**Introduction:** Women of reproductive age are less prone to cardiovascular disease (CVD) than men, partly because of the cardioprotection of estrogens. However, diabetes mellitus (DM) negates this female advantage. Of note, women can develop CVD with a lower glucose level than men and may be at a higher risk of CVD associated with prediabetes (pre-DM). Women are more likely to have undiagnosed DM than men because of inequitable healthcare access.
and screening and lower disease risk awareness. Untreated DM is associated with a higher mortality risk and CVD hospitalization than diagnosed/controlled DM. Among individuals with pre-DM or undiagnosed DM, the raised cardiometabolic risk factors are likely to go undetected and untreated, contributing to future risk of CVD, particularly in women. Understanding of cardiovascular complications in DM and the sex difference in diabetic CVD are primarily based on late middle-aged and elderly cohorts.

Premenopausal women with pre-DM or DM may already have accumulated more pronounced cardiometabolic risks than men of the same age, which is yet to be verified. Furthermore, the prevalence change of pre-DM and DM among premenopausal women has not been clearly described. This study examined the 20-year trends of pre-DM, diagnosed DM, and undiagnosed DM and associated cardiometabolic risk factors in premenopausal women compared with those in age-matched men and postmenopausal women.

METHODS

Data were drawn from the National Health and Nutrition Examination Survey (NHANES) (1999–2000 to 2017–2018). The study included men and nonpregnant women aged 20–84 years with information on DM measurements, menopause status (women), and other key covariates. For regression analysis, we excluded those with a previous history of CVD (Figure 1, available online).

Premenopausal status was defined as having regular periods over the last 12 months, not having regular periods owing to menopause (i.e., pregnancy; breastfeeding; medical conditions/treatments, including contraceptive use), or being aged <41 years. A lower limit of 41 years was chosen for premenopause because the average age of menopause in the U.S. is 51 years and because perimenopause may last up to 10 years. Postmenopausal women in this study were those without regular periods over the last 12 months owing to menopause.

Diagnosed DM was self-reported. For those without a diagnosis, fasting glucose (FG) ≥126 mg/dL, HbA1c ≥6.5% (FG and HbA1c were available for all cycles), or oral glucose tolerance test ≥200 mg/dL (available from cycle 2005–2006 to 2017–2018) was classified as undiagnosed DM. Pre-DM was defined by FG of 100–126 mg/dL, HbA1c of 5.7%–6.5%, or oral glucose tolerance test of 140–200 mg/dL. Outcomes included obesity (BMI ≥30 kg/m²), central obesity (waist circumference ≥102 cm in men and ≥88 cm in women), hypercholesterolemia (total cholesterol ≥240 mg/dL), hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), and hypertriglyceridemia (triglycerides ≥200 mg/dL).

The study calculated the age-adjusted prevalence of pre-DM, diagnosed DM, and undiagnosed DM by the direct methods of the 2000 U.S. Census standard population. Multivariable logistic regressions were performed for the association between cardiometabolic risk factors and pre-DM, diagnosed DM, and undiagnosed DM in premenopausal women; age-matched men (1:1 match; Appendix Text 1, available online); and postmenopausal women adjusted for age, race/ethnicity, education, income, insurance, smoking, BMI, total calorie intake, physical activity, and use of any antihypertensive or lipid-lowering medications. The study employed survey-related commands to adjust for the complex survey design effect. The primary sampling unit and stratum for each observation were considered in the analyses. SAS, Version 9.4 (SAS Institute Inc, Cary, NC), was used for analysis.

RESULTS

In women of reproductive age, nearly 1 in 4 had pre-DM, 5.2% had diagnosed DM, and 2.5% had undiagnosed DM (Appendix Tables 1 and 2, available online). The result showed an increased prevalence of pre-DM in premenopausal women, rising from 20% in years 2005–2008 to 28% in the years 2015–2018, contrasting with the high but steady trend of pre-DM in all adults (~34.5%). The prevalence of undiagnosed DM in premenopausal women doubled from the years 1999–2002 (1.7%) to the years 2015–2018 (3.5%) as opposed to a slight decline in all adults (3.1%–2.9%). Diagnosed DM steadily increased in premenopausal women (Figure 1).

