American Journal of
Preventive Medicine

RESEARCH ARTICLE

Sex Differences in Cardiovascular Risk Associated With Prediabetes and Undiagnosed Diabetes

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Introduction: Women with Type 2 diabetes (T2D) face up to 50% higher risk of cardiovascular disease than men. This study evaluated the extent to which prediabetes and undiagnosed T2D are associated with a greater excess risk of cardiovascular disease in women versus in men.

Methods: Data were pooled from 18,745 cardiovascular disease–free individuals from the Atherosclerosis Risk in Communities Study, the Multi-Ethnic Study of Atherosclerosis, and the Jackson Heart Study. The risk of coronary heart disease, ischemic stroke, and atherosclerotic cardiovascular disease (coronary heart disease or stroke) associated with prediabetes or undiagnosed T2D was estimated using Cox models adjusting for sociodemographic factors, concomitant risk factors, medication use, and menopausal status. Data were collected in 2022, and the analysis was performed in 2023.

Results: During a median follow-up of 18.6 years, the associations between prediabetes and risk of atherosclerotic cardiovascular disease were only significant in women (hazard ratio=1.18, 95% CI=1.01, 1.34, p=0.03) but not in men (hazard ratio=1.08, 95% CI=1.00, 1.28, p=0.06) (p-interaction=0.18). The associations between undiagnosed T2D and cardiovascular disease outcomes were significant in both sexes, but the effect was more pronounced in women (coronary heart disease: hazard ratio=1.83, 95% CI=1.4, 2.41, p<0.0001 in women vs hazard ratio=1.6, 95% CI=1.38, 2.07, p=0.007 in men; stroke: hazard ratio=1.99, 95% CI=1.39, 2.72, p<0.0001 vs hazard ratio=1.81, 95% CI=1.36, 2.6, p<0.0001; atherosclerotic cardiovascular disease: hazard ratio=1.86, 95% CI=1.5, 2.28, p<0.0001 vs hazard ratio=1.65, 95% CI=1.4, 1.98, p<0.0001) (all p-interactions≤0.2). Both White and Black patients exhibit similar sex differences.

Conclusions: Prediabetes or undiagnosed T2D was associated with a greater excess risk of cardiovascular disease in women than in men. The sex differential in cardiovascular disease risk among those without the T2D diagnosis suggests the need for sex-specific guidelines in T2D screening and treatment.

INTRODUCTION

Women with Type 2 diabetes (T2D) face up to 50% higher risk of cardiovascular disease (CVD) than men with T2D; the reasons for this sex disparity are not fully elucidated.[1] These authors and others reported that during the prediabetes (pre-DM) stage, women experience a greater deterioration in metabolic risk factors, including excessive abdominal adiposity, hypertension, lipid dysregulation, and endothelial dysfunction, than their male counterparts.[2–4] This indicates that the sex differential in metabolic risk burden during

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0749-3797/$36.00
https://doi.org/10.1016/j.amepre.2023.05.011

the pre-DM stage may predispose women to a greater excess risk of CVD than men. However, a limited number of studies have reported sex differences in CVD risk associated with pre-DM,[5] and findings have been inconsistent and mostly restricted to single-race samples.[6−9] Quantifying sex-specific CVD risk with pre-DM based on a racially diverse sample will aid in precision medicine in preventing individuals with intermediate hyperglycemia from progressing into overt T2D, consequently reducing cardiovascular disparities in T2D.

In contrast to a declining prevalence of undiagnosed T2D in the overall adult population in the U.S., authors' recent analysis reveals an upward trend of undiagnosed T2D among young women over the past 20 years.[10] The rise of undiagnosed rates is accounted for by racial minority women.[11] These findings signal multiple issues, including sex inequalities in healthcare access and usage, screening, risk awareness, and diagnostic inertia in T2D, all of which contribute to the sex disparities in diabetic complications, including CVD.[12] It is recognized that individuals with undiagnosed T2D or a delayed diagnosis had a higher risk of hospitalization, CVD events, and mortality than those with timely diagnosis and management of T2D.[13,14] However, to what extent undiagnosed T2D is associated with the sex disparity in risk of CVD has not been examined.

