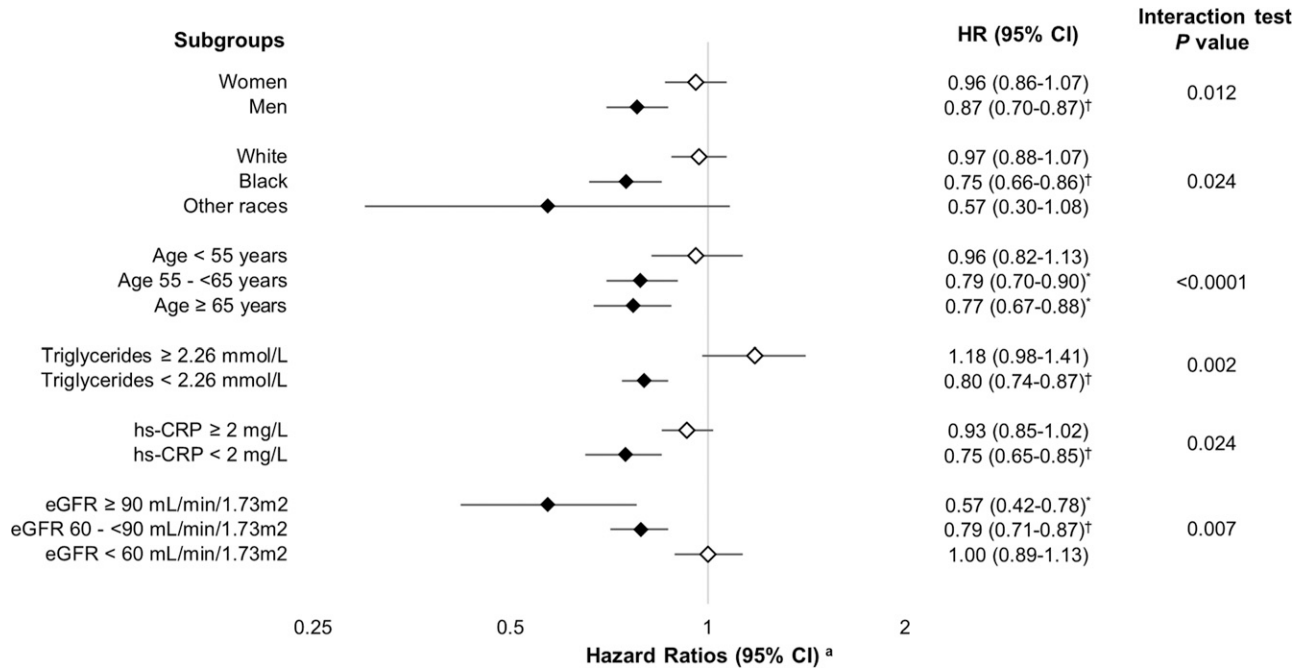

Figure 2—HRs for CVD events in comparison of DM+/CVD− vs. DM−/CVD+ in subgroups. CVD risks were similar (or higher) in comparison of DM+/CVD− vs. DM−/CVD+ among the following subgroups of women: those of White race or age <55 years and those with triglycerides ≥2.26 mmol/L, hs-CRP ≥2 mg/L, or eGFR < 60 mL/min/1.73 m^2. [a]HRs were adjusted for age, sex, race, family history of CVD, education, smoking, alcohol use, SBP, BMI, triglycerides, HDL-C, hs-CRP, serum creatinine, lipid-lowering medication, hypertension medication, and other two DM/CVD groups. *$P < 0.001$; †$P < 0.0001$.

those DM−/CVD+ for women and those of younger age or White race or with elevated triglycerides, hs-CRP, or decreased kidney function, indicating that having diabetes is more detrimental in these subgroups. With the above identified factors, we developed an algorithm to define CVD risk equivalent diabetes. Only 20% of subjects with diabetes in the current study were found to have CVD risk equivalent diabetes. They had a lower 10-year PCE risk score; however, their observed CVD risk was twice as high as the risk for those with non–CVD risk equivalent diabetes.

