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Original Article

Female-specific risk factors of parity and menopause age and risk of carotid plaque: the multi-ethnic study of atherosclerosis

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Abstract: Background: Female-specific factors of grand multiparity (≥5 births) and early menopause age are associated with an increased risk of cardiovascular disease (CVD). However, mechanisms are incompletely understood. Carotid plaque is a marker of subclinical atherosclerosis and associated with increased CVD risk. We evaluated the association of female-specific factors with plaque burden. Methods: We included 2,313 postmenopausal women in the Multi-Ethnic Study of Atherosclerosis, free of clinical CVD, whose parity and menopause age were ascertained by questionnaires and carotid plaque measured by ultrasound at baseline and 10 years later. Parity was categorized as nulliparity (reference), 1-2, 3-4 and ≥5 live births. Menopause age was categorized as <45, 45-49, 50-54 (reference) and ≥55 years. Multivariable regression was performed to evaluate the association of parity and menopause age with carotid plaque presence (yes/no) and extent [carotid plaque score (CPS)]. Results: The mean age was 64±9 years; 52.3% had prevalent carotid plaque at baseline. Compared to nulliparity, grand multiparity was significantly associated with prevalent carotid plaque after adjustment for CVD risk factors (prevalence ratio 1.17 (95% CI 1.03-1.35)) and progression of CPS over 10 years [percent difference 13% (95% CI 3-23)]. There was not any significant association of menopause age with carotid plaque presence or progression in fully-adjusted models. Conclusion: In a multiethnic cohort, grand multiparity was independently associated with carotid plaque presence and progression. Early menopause, a known risk factor for CVD, was not captured by carotid plaque in this study. These findings may have implications for refining CVD risk assessment in women.

Keywords: Parity, menopause age, carotid plaque, subclinical atherosclerosis, risk factors, women, cardiovascular disease prevention

Introduction

Cardiovascular disease (CVD) is the leading cause of death globally [1]. Despite progress in understanding and addressing many traditional risk factors contributing to CVD, myocardial infarction and CVD mortality rates have been increasing in younger women <65 years in the United States (U.S.) [2-4]. While CVD affects both women and men, the frequency, time of onset, and severity may differ between sexes [1, 5, 6]. Women generally have a worse prognosis, higher rates of hospitalization, and higher mortality after cardiovascular events than men [6-9]. Certain well-known risk factors, such as diabetes mellitus and smoking, impact women more than men. Additionally, female-specific factors, such as age at menarche, parity, adverse pregnancy outcomes, age at menopause, and sex hormones all play a significant

role in a woman's probability of developing CVD [10-22]. An increased awareness of how these sex-specific risk factors impact the risk of CVD among women is pertinent to decreasing morbidity and mortality in women [23].

Parity, or the number of live births, has been identified as a risk factor of CVD. Multiparity, particularly grand multiparity (most commonly defined as ≥5 live births), has been independently associated with incident atherosclerotic CVD even after adjusting for traditional risk factors [13, 24-26]. We previously showed in the Multi-Ethnic Study of Atherosclerosis (MESA) that women with a history of grand multiparity were less likely to be in optimal cardiovascular health, as defined by American Heart Association's Life Simple 7 metrics, at middle and older ages, and were more likely to have elevated body mass index (BMI), compared to nulliparous women [27].

Menopause is diagnosed clinically by 12 consecutive months of amenorrhea [28]. Postmenopausal women have an increased risk for CVD compared to pre-menopausal women [15, 16, 22, 29, 30]. In addition to the effect of menopause itself, the age of onset of menopause is important in evaluating the risks for different diseases. The average age of menopause occurs at around 52 years old. Early onset menopause is defined as occurring before 45 years of age (and premature menopause as before 40 years), while late onset menopause is defined as occurring after 55 years of age [29]. Various studies have noted that earlier onset menopause is associated with an increased risk for CVD and mortality [15, 16, 22, 29, 30].

Detection of subclinical atherosclerosis, an early sign of atherosclerotic presence visualized on imaging techniques before CVD is clinically manifested, is important for early initiation of preventive therapies [31]. Carotid intima media thickness (IMT) and carotid plaque score are commonly used surrogates for CVD risk [32-34] with carotid plaque representing atherosclerosis [33, 35]. Carotid plaque is often present even before the development of calcified coronary plaque and therefore may be a greater predictor of CVD risk as evidenced in prior MESA studies [33]. The presence of carotid plaque predicts incident CVD even among individuals with a coronary artery calcium (CAC) score of 0 [35]. At any given age, women are more likely to have CAC scores of 0 than men [36]. Previously in MESA, we showed that >50% of middle-aged post-menopausal women with a history of early menopause had a CAC score of 0, similar to those without early menopause [37]. Thus, the identification of carotid plaque may represent an opportunity for early implementation of CVD preventive therapies (i.e. statins) and more targeted lifestyle modifications in women.