There is lacking sex-specific clinical guidelines in T2D screening and treatment in the absence of definitive evidence for sex-varying cardiovascular impact among those without the T2D diagnosis. The objective of this study was to leverage 3 community-based prospective cohorts in the U.S. to examine the impacts of pre-DM and undiagnosed T2D on CVD risk in men and women. Taking advantage of the multi-ethnic design of the cohorts, the sex differences in these associations in non-Hispanic White (White) and non-Hispanic Black (Black) individuals were also assessed separately.

METHODS

Study Sample

A pooled data set was composed of the Atherosclerosis Risk in Communities Study (ARIC), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Jackson Heart Study (JHS). ARIC enrolled 15,792 adults aged 45−64 years from 4 U.S. communities, including Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD.[15,16] MESA enrolled 6,815 adults aged 45−84 years from 6 U.S. communities, which included Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St. Paul, MN.[17] JHS is a single-site study that enrolled 5,306 African American adults aged 35−84 years from Jackson, MS.[18] The 3 cohorts are similarly designed. Harmonization is minimal for this pooled analysis. The algorithmic transformation was performed on demographic variables such as recategorizing detailed education levels into binary high (high school or higher) versus low (lower than high school) education attainment. The consistency of the transformed variables in the individual cohort was evaluated by descriptive analysis before concatenating 3 cohorts into a master data set. Detailed methods of each cohort's study design, recruitment strategy, and visit protocols have been described previously (also summarized in Appendix Table 1, available online).[15−18] The data were acquired from the National Heart, Lung and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center in 2022. Owing to the availability of HbA1c measurement, ARIC Visit 2 and MESA Visit 2 were set as the baseline. Overall, data from ARIC Visit 2 through Visit 6 (1990−2017), MESA Visit 2 through Visit 5 (2002−2011), and JHS Visit 1 through Visit 3 (2000−2013) were included. Written informed consent was provided by participants for the original 3 studies. This secondary analysis involved existing deidentified data, which did not require review from the Tulane University IRB.

Inclusion and exclusion criteria included men and women (sex was self-reported) free from CVD and T2D with measurements on HbA1c and fasting glucose (FG) from the baseline measurements of the 3 cohorts. Those with missing glycemic measures or outcomes were excluded from the analysis. A total of 18,745 individuals were included in the final analysis (Figure 1).

Measures

Pre-DM was defined as FG of 100 mg/dl to 126 mg/dL or HbA1c of 5.7%−6.5%. *Undiagnosed T2D* was defined as FG ≥126 mg/dL or HbA1c ≥6.5% without a clinical diagnosis of T2D.

For all 3 cohorts, *incident CHD* was defined as a myocardial infarction (MI), CHD death, or cardiac procedure (percutaneous coronary interventions, bypass surgery, or coronary revascularization). *Stroke* was defined as an ischemic stroke. A composite measure of *atherosclerotic CVD* (ASCVD) was also included, which was defined as a MI, CHD death, cardiac procedure (see as mentioned earlier), or ischemic stroke. Hemorrhagic stroke cases were not included owing to few counts. The adjudication process for events involved a panel to review hospitalization and death data per study protocols previously reported for all 3 cohorts.[17,19,20] All events were adjudicated from medical records and death certificates for end-point classification.

Sociodemographic and medication information such as age, race/ethnicity, education attainment (lower than high school or high school or higher), insurance status