It has been widely accepted that adults with diabetes have heterogenous CVD risks and having diabetes does not guarantee CVD risk equivalence. Our study confirms earlier findings showing the primary prevention population with diabetes to have lower CVD risks than the secondary prevention population without diabetes. In the contemporary era, early detection and diagnosis of diabetes, newer diabetes therapies with CVD risk–reducing benefits, and the overall improved diabetes management all contribute to reduced CVD risk. Our analysis also shows a cohort effect: diabetes confers a higher CVD risk for the older cohort of ARIC than for the newer cohort pooled from JHS, MESA, and FRS-Offspring.

In the current study, we found that diabetes with high HbA_{1c}, long diabetes duration, and diabetes medication use tended to be risk equivalents for future CVD events, which is consistent with the results of several prior studies. Schramm et al. (2) reported that patients with diabetes requiring glucose-lowering therapy carry the same cardiovascular risk as those without diabetes but a prior MI. Both the study by Rana et al. (6) using Northern California Kaiser Permanente data and the meta-analysis by Wannamethee et al. (17) reported that diabetes over 10 years was a CHD risk equivalent condition. Mondesir et al. (18) defined severe diabetes based on insulin use and/or albuminuria (urinary albumin–to–creatinine ratio ≥30 mg/g) and that only severe diabetes was a CHD risk equivalent.

In addition to the diabetes severity indicators, sex, race, age, triglyceride, hs-CRP levels, and kidney function also modified the diabetes-conferred CVD risk. It is well established that diabetes is associated with greater relative CVD risk increase among women than among men (19). In the Finnish Acute Myocardial Infarction (FINAMI) study, women with diabetes suffered MI risk similar to that of women with prior MI but not that of men (9). Another study found that women with known diabetes had higher CHD risk than those DM−/CHD+ among the young Middle East population (20). In addition, diabetes onset at a younger age indicated early insulin resistance, and was found to be associated with higher relative CVD risk than late-onset diabetes (21–24). The age-specific association of HbA_{1c} and CVD is consistent with prior results where HRs of HbA_{1c} for CVD were found to be higher for those at a younger age (25). Our findings that the DM+/CVD− group has CVD risk similar to that of the DM−/CVD+ group among White persons helps explain why most European studies on the topic concluded that diabetes is a CVD risk equivalent (3,4) while U.S. studies with diverse race groups have tended to refute this conclusion (6,26).

Further, we developed an algorithm to determine whether an individual with diabetes really had the CVD risk equivalent diabetes and demonstrated the importance of assessing CVD risk equivalent diabetes status. The

algorithm works in a way somewhat similar to how the cardiovascular risk scores work. Instead of calculating the 10-year predicted CVD risk, it calculates the relative CVD risk of being DM+/CVD− versus DM+/CVD− in the same person based on his/her profile. Based on the relative CVD risk, we classified those DM+/CVD− into the categories of CVD risk equivalent diabetes versus non–CVD risk equivalent diabetes. One in five of subjects in the study had sufficiently severe diabetes for it to be a CVD risk equivalent. It is worth noting that these subjects had lower 10-year ASCVD risk scores, yet their diabetes conferred higher CVD risk—almost twice as high as that in those with non–CVD risk equivalent diabetes. Given the current risk stratification criteria (27), >60% of the subjects with CVD risk equivalent diabetes did not reach the 20% high risk threshold, yet their observed CVD risk was estimated to be equivalent or even higher than that of their counterparts with a CVD history.