This study aims to determine if there is an association between female-specific factors, specifically, multiparity and menopause age, and carotid plaque in women enrolled in the MESA study.

Material and methods

Data availability statement

Data from the MESA study can be requested through the NIH BioLincc Open program at: https://biolincc.nhlbi.nih.gov/studies/mesa/.

Study population

The MESA study registered 6,814 men and women free of CVD at the baseline exam (2000-2002). The participants were aged 45-84 years and were from six centers across the U.S. (Johns Hopkins University, Baltimore, Columbia University, New York, Northwestern University, Chicago, UCLA, Los Angeles, University of Minnesota, Twin Cities, and Wake Forest University, Winston Salem). Participants were followed longitudinally for CVD events. In addition, participants returned for up to 5 additional study visits [MESA Exam 2 (2002-2004), Exam 3 (2004-2005), Exam 4 (2005-2007), Exam 5 (2010-2012), and Exam 6 (2016-2018)]. Detailed descriptions of the MESA study design have been previously published [38].

In this study, we included 2,313 postmenopausal women, free of CVD at baseline, who had complete data on parity, menopause age and carotid ultrasound studies with determination of plaque score at baseline exam. **Figure 1** shows the inclusion and exclusion criteria used to arrive at this sample number. Participants were consented for each MESA study, and the MESA study protocols were approved at each field center by the respective institutional review boards.

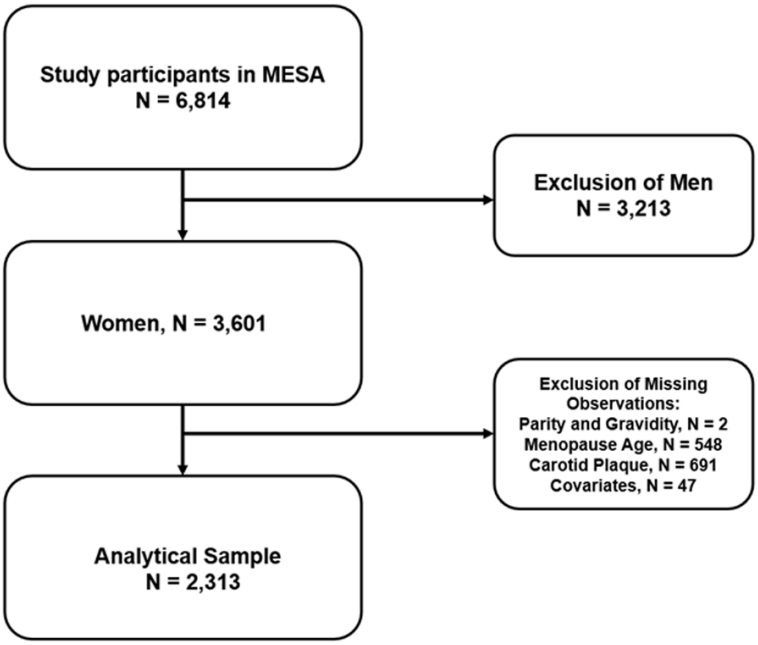

Figure 1. Flowchart of study participants.

Independent variables (parity and menopause age)

Both parity and menopause age were self-reported at the MESA baseline exam assessed in 2000-2002. We used previously established algorithms in MESA for both parity [27, 39] and menopause age [18, 40] to address any incongruities in the self-reported data. Parity was classified consistent with prior MESA studies as follows: nulliparity (reference), 1-2, 3-4 and ≥5 live births. Menopause age was categorized as <45, 45-49, 50-54 (reference) and ≥55 years [27]. It should be noted that other important female-specific factors such as adverse pregnancy outcomes like preeclampsia were not assessed in the MESA cohort, so *a priori,* we decided to focus on parity and menopause age as our exposure variables of interest. We also examined gravidity (number of pregnancies) in a supplemental analysis.

Outcome variable (carotid plaque)

Carotid plaque was measured at baseline exam (2000-2002), and again at MESA Exam 5 (2010-2012). B-mode ultrasonography of the bilateral common, bifurcation, and internal carotid artery segments was performed. The presence of carotid plaque was defined as a focal abnormal wall thickness (IMT >1.5 mm) or a focal thickening of >50% of the surrounding IMT [33, 39]. One point was allocated for plaque in each segment assessed which included the common carotid artery near wall, common carotid artery far wall, carotid bulb near wall, carotid bulb far wall, internal carotid near wall, internal carotid far wall, for both the right and left carotid arteries [35, 41]. A total plaque score (range 0-12) was calculated to describe the total carotid plaque burden.