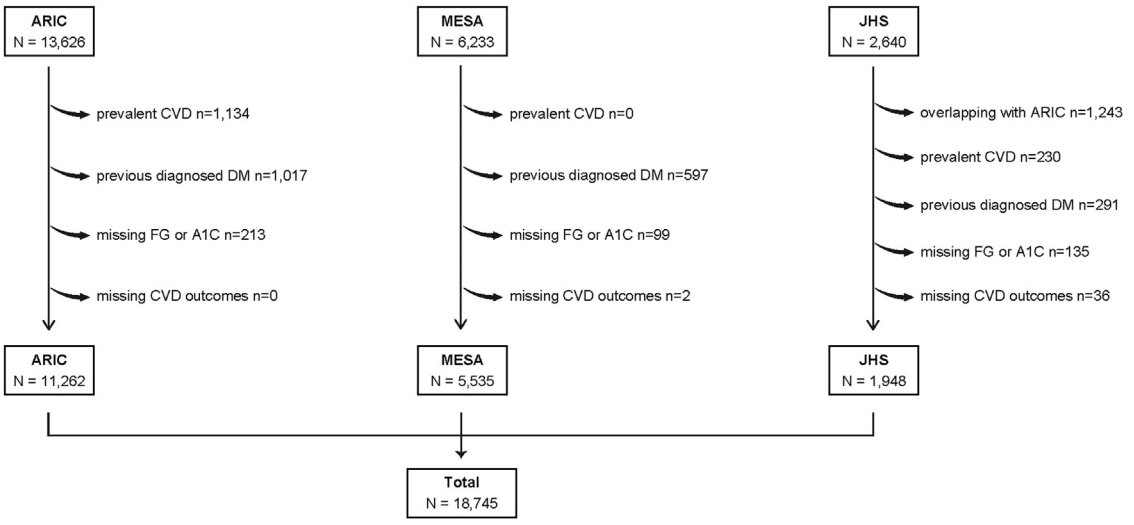

Figure 1. Sample selection.
ARIC, Atherosclerosis Risk in Communities Study; CVD, cardiovascular disease; DM, diabetes; FG, fasting glucose; JHS, Jackson Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis.

(had public, private, or military insurance versus none of these), use of antihypertensive medications, and use of lipid-lowering medications were included. This information has been collected using standard questionnaires from the 3 studies. Traditional cardiovascular risk factors were also included, such as hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), hypercholesterolemia (total cholesterol >200 mg/dL), smoking status, central obesity (waist circumference >94 cm for men and >80 cm for women or waist-to-hip ratio ≥1 for men and ≥8.5 for women), and menopausal status (women only). At ARIC and JHS baseline, a woman was defined as postmenopausal if she (1) had at least 24 consecutive months of amenorrhea, (2) had a bilateral oophorectomy, (3) started using postmenopausal hormone therapy, or (4) was aged ≥55 years at the interview.[21,22] *Postmenopausal status in MESA* was defined similarly, but the primary amenorrhea was based on a previous 12-month period.[23] A woman was categorized as premenopause or perimenopause if she (1) had menstruated in the last 2 years (ARIC, JHS) or last 1 year (MESA) or (2) had a hysterectomy without oophorectomy and aged ≤55 years at the time of the interview. The selection of the covariates in this study was based on empirical evidence that shows confounding effects on the association of interest.[5,24,25] Detailed measurement procedures for the cohorts have been previously published[17,19,20] and are summarized in Appendix Table 2 (available online).

Statistical Analysis

Categorical covariates are presented as numbers with percentages, and continuous covariates are presented as means (SD). The association of pre-DM, undiagnosed T2D, and CVD outcomes was evaluated using the Cox proportional hazards models adjusting for baseline covariates (mentioned earlier). Because the aim of this study is to evaluate the long-term relationship between pre-DM or undiagnosed diabetes (DM) status at baseline and CVD risk, we used fixed-covariate Cox regression.[26] The proportional hazards assumption was verified before the regression. The sex-modifying effect of the association was tested by adding an interaction term, sex X pre-DM or sex X undiagnosed T2D in the fully adjusted models, followed by sex-stratified analyses. p-interaction≤0.2 was deemed to be statistically significant. Race-stratified analysis was also performed following the overall analysis. All analyses were performed using SAS 9.4 in 2023 (SAS Institute, Inc, Cary, NC).

RESULTS

Among 18,745 CVD-free individuals without a previous T2D diagnosis at baseline, 8,920 (47%) were normoglycemic; 8,518 (45%) had pre-DM; and 1,307 (7%) had undiagnosed DM. The mean age for the pre-DM or undiagnosed DM group was around 58 years. In both men and women with pre-DM, there were more Black individuals. More than half of undiagnosed women were White, whereas more than half of the undiagnosed men were Black. In both pre-DM and undiagnosed DM groups, more men had health insurance than women (92% vs 90% in pre-DM and 88% vs 83% in undiagnosed DM groups, respectively). In the undiagnosed group, more women were centrally obese than men (89% vs 82%). Women also had higher rates of