Our data support the need for consideration of more intensified clinical management for adults with CVD risk equivalent diabetes. For instance, aspirin is not currently recommended to all patients with diabetes, given the limited CVD benefit and potentially increased bleeding risk, but has been recommended for those with diabetes at higher risk or with preexisting CVD (27,28). With the identification of CVD risk equivalence among the adults with diabetes, the effect of aspirin can be reevaluated for those where the benefit of aspirin would outweigh the harm. Similar consideration could be given for more intensified treatment targets (or thresholds that should be reached), as in the case of secondary prevention, and where additional nonstatin therapy may be indicated. Further, in clinical trials, those with CVD risk equivalent diabetes warrant consideration for inclusion as a high-risk primary prevention population where additional therapies may be warranted to reduce residual risks. Another important clinical implication of our study is that we identified a key problem of current CVD risk assessment tools that include diabetes as a binary predictor and neglect indicators for diabetes severity. Risk scores like FRS and PCE cannot accurately depict diabetes-associated CVD risks and can even lead to underestimation of CVD risks, as is shown in our study. There is a need to develop risk scores specifically for the population with diabetes and include indicators of diabetes severity as important predictors. Such diabetes-specific CVD risk scores may have better performance than those that have been developed more for the general population (29–31).

Our study has several strengths and limitations. Our pooled cohort was all community based with diverse race/ethnicity and a wide age range. The standard protocol and event adjudication process guaranteed the quality and validity of data. Meanwhile, our findings should be interpreted with the following limitations. First, the end point definition of PVD was slightly different across cohorts. But since incident PVD was not as common as other initial CVD end points in our cohorts, it may have limited impact. Another limitation is that we did not examine the CVD risk equivalence for each individual CVD end point, while previous studies have focused on whether diabetes may still be CVD risk equivalent for a variety of end points including stroke, PVD, total mortality, and even health care cost (32–35). Finally, subjects in MESA were CVD free at exam 1, so at our baseline (exam 2) MESA had fewer subjects with prior CVD than the other cohorts. However, the combined distribution of prevalent diabetes and prevalent CVD in our pooled cohort was similar to that of many prior studies, indicating a well-represented cohort that allows generalizability of the study findings.

The results of our study confirm that adults with diabetes have heterogenous CVD risks and that diabetes does not automatically confer CVD risk equivalence. Severe diabetes, defined as HbA_{1c} ≥7%, diabetes duration over 10 years, or diabetes medication use, tended to be a CVD risk equivalent condition. Diabetes confers higher CVD risk among those of younger age, women, those of White race, and those with elevated triglycerides or hs-CRP or decreased kidney function. Our algorithm developed in this study allows for better defining the CVD risk equivalent diabetes in a primary prevention population, enhancing opportunities to optimize diabetes management. Whether such refined tailoring of treatment may ultimately improve CVD outcomes in the higher-risk population with diabetes deserves further investigation.

Acknowledgments. The authors thank the investigators, the staff, and the participants from all studies for their valuable contributions.

Funding. The Atherosclerosis Risk in Communities study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under contract nos. HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, and HHSN268201700004I. The Framingham Heart Study is funded by the National Heart, Lung, and Blood Institute under contract no. 75N92019D00031. The JHS is supported and conducted in collaboration with Jackson State University (HHSN268201800013I), Tougaloo College (HHSN268201800014I), Mississippi State Department of Health (HHSN268201800015I/HHSN26800001), and University of Mississippi Medical Center (HHSN268201800010I, HHSN268201800011I, and HHSN268201800012I) contracts from the National Heart, Lung, and Blood Institute and the National Institute for Minority Health and Health Disparities. The original MESA was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, UL1-TR-000040, N01-HC-95162, UL1-TR-001079, N01-HC-95163, N01-HC-95164, N01-HC-95165, UL1-TR-001420, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences.

Duality of Interest. N.D.W. reports research funding through the University of California, Irvine, not related to the current study from Amgen, Amarin, Boehringer Ingelheim, Novartis, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. Y.Z. designed the study, researched data, and wrote the manuscript. S.M., K.E.W., and N.D.W. supervised research, contributed to the discussion, and reviewed and edited the manuscript. E.S. contributed to the study design. All authors reviewed and edited the manuscript. Y.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented as an abstract at the 2020 American Heart Association Scientific Sessions, virtual meeting, 13–17 November 2020.

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