In adjusted analysis, premenopausal women with pre-DM were associated with an almost threefold risk of obesity (OR=2.8; 95% CI=2.1, 3.7) and central obesity (OR=2.8; 95% CI=2, 3.9) compared with those with normoglycemia; the magnitude of the association was less pronounced in age-matched men or postmenopausal women. Undiagnosed DM was associated with more than fourfold obesity risk in premenopausal women (obesity OR=5.4, 95% CI=2.6, 11.4; central obesity OR=4, 95% CI=1.2, 12.9) and men (obesity OR=4.8, 95% CI=1.8, 12.6; central obesity OR=4.6, 95% CI=2, 10.2) and with twofold obesity risk in postmenopausal women (obesity OR=2, 95% CI=1.3, 3.2; central obesity OR=2.6, 95% CI=1.3, 4.7). The magnitude of the association between diagnosed DM and obesity/central obesity was greater in premenopausal women than in age-matched men or postmenopausal women (Figure 2).

The association between undiagnosed DM and hypertension was significant in premenopausal women only (OR=2.1; 95% CI=1.1, 4.2), whereas the association between pre-DM and hypertension was significant in age-matched men only. Pre-DM was associated with hypertriglyceridemia risk in premenopausal women (OR=2.5; 95% CI=1.4, 4.4), age-matched men (OR=3.8; 95% CI=2.4, 6), and postmenopausal women (OR=4.1; 95% CI=1.7, 9.7). Undiagnosed DM was associated with hypertriglyceridemia risk in age-matched men (OR=3.1; 95% CI=1.3, 7.6) and postmenopausal women (OR=2.8; 95% CI=1.3, 6.6) but not in premenopausal women (Figure 2).
DISCUSSION

The study found upward trends of undiagnosed DM and pre-DM among premenopausal women. In all adults, a declining trend of undiagnosed DM is related to changes in diabetes diagnostic and screening practices. The increasing prevalence of undiagnosed DM and pre-DM in premenopausal women signals a lack of screening and low awareness of DM risk in this group relative to that in men of the same age and older women. In addition, the upward trends of pre-DM and DM in premenopausal women run parallel to the rising obesity in young

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Figure 1. Age-adjusted prevalence of (A) prediabetes, (B) diagnosed diabetes, (C) undiagnosed diabetes in premenopausal W and all adults, NHANES 1999−2000 to 2017−2018. NHANES, National Health and Nutrition Examination Survey; W, women.
and middle-aged adults, suggesting the need for a more robust effort to improve nutrition and physical activity in women of reproductive age.

Premenopausal women with pre-DM or DM face more cardiometabolic risk factors than those with normoglycemia. Notably, their risk profiles were equivalent to or even worse than those of men of the same age and postmenopausal women. Previous research suggests that obesity, hypertension, and dyslipidemia are concomitant risk factors in DM, and aggregation of these risk factors synergistically increases the risk of CVD. However, these findings were mainly derived from middle-aged or elderly cohorts. This study quantifies the extent to which pre-DM, diagnosed DM, and undiagnosed DM correlate with cardiometabolic risk factors in women of reproductive age and highlights the concerning cardiovascular consequences if risk factors are left uncontrolled. These findings, in part, explain women’s disadvantage in diabetic CVD in middle and late adulthood and suggest that the decline of cardiometabolic health in women starts as early as young adulthood.

Limitations
Limitations of this study included self-reported menopausal status. In addition, the cross-sectional design of NHANES precludes quantifying future CVD risk in premenopausal women.

CONCLUSIONS
Although premenopausal women have a lower prevalence of pre-DM, DM, and undiagnosed DM, all the 3 conditions have been increasing at a greater rate among women of reproductive age than among the overall adult population. Premenopausal women face a significant cardiovascular risk burden associated with pre-DM and DM. This study indicates the need to increase cardiometabolic risk screening and improve patient education about the risks and consequences of pre-DM and DM in women of reproductive age.

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SUPPLEMENTAL MATERIAL
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REFERENCES