hypercholesterolemia in both pre-DM (59% vs 50%) and undiagnosed DM (63% vs 51%) groups. However, men had higher current smoking rates in both pre-DM (23% vs 20%) and undiagnosed DM (22% vs 16%) groups. Women had higher rates of using antihypertensive medications in both pre-DM (38% vs 31%) and undiagnosed DM (55% vs 42%) groups. More than 80% of women across glycemic status were postmenopausal in this study. Women with pre-DM had slightly higher HbA1c than men with pre-DM, whereas men with pre-DM or undiagnosed DM had higher FG than their female counterparts (Table 1). Men with pre-DM or undiagnosed DM at baseline had higher crude incident CHD or ASCVD during follow-up than their female counterparts ($p<0.0001$) (Table 1). Baseline characteristics in each cohort are presented in Appendix Table 3 (available online).

During a median follow-up of 18.6 years, in the fully adjusted analysis, pre-DM was significantly associated with a higher risk of CHD (hazard ratio [HR]=1.19, 95% CI=1.08, 1.31, $p=0.0003$) and ASCVD (HR=1.17, 95% CI=1.08, 1.27, $p=0.0002$) but not stroke (HR=1.12, 95% CI=0.97, 1.29, $p=0.1$) than normoglycemic individuals in the overall analysis (Figure 2). The HRs for pre-DM and CHD were 1.2 (95% CI=1.04, 1.37, $p=0.05$) in women and 1.16 (95% CI=1.03, 1.32, $p=0.01$) in men, respectively. The associations between pre-DM and higher risk of ASCVD were significant in women (HR=1.18, 95% CI=1.01, 1.24, $p=0.03$) and in men (HR=1.08, 95% CI=0.99, 1.28, $p=0.06$) (p-interactions$\leq$0.2) (Figure 2). When stratifying the analysis by race, the association between pre-DM and CVD outcomes in Whites was consistent with that in the race-combined analysis, with pre-DM associated with a stronger risk of CHD and ASCVD in women than in men (Appendix Figure 1A and B, available online). In Black individuals, those with pre-DM, especially women with pre-DM, appeared to have an increased risk of ASCVD, but the association did not reach statistical significance (Appendix Figure 1B, available online).

People with undiagnosed DM had a significantly higher risk of CHD (HR=1.75, 95% CI=1.5, 2.02, $p<0.0001$), stroke (HR=2.0, 95% CI=1.55, 2.49, $p<0.0001$), and ASCVD (HR=1.77, 95% CI=1.61, 1.94, $p<0.0001$) than people with normoglycemia (Figure 3). The associations between undiagnosed T2D and CVD outcomes were significant in both sexes. The effect of undiagnosed T2D on CVD risk was more pronounced in women (all p-interactions$\leq$0.2) (Figure 3). Undiagnosed T2D was associated with an 83% higher risk of CHD (95% CI=1.4, 2.41, $p<0.0001$), 99% higher risk of stroke (95% CI=1.39, 2.72, $p<0.0001$), and 86% higher risk of ASCVD (95% CI=1.5, 2.28, $p<0.0001$) in women. In men, the risk was 60% higher for CHD (95% CI=1.38, 2.07, $p=0.007$), 81% higher for stroke (95% CI=1.36, 2.6, $p<0.0001$), and 65% higher for ASCVD (95% CI=1.4, 1.98, $p<0.0001$) among those with undiagnosed T2D than among normoglycemic participants (Figure 3). In the race-stratified analysis, among Whites, a significant risk of all CVD outcomes associated with the undiagnosed T2D, and a marked sex difference in the associations (all p-interaction$\leq$0.2) was observed (Appendix Figure 2A, available online). In Black individuals, undiagnosed T2D was associated with a significantly higher risk of CVD outcomes, with women showing a higher magnitude of risk than men. However, statistical significance for sex difference was only evident in the association between undiagnosed DM and risk of stroke (p-interaction=0.1) (Appendix Figure 2B, available online).

In further stratified analysis by major cardiovascular risk factors, central obesity was found to be a significant effect modifier for the sex differential risk associated with pre-DM or undiagnosed DM. That is, women with pre-DM or undiagnosed who were also centrally obese at baseline had a stronger association with the risk of ASCVD than their male counterparts (Appendix Table 4, available online).