Covariates

Covariates were assessed at baseline exam and included age, race/ethnicity, study site, education, cigarette smoking status, physical activity, menopause status, current use of menopausal hormone therapy, BMI (in kg/m^2), systolic blood pressure, hypertension medication use, total cholesterol, high-density lipoprotein cholesterol (HDL-C), use of lipid-lowering medications, and diabetes.

The information on the participant's age, race/ethnicity, education, smoking status, and physical activity were assessed through the use of questionnaires. Physical activity was estimated using the 28-item Typical Week Physical Activity Questionnaire. Medication use was evaluated through inventory. BMI was calculated by dividing weight by squared height (kg/m^2). Diabetes status was identified by self-report, the use of diabetes medications, or having a fasting blood glucose level of ≥126 mg/dL. Blood pressure was measured using the average of the last 2 out of 3 blood pressure readings using a Dinmap automated device in the seated position.

Statistical analysis

Carotid plaque presence was defined as having a carotid plaque score (CPS) >0 at the baseline exam. Carotid plaque incidence was defined as CPS >0 at exam 5 among individuals with a

CPS = 0 at baseline. For the extent and progression analyses, all participants were included, including those with CPS = 0 at baseline, and for progression analysis, we evaluated the change in the CPS including new plaque or increase in plaque score. Given its skewed distribution, the CPS was natural log-transformed for the analyses of carotid plaque extent and progression and examined as ln (CPS + 1), as has been done in prior MESA analyses [35].

To analyze the association between the female-specific risk factors (parity and menopause age) and carotid plaque presence, prevalence ratios were derived from multivariable adjusted Poisson regression models with robust variance estimation. Similarly, for incident carotid plaque, incident rate ratios were also derived from Poisson regression models with robust variance estimation.

The associations of the female-specific risk factors (parity and menopause age) with the baseline extent and progression of carotid plaque were calculated using multivariable-adjusted linear mixed effects regression models using the log-transformed CPS. The beta-coefficients were then exponentiated by the formula [Exp (β) - 1] *100 to express as percent differences. Linear mixed effect analyses allow for both baseline and longitudinal changes in plaque scores to be accounted for from all available time points, and these methods have been used previously in MESA [42-45].

Models were progressively adjusted as follows: Model 1 adjusted for demographics (age, race/ethnicity) and study site. Model 2 adjusted for model 1, in addition to lifestyle and physiologic factors (education, smoking, physical activity, BMI, menopause status, and current use of hormone therapy). Lastly, model 3 adjusted for model 2 + CVD risk factors and medications (total cholesterol, HDL-C, use of lipid-lowering medication, systolic blood pressure, use of anti-hypertensive medication and diabetes). In the analysis for menopausal age and carotid plaque, only post-menopausal women were included and thus menopause status was excluded from model 2.

Statistically significant results were defined as $P<0.05$. Analyses were performed using Stata Version 16.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 2,313 women included in this study, overall, and by the presence or absence of carotid plaque at the baseline exam. The mean age of the participants was 64 + 9 years, and the race/ethnicity profile was 38% White, 28% Black, 12% Chinese, and 22% Hispanic. Among the participants, 17%, 38%, 30%, and 15% had a history of 0, 1-2, 3-4 and ≥5 live births, respectively. In addition, 23%, 29%, 36%, and 12% reached menopause at an age <45, 45-49, 50-54, ≥55 years old, respectively.

There were 1,209 (52.3%) participants with prevalent carotid plaque at baseline exam. In unadjusted analysis, factors associated with carotid plaque presence included grand multiparity (≥5 live births), early (<45 years) and late (≥55 years) menopause age, older baseline age, current smoking, higher systolic blood pressure, greater use of antihypertensive medications, higher total cholesterol, greater use of lipid-lowering therapy, and the presence of diabetes (**Table 1**).

Association between parity and carotid plaque

The adjusted associations of parity groups with the presence of carotid plaque (yes/no) are shown in **Table 2** and **Figure 2**. Compared to nulliparity, grand multiparity (≥5 live births) was significantly associated with the presence of carotid plaque after adjustment for demographic factors (age, race/ethnicity) and study site [prevalence ratio 1.19 (95% CI, 1.04, 1.36), model 1], and remained statistically significantly associated with carotid plaque presence even after further adjustment for lifestyle factors (model 2) and CVD risk factors (model 3). Parity was not associated with the extent of baseline carotid plaque (CPS assessed continuously) in adjusted models (**Table 3**).