DISCUSSION

In this pooled prospective cohort analysis, after accounting for sociodemographics, concomitant risk factors, and menopausal status, a significant association between pre-DM and risk of ASCVD in women but not in men was found. This highlights the effect modification of the female sex in the relationship between pre-DM and cardiovascular complications, which can be explained by intrinsic biological sex differences and sex differential in risk factor management. Women are more insulin sensitive than men.[27] The findings support the notion that women must experience a greater overall metabolic deterioration; that is, they must accumulate more fat and experience greater insulin resistance and related risk factors to evolve from normoglycemia to T2D.[27] Women's higher diabetic CVD risk than that of men is in part due to their greater and more prolonged decline in metabolic homeostasis during the pre-DM stage.[4,28]

Among biological risk factors, central adiposity plays a central role in the sex differences of CVD associated with T2D. Previous findings suggest that central obesity conferred a greater excess risk of MI in women than in men.[29,30] In addition, emerging evidence suggests that central obesity and associated metabolic dysfunction suppresses women's protective effect of sex hormones on CVD.[31,32] Indeed, in the additional analysis stratified by central obesity, the effect of pre-DM on ASCVD was more pronounced in women than in men. This further suggests the more profound implication of central

Table 1. Baseline Characteristics of Study Participants by Sex and Glycemic Status

	Normoglycemia (*n*=8,920, 47.6%)			Pre-DM (*n*=8,518, 45.4%)			Undiagnosed (*n*=1,307, 7.0%)		
Characteristics	**Women (5,441, 61%)**	**Men (3,479, 39%)**	***p*-value**	**Women (4,381, 51.4%)**	**Men (4,137, 48.6%)**	***p*-value**	**Women (686, 52.5%)**	**Men (621, 47.5%)**	***p*-value**
Age (years) mean±SD	56.1±9.5	57.0±9.9	0.002	58.1±8	58.2±8	0.7	58.1±7.7	59.1±8.2	0.03
Race/ethnicity, *n* (%)			<0.0001			<0.0001			<0.0001
White	1,524 (28%)	923 (26.5%)		1,625 (37.1%)	1,165 (28.2%)		362 (52.8%)	233 (37.5%)	
Black	3,370 (61.9%)	2,069 (59.5%)		2,434 (55.6%)	2,663 (64.37%)		262 (38.2%)	322 (51.9%)	
Others	547 (10.1%)	487 (14%)		322 (7.4%)	309 (7.5%)		62 (9%)	66 (10.6%)	
Education; less than high school, *n* (%)	902 (16.6%)	590 (16.9%)	0.6	765 (17.46%)	688 (16.63%)	0.3	162 (23.6%)	151 (24.3%)	0.8
Insured, *n* (%)	5,043 (92.7%)	3,210 (92.3%)	0.5	3,965 (90.5%)	3,815 (92.2%)	0.005	567 (82.6%)	549 (88.4%)	0.001
Central obesity, *n* (%)	3,121 (57.4)	1,822 (52.4)	<0.0001	3,302 (75.4)	3,185 (76.9)	0.08	613 (89.3%)	506 (81.5%)	<0.0001
Total cholesterol ≥200 mg/dL, *n* (%)	2,883 (53%)	1,436 (41.3%)	<0.0001	2,573 (58.7%)	2,046 (49.5%)	<0.0001	432 (62.9%)	318 (51.2%)	<0.0001
Hypertension (SBP≥140 or DBP≥90 mmHg), *n* (%)	803 (14.8%)	554 (15.9%)	0.13	838 (19.1%)	829 (20%)	0.28	188 (27.4%)	187 (30.1%)	0.28
Current smoker, *n* (%)	825 (15.2%)	614 (17.6%)	0.002	885 (20.2%)	951 (23%)	0.002	111 (16.2%)	134 (21.6%)	0.01
Antihypertensive medication, *n* (%)	1,344 (24.70%)	822 (23.63%)	0.24	1,665 (38%)	1,261 (30.5%)	<0.0001	376 (55.3%)	258 (41.7%)	<0.0001
Lipid-lowering medication, *n* (%)	289 (5.31%)	262 (7.53%)	<0.0001	286 (6.5%)	227 (5.5%)	0.05	37 (5.4%)	48 (7.7%)	0.09
Menopausal status, *n* (%)			<0.0001			<0.0001			<0.0001
Pre/perimenopausal	901 (18.8%)	NA		486 (12.5%)	NA		65 (10.7%)	NA	
Postmenopausal	3,885 (81.2%)	NA		3,414 (87.5%)	NA		543 (89.3%)	NA	
HbA1c, %, mean±SD	5.2±0.3	5.2±0.3	0.06	5.7±0.4	5.6±0.4	<0.0001	7.0±1.4	7.0±1.5	0.7
Fast glucose (mg/dL), mean±SD	88.9±7.4	90.0±6.9	<0.0001	102.6±10.3	104.9±9.6	<0.0001	142.3±45.5	148.7±52.1	0.02
Outcome, *n* (%)									
CHD	352 (6.5%)	418 (12%)	<0.0001	439 (10%)	834 (20.1%)	<0.0001	97 (14.1%)	164 (26.4%)	<0.0001
Stroke	195 (3.6%)	141 (4.1%)	0.26	230 (5.3%)	263 (6.3%)	0.05	59 (8.6%)	63 (10.1%)	0.3
ASCVD	518 (9.5%)	520 (14.9%)	<0.0001	621 (14.2%)	1,025 (24.7%)	<0.0001	143 (20.8%)	201 (32.3%)	<0.0001

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; DBP, diastolic blood pressure; NA, not available; pre-DM, prediabetes; SBP, systolic blood pressure.

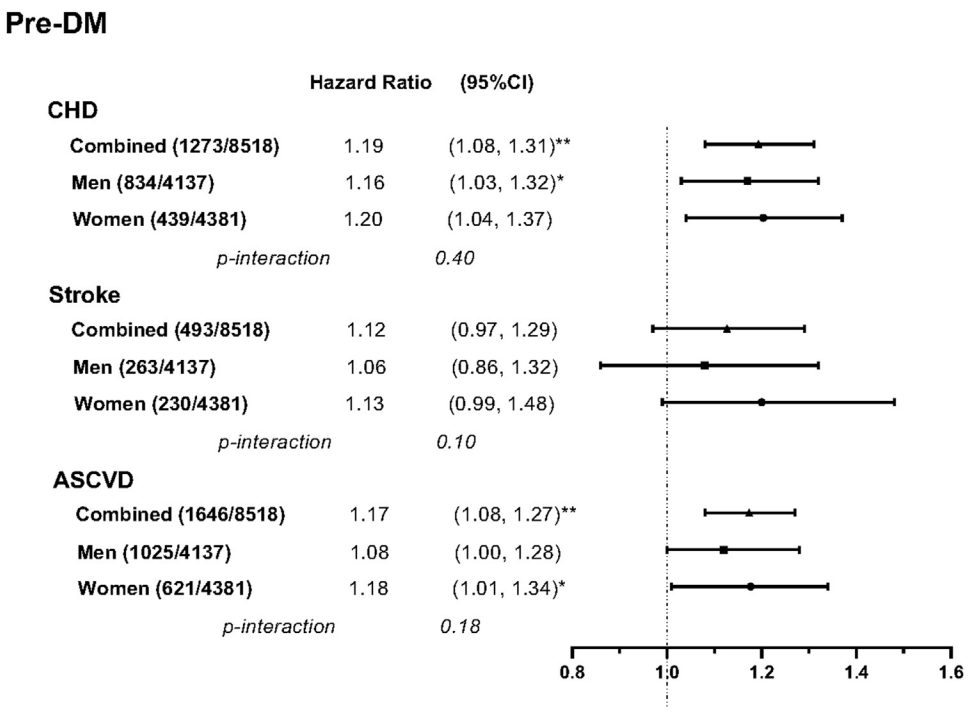

Figure 2. Adjusted hazard ratios of pre-DM and risk of CVD outcomes by sex.
Adjusted for age, race/ethnicity, health insurance status, central obesity, hypertension, hypercholesterolemia, current smoking status, antihypertensive medication use, lipid-lowering medication use, and menopause status (women only). *p<0.05 and **p<0.001.
ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; pre-DM, prediabetes.