Table 4 shows the association of parity and incident carotid plaque at exam 5 (n = 690), among women with an initial CPS = 0. There was a 38% greater incidence of carotid plaque at exam 5 among women with grand multiparity vs nulliparity; however this failed to reach statistical significance in fully-adjusted models

Table 1. Baseline characteristics of study participants by the presence and absence of carotid plaque

	Total, N = 2,313	Present, N = 1,209	Absent, N = 1,104	*P* value
Parity				0.001
0	389 (17%)	184 (15%)	205 (19%)	
1-2	882 (38%)	446 (37%)	436 (39%)	
3-4	700 (30%)	368 (30%)	332 (30%)	
≥5	342 (15%)	211 (17%)	131 (12%)	
Menopausal age, years				0.020
<45	526 (23%)	285 (24%)	241 (22%)	
45-49	666 (29%)	329 (27%)	337 (31%)	
50-54	834 (36%)	424 (35%)	410 (37%)	
≥55	287 (12%)	171 (14%)	116 (11%)	
Age, years	64 (9)	66 (9)	61 (9)	<0.001
Race/ethnicity				<0.001
White	870 (38%)	502 (42%)	368 (33%)	
Chinese-American	285 (12%)	114 (9%)	171 (15%)	
Black	649 (28%)	346 (29%)	303 (27%)	
Hispanic	509 (22%)	247 (20%)	262 (24%)	
Education				0.003
≥ bachelor's degree	653 (28%)	309 (26%)	344 (31%)	
< bachelor's degree	1,660 (72%)	900 (74%)	760 (69%)	
Smoking status				<0.001
Never	1,348 (58%)	648 (54%)	700 (63%)	
Former	694 (30%)	390 (32%)	304 (28%)	
Current	271 (12%)	171 (14%)	100 (9%)	
Physical activity, MET-min/wk	3615 (1725, 6548)	3495 (1620, 6450)	3735 (1766, 6634)	0.145
BMI, kg/m^2	29 (6)	28 (6)	29 (6)	0.381
Menopause				0.009
Yes	2,245 (97%)	1,184 (98%)	1,061 (96%)	
No	68 (3%)	25 (2%)	43 (4%)	
Hormone therapy				0.083
Yes	747 (32%)	371 (31%)	376 (34%)	
No	1,566 (68%)	838 (69%)	728 (66%)	
Systolic blood pressure, mmHg	129 (24)	133 (24)	124 (22)	<0.001
Total cholesterol, mg/dL	201 (36)	203 (37)	199 (34)	0.002
HDL-C, mg/dL	57 (16)	57 (16)	56 (15)	0.495
Use of antihypertensive medication	945 (41%)	569 (47%)	376 (34%)	<0.001
Use of lipid-lowering medication	411 (18%)	280 (23%)	131 (12%)	<0.001
Diabetes	272 (12%)	178 (15%)	94 (9%)	<0.001

Abbreviations: BMI, body mass index; HDL-C, high density lipoprotein-cholesterol; MET; metabolic equivalent of task. Data were presented as mean (SD), median (IQR) or number (%).

[Incidence Ratio 1.38 (0.98, 1.95), model 3]. However, when all women were included (including those with CPS = 0 at baseline), grand multiparity was associated with greater plaque progression, compared to nulliparous women [percent difference in CPS progression of 13% (3, 23), model 3] (**Table 5**).

Association between menopause age and carotid plaque

There was no statistically significant association between menopause age and carotid plaque presence in any of the adjusted models (**Table 2** and **Figure 3**). Compared to women

Table 2. Association of parity and menopausal age with carotid plaque at baseline, N = 2,313

	Model 1	Model 2	Model 3
Prevalence ratio (95% CI)			
Parity			
0	Reference	Reference	Reference
1-2	1.11 (0.99, 1.25)	1.09 (0.97, 1.23)	1.08 (0.96, 1.22)
3-4	1.11 (0.98, 1.26)	1.10 (0.98, 1.25)	1.11 (0.98, 1.25)
≥5	1.19 (1.04, 1.36)	1.16 (1.01, 1.33)	1.17 (1.03, 1.35)
Menopausal age			
<45	1.04 (0.94, 1.15)	1.01 (0.92, 1.12)	0.99 (0.90, 1.09)
45-49	1.03 (0.93, 1.13)	1.01 (0.92, 1.12)	1.00 (0.91, 1.09)
50-54	Reference	Reference	Reference
≥55	1.08 (0.96, 1.21)	1.07 (0.96, 1.20)	1.04 (0.93, 1.17)

Prevalence ratios were derived from Poisson regression models with robust variance estimation. Statistically significant results at P<0.05 are in bold font. Model 1: demographics (age, race/ethnicity) and study site. Model 2: model 1 + lifestyle and physiologic factors (education, smoking, physical activity, BMI, menopause and current use of hormone therapy). Model 3: model 2 + CVD risk factors and medications (total cholesterol, HDL-C, use of lipid-lowering medication, systolic blood pressure, use of anti-hypertensive medication and diabetes). In the analysis for menopausal age and carotid plaque, menopause was excluded from model 2.

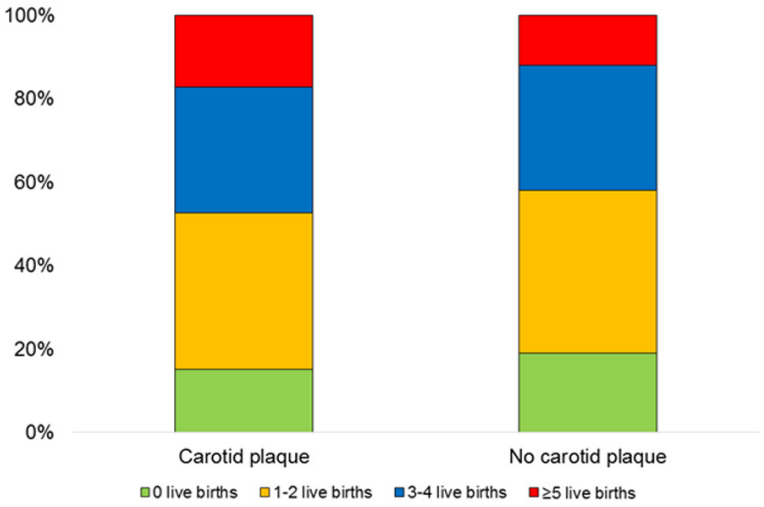

Figure 2. Distribution of the presence and absence of carotid plaque by parity categories among women of the Multi-Ethnic Study of Atherosclerosis. Parity was categorized as 0 live births, green; 1-2 live births, orange; 3-4 live births, blue and ≥5 live births, red.

with menopause age 50-54 years, women who reached menopause at an early age, <45 years old, had a statistically significant greater CPS at baseline, when adjusted for demographics (age, race/ethnicity) [percent difference 10% (2, 17) (model 1)] (**Table 3**). This remained significant after adjustment for lifestyle factors in model 2, but was attenuated and no longer statistically significant after further adjustment for CVD risk factors in model 3.

None of the menopause age groups were significantly associated with a greater risk of incident carotid plaque at exam 5 (**Table 4**) or greater carotid plaque progression (**Table 5**), compared to menopause age of 50-54 years.

Association of gravidity and carotid plaque

The association of gravidity and carotid plaque presence is shown in Table S1. Multigravidity status (≥5 pregnancies) was significantly associated with the presence of carotid plaque when adjusted for demographics [Prevalence Ratio 1.16 (1.01, 1.33) (model 1)], compared to women with null-gravidity. This association was attenuated when adjusted both for lifestyle factors in model 2 and CVD risk factors in model 3.

The association of gravidity and carotid plaque extent is shown on Table S2. Women with multigravidity had significantly greater extent of carotid plaque when adjusted for demographics [percent difference 10% (1, 21) (model 1)], but not in further adjusted models.

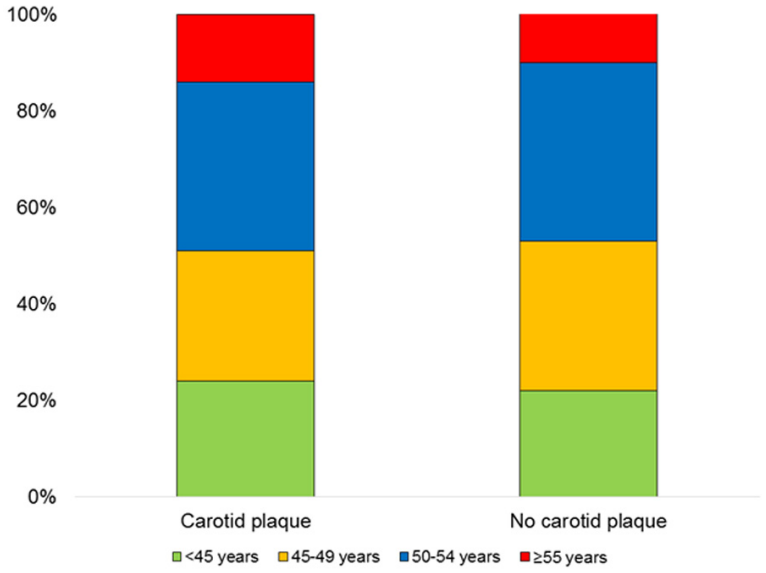

Figure 3. Distribution of the presence and absence of carotid plaque by menopausal age categories among women of the Multi-Ethnic Study of Atherosclerosis. Menopausal age was categorized as <45 years, green; 45-49 years, orange; 50-54 years, blue and ≥55 years, red.

Table 3. Association of parity and menopausal age with carotid plaque score at baseline, N = 2,313

	Model 1	Model 2	Model 3
Percent difference (95% CI)			
Parity			
0	Reference	Reference	Reference
1-2	7 (0, 15)	5 (-2, 13)	4 (-3, 12)
3-4	5 (-3, 13)	4 (-4, 12)	4 (-4, 12)
≥5	8 (-2, 19)	5 (-4, 16)	6 (-4, 16)
Menopausal age			
<45	10 (2, 17)	7 (0, 15)	6 (-1, 13)
45-49	6 (-1, 12)	4 (-2, 10)	3 (-3, 9)
50-54	Reference	Reference	Reference
≥55	4 (-5, 13)	3 (-5, 12)	2 (-6, 10)

Results were presented as percent difference of carotid plaque score at baseline derived from linear mixed effects regression models and calculated from [Exp (β) - 1] *100. Statistically significant results at P<0.05 are in bold font. Model 1: demographics (age, race/ethnicity) and study site. Model 2: model 1 + lifestyle and physiologic factors (education, smoking, physical activity, BMI, menopause and current use of hormone therapy). Model 3: model 2 + CVD risk factors and medications (total cholesterol, HDL-C, use of lipid-lowering medication, systolic blood pressure, use of anti-hypertensive medication and diabetes). In the analysis for menopausal age and carotid plaque, menopause was excluded from model 2. Interaction by BMI was not statistically significant: P = 0.911 for parity and P = 0.702 for menopausal age.

Discussion

In a multi-ethnic cohort of women, our principal finding was that a history of grand multiparity (≥5 live births) was associated with carotid plaque presence at baseline, as well as progression of carotid plaque score over 10-years, after adjustment for traditional CVD risk factors, compared to history of nulliparity. On the other hand, we did not observe an independent association of menopause age with carotid plaque presence or progression.

Many studies highlighting the risk factors leading to CVD fail to recognize the added unique sex-specific risks that women experience related to pregnancy, sex hormones, and menopause [11, 12]. This study highlights the association between female-specific factors, specifically multiparity and age of onset of menopause, and the presence and progression of carotid plaque. It should be noted that both parity and menopause age have been examined in prior studies with CAC [37, 46], so we decided *a priori* to focus on carotid plaque for our outcome variable of interest in this study. In the MESA cohort, parity had previously been associated with subclinical atherosclerosis as measured by the CAC score [46]. Additionally, in a prior MESA study, women who experienced early menopause had a slightly lower prevalence of a favorable CAC = 0 score (55.1%) compared to women without early menopause (59.7%) (P = 0.04) despite similar mean age. However, the presence of a zero CAC score was still common (>50%) in both groups [37].

Despite being more likely to have a CAC score of 0 and lower 10-year CVD risks compared to men at a given age, women still experience significant CVD risks over their lifetime [35]. A more accurate way of assessing cardiovascular

Table 4. Association of parity and menopausal age with incident carotid plaque at exam 5, N = 690

	Model 1	Model 2	Model 3
Incident rate ratio (95% CI)			
Parity			
0	Reference	Reference	Reference
1-2	1.13 (0.87, 1.48)	1.12 (0.86, 1.47)	1.14 (0.87, 1.49)
3-4	1.25 (0.95, 1.63)	1.27 (0.97, 1.67)	1.28 (0.97, 1.68)
≥5	1.34 (0.96, 1.88)	1.38 (0.98, 1.94)	1.38 (0.98, 1.95)
Menopausal age			
<45	0.99 (0.78, 1.27)	0.98 (0.77, 1.25)	0.99 (0.78, 1.26)
45-49	1.13 (0.92, 1.39)	1.12 (0.92, 1.37)	1.12 (0.92, 1.38)
50-54	Reference	Reference	Reference
≥55	1.08 (0.82, 1.43)	1.10 (0.83, 1.44)	1.09 (0.83, 1.43)

Incident rate ratios were derived from Poisson regression models with robust variance estimation. Incident carotid plaque was defined as carotid plaque score >0 at exam 5 among participants with carotid plaque score = 0 at baseline. Statistically significant results at P<0.05 are in bold font. Model 1: demographics (age, race/ethnicity) and study site. Model 2: model 1 + lifestyle and physiologic factors (education, smoking, physical activity, BMI, menopause and current use of hormone therapy). Model 3: model 2 + CVD risk factors and medications (total cholesterol, HDL-C, use of lipid-lowering medication, systolic blood pressure, use of anti-hypertensive medication and diabetes). In the analysis for menopausal age and carotid plaque, menopause was excluded from model 2.

Table 5. Association of parity and menopausal age with carotid plaque progression at exam 5, N = 2,313

	Model 1	Model 2	Model 3
Percent change (95% CI)			
Parity			
0	Reference	Reference	Reference
1-2	1 (-5, 9)	1 (-5, 9)	1 (-5, 9)
3-4	7 (0, 15)	7 (0, 15)	7 (0, 15)
≥5	13 (3, 23)	13 (3, 23)	13 (3, 23)
Menopausal age			
<45	-3 (-9, 4)	-3 (-9, 4)	-3 (-9, 4)
45-49	1 (-5, 7)	1 (-5, 7)	1 (-5, 7)
50-54	Reference	Reference	Reference
≥55	2 (-6, 11)	3 (-5, 11)	2 (-5, 11)

Results were presented as percent change of carotid plaque score at exam 5 derived from linear mixed effects regression models and calculated from [Exp (β) - 1] *100. Statistically significant results at P<0.05 are in bold font. Model 1: demographics (age, race/ethnicity) and study site. Model 2: model 1 + lifestyle and physiologic factors (education, smoking, physical activity, BMI, menopause and current use of hormone therapy). Model 3: model 2 + CVD risk factors and medications (total cholesterol, HDL-C, use of lipid-lowering medication, systolic blood pressure, use of anti-hypertensive medication and diabetes). In the analysis for menopausal age and carotid plaque, menopause was excluded from model 2.

risk in women is needed. Measuring carotid plaque is a noninvasive method of directly visualizing atherosclerosis and can detect non-calcified plaque without radiation exposure. Early detection of carotid plaque may be important for reducing CVD risk as lifestyle changes and preventive medications (i.e., statins) can be started earlier to prevent morbidity and mortality [34, 47].

Few studies have examined the association of parity with carotid plaque. A previous study of elderly Chinese women found a positive association between higher parity and greater risk for carotid artery plaques [48]. We now extend these findings in a multi-ethnic U.S. cohort of women. In this present study, we showed that women with a history of grand multiparity was significantly associated with carotid plaque presence and progression after full covariate adjustment. This is consistent with the literature showing grand multiparity is associated with poor cardiovascular health later in life [27] and greater future CVD risk [13, 24-26]. Carotid plaque may be an intermediary step between parity history and future CVD, and the detection of carotid plaque may present an opportunity to optimize CVD risk by initiating preventive therapies.

The mechanisms linking parity to atherosclerosis and future CVD are not fully elucidated. One mechanism linking the development of carotid plaque with parity may be the higher dehydroepiandrosterone (DHEA) and lower sex hormone binding globulin (SHBG) that results after

parity. We previously showed that women with grand multi-parity were more likely to have a more androgenic ("male-like") sex hormone pattern with higher testosterone to estradiol ratio [49]. A high DHEA and low SHBG have been associated with lower carotid artery distensibility and therefore, vascular remodeling leading to increased risk of carotid plaque progression [39].

Adiposity may be another possible link between multiparity and increased presence of carotid plaque, as obesity plays a key role in the development of atherosclerosis through the process of inflammation. This link between adiposity and CVD is hypothesized to be due to adipokines, signaling molecules released from adipose tissue, leading to an increase in insulin resistance, inflammation, and endothelial dysfunction [50]. Women tend to gain weight on average with each pregnancy, and grand multiparity is associated with higher BMI later in life compared to nulliparous women [27]. A previous MESA paper showed that women with grand multiparity had increased levels of the adipokines that are associated with poor cardiovascular health (i.e. leptin and resistin) and decreased levels of the cardioprotective adipokine adiponectin [51]. Although we adjusted for BMI in our analysis, this may not have fully captured adiposity-mediated risks.

Menopause marks an important transition in a woman's life with many hormonal changes contributing to the cessation of ovarian function. Changes in hormonal profiles at menopause are associated with increased renin-angiotensin-aldosterone activation, body fat distribution changes with increased visceral fat deposition, and lipid dysregulation [16]. A more androgenic sex hormone pattern in post-menopausal women is associated with a greater risk for CVD events [18] and with greater subclinical atherosclerosis as measured by the CAC score [42] and endothelial dysfunction measured by brachial reactivity [52]. Thus, an earlier onset of menopause and loss of estradiol allows for a longer exposure to a hormonal profile that is detrimental and increases the development of CVD.

Earlier onset of menopause has been independently associated with increased atherosclerotic CVD risk [16, 53, 54]. This has led to recent primary prevention guidelines considering early menopause a "risk-enhancing" factor that would favor statin initiation among women at otherwise borderline or intermediate risk based on their estimated 10-year CVD risk scores [55]. Although the premature and early onset of menopause are associated with adverse CVD outcomes in large cohorts, in our study, early onset menopause was not significantly associated with carotid plaque presence or progression in the fully-adjusted model. This finding was contrary to our hypothesis and suggests carotid plaque may not fully capture CVD risk in this higher-risk subset of women.

Strengths and limitations

This study analyzed the relationship between two female-specific factors (parity and menopause age) with carotid plaque presence and progression. This study has many strengths, including a diverse and representative cohort of women from multiple areas across the United States. Also, this study included a wide range of data available to adjust for multiple cardiovascular and demographic risk factors.

However, our study also had a number of limitations. The observational nature of this analysis precludes the ability to establish causality, and residual confounding may explain the associations that we observed. Additionally, we may have been underpowered to detect small differences in associations given small sample size and because of the highly skewed dependent variable of CPS (with significant 0 values). Nearly half of the women did not have carotid plaque at baseline, and only 690 (29.8%) women had incident carotid plaque available for analysis. Another limitation is that the carotid plaque score used is only semi-quantitative, and future studies could consider using more advanced imaging techniques such as 4D MRI to focus on shear wall stress, and plaque burden by area and volume.

Notably, many other critical female-specific factors such as menarche age, polycystic ovary syndrome, adverse pregnancy outcomes (e.g., preeclampsia, gestational diabetes, preterm birth), the use of assisted reproductive technology, breastfeeding history, and vasomotor symptoms were not ascertained in the MESA cohort, and as such, we were not able to examine these exposures. Despite these limitations, we believe this study highlights important

results evaluating the association between parity and menopause age with carotid plaque.

Conclusion

In a multi-ethnic cohort of women, we found that grand multiparity was independently and significantly associated with carotid plaque presence and progression even after adjusting for traditional CVD risk factors. In conclusion, carotid plaque may be a way of assessing increased CVD risk in multiparous women; its role in refining CVD risk in post-menopausal women warrants further investigation.

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Disclosure of conflict of interest

None.

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References

[1] Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, Elkind MSV, Evenson KR, Ferguson JF, Gupta DK, Khan SS, Kissela BM, Knutson KL, Lee CD, Lewis TT, Liu J, Loop MS, Lutsey PL, Ma J, Mackey J, Martin SS, Matchar DB, Mussolino ME, Navaneethan SD, Perak AM, Roth GA, Samad Z, Satou GM, Schroeder EB, Shah SH, Shay CM, Stokes A, VanWagner LB, Wang NY and Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. Circulation 2021; 143: e254-e743.

[2] Curtin SC. Trends in cancer and heart disease death rates among adults aged 45-64: united states, 1999-2017. Natl Vital Stat Rep 2019; 68: 1-9.

[3] Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, Porterfield D, Blankstein R, Rosamond WD, Bhatt DL and Caughey MC. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. Circulation 2019; 139: 1047-1056.

[4] Khan SU, Yedlapati SH, Lone AN, Khan MS, Wenger NK, Watson KE, Gulati M, Hays AG and Michos ED. A comparative analysis of premature heart disease- and cancer-related mortality in women in the USA, 1999-2018. Eur Heart J Qual Care Clin Outcomes 2022; 8: 315-323.

[5] Peters SAE, Muntner P and Woodward M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. Circulation 2019; 139: 1025-1035.

[6] Maas AH and Appelman YE. Gender differences in coronary heart disease. Neth Heart J 2010; 18: 598-602.

[7] Dreyer RP, Dharmarajan K, Kennedy KF, Jones PG, Vaccarino V, Murugiah K, Nuti SV, Smolderen KG, Buchanan DM, Spertus JA and Krumholz HM. Sex differences in 1-year all-cause rehospitalization in patients after acute myocardial infarction: a Prospective Observational Study. Circulation 2017; 135: 521-531.

[8] Dreyer RP, Wang Y, Strait KM, Lorenze NP, D'Onofrio G, Bueno H, Lichtman JH, Spertus JA and Krumholz HM. Gender differences in the trajectory of recovery in health status among young patients with acute myocardial infarction: results from the variation in recovery: role of gender on outcomes of young AMI patients (VIRGO) study. Circulation 2015; 131: 1971-1980.

[9] DeFilippis EM, Collins BL, Singh A, Biery DW, Fatima A, Qamar A, Berman AN, Gupta A, Cawley M, Wood MJ, Klein J, Hainer J, Gulati M, Taqueti VR, Di Carli MF, Nasir K, Bhatt DL and Blankstein R. Women who experience a myocardial infarction at a young age have worse outcomes compared with men: the Mass Gen-

eral Brigham YOUNG-MI registry. Eur Heart J 2020; 41: 4127-4137.
[10] Agarwala A, Michos ED, Samad Z, Ballantyne CM and Virani SS. The use of sex-specific factors in the assessment of women's cardiovascular risk. Circulation 