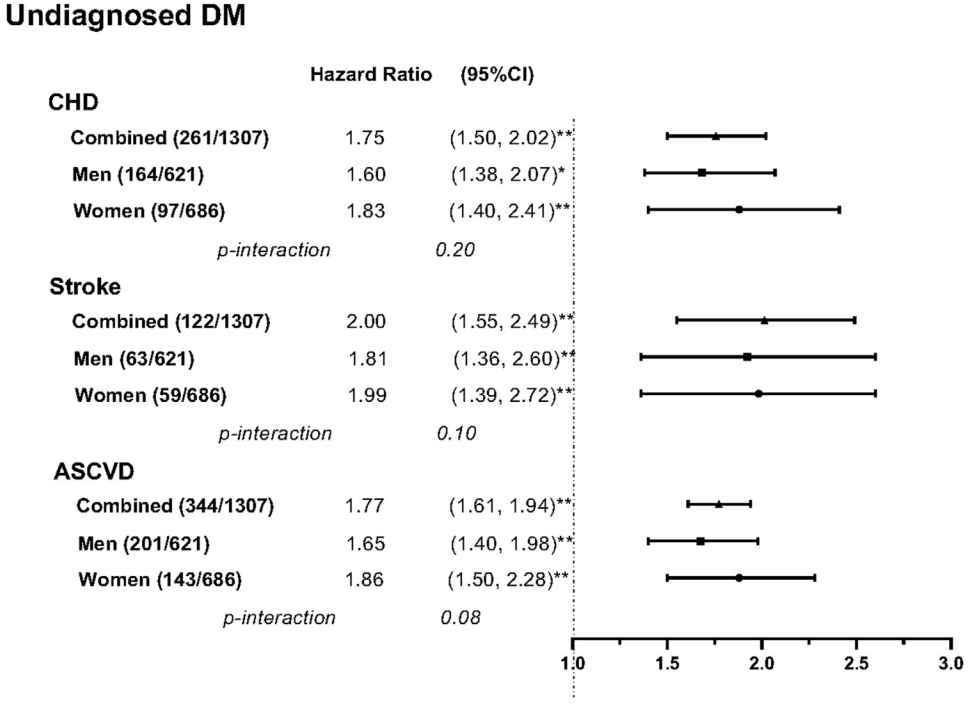

Figure 3. Adjusted hazard ratios of undiagnosed diabetes and risk of CVD outcomes by sex.
Adjusted for age, race/ethnicity, health insurance status, central obesity, hypertension, hypercholesterolemia, current smoking status, antihypertensive medication use, lipid-lowering medication use, and menopause status (women only). *p<0.05 and **p<0.001.
ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; pre-DM, prediabetes.

obesity in the pathogenesis of CVD in women than in men. Other pathophysiologic factors also play a role in the sex differences in CVD risk with pre-DM. For example, glucose intolerance is more prominently related to the increase in left ventricular hypertrophy in women than in men through obesity and pressure overload.[33] Correspondingly with the traditional risk markers, progression from normal glucose metabolism to T2D in women was associated with a greater degree of dysregulated fibrinolysis and coagulation than in men.[3]

The findings also reflect poor risk factor management among women with pre-DM and urge a more robust effort to promote health education and management. Clinicians and patients may be less aware of the adverse cardiovascular consequences of pre-DM and less likely to prescribe or seek interventions to control risk factors.[34,35] Despite the American Diabetes Association's recommendation for metformin use among people with pre-DM, the prevalence of its use is extremely low (<1%).[34] One Danish cohort study reported that people with HbA1c ranges of 6.2%−6.4% had a significantly higher risk of major cardiovascular events and all-cause mortality than those who reached the T2D diagnosis threshold (6.5%−6.6%), indicating a missed opportunity to prevent complications in pre-DM with the available treatment.[35] These results suggest that the female sex is a factor for therapeutic consideration in addition to lifestyle changes during the pre-DM stage. Additional studies are warranted to examine the potential cardiovascular benefits of multifactorial treatment in pre-DM with a sex-specific perspective.

The second principal finding of this study is that undiagnosed T2D is associated with a more pronounced CVD risk in women than in men. The undiagnosed or delayed diagnosis of T2D, resulting in a prolonged untreated period, is detrimental to T2D prognosis, but sex differences in the undiagnosed T2D and CVD outcomes were scantly reported. A previous study found that CVD death rates were 7 times higher in individuals without a timely diagnosis and early intervention for T2D than in those with the diagnosis and intervention.[13] It is recognized that women receive fewer diagnoses than men in cardiometabolic disease, which is attributed to the inequitable screening and care between sexes.[36] Notably, one study found that even if screening occurs, diagnosis delays still exist, particularly in women.[37] Nearly one third of participants with electronic medical record−documented hyperglycemia was not clinically diagnosed within 1 year, raising questions about patients' health literacy, interaction and engagement with the healthcare system, and advances in the electronic medical record to trigger the documentation and subsequent care options.[37] The risk of CVD with undiagnosed T2D may also result from sex inequalities in clinical inertia, which refers to the failure to initiate or intensify treatment promptly according to evidence-based guidelines.[12] The findings of this study resonate with previous studies that identified missed opportunities for timely diagnosis of T2D in women and showed significant CVD risk with the undiagnosed T2D status.

Limitations

Several limitations merit mentioning. First, none of the 3 cohorts had a baseline measure of oral glucose tolerance. Therefore, this criterion cannot be integrated into defining pre-DM and undiagnosed T2D. It has been reported that women are more responsive to oral glucose tolerance tests.[27] It is speculated that an underestimated prevalence of pre-DM and undiagnosed T2D among women in this study probably resulted in a conservative estimation of CVD risk in women with pre-DM or undiagnosed T2D. In addition, finer ethnic subgroup stratification could not be examined owing to insufficient counts. Moreover, residual confounding from unmeasured covariates (e.g., length of pre-DM or undiagnosed DM) may not be adjusted for in the analysis. Furthermore, the observational nature of the study precludes causal inference.

Despite the limitations, this study used 3 large, long-running, and well-characterized community-based cohorts, which provides sufficient power to investigate sex differences in CVD risk associated with pre-DM and undiagnosed T2D. The inclusion of both White and Black participants from varied geographic origins provides more representative estimates. This study shows a significant association between pre-DM and ASCVD risk in women, providing additional evidence for a biological link between intermediate hyperglycemia and CVD independent of concomitant metabolic risk factors. This study also showed a stronger association between undiagnosed T2D and CVD risk in women, suggesting female-specific issues in diagnosis and treatment delay. This study is among the first to underscore sex disparities in CVD risk in people with pre-DM or undiagnosed T2D, 2 hidden subgroups significantly challenged by inadequate risk factor management.

CONCLUSIONS

Pre-DM and undiagnosed T2D play a more prominent role in the risk of CVD in women than in men. Additional prospective studies in broader populations need to validate these results. The empirical evidence will likely support sex-specific guidelines in the diagnosis and treatment of T2D.

ACKNOWLEDGMENTS

The authors thank other investigators, the staff, and the participants of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study for their contribution. We also thank the staff of the National Heart, Lung and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center for their coordination of our data access.

This project was supported by a grant (NIH K12HD043451) from the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the Building Interdisciplinary Research Careers in Women's Health Scholar and a grant from the American Heart Association (23CDA1054444). FMJ was supported by NIH grants (DK107444 and DK074970), a U.S. Department of Veterans Affairs Merit Award (BX003725), and the Tulane Center of Excellence in Sex-Based Biology & Medicine.

YY designed the study and contributed to the data management and analysis; to the result interpretation; and to the drafting, reviewing, and editing of the manuscript. ZC contributed to data management, analysis, and figure making. VAF and FMJ provided critical comments on the study and reviewed and edited the manuscript. YY 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.

No financial disclosures were reported by the authors of this paper.

CREDIT AUTHOR STATEMENT

Yilin Yoshida: Conceptualization, Data curation, Formal analysis, Writing — original draft, Supervision. Zhipeng Chen: Formal analysis. Vivian A. Fonseca: Writing — review & editing. Franck Mauvais-Jarvis: Writing — review & editing.

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2023.05.011.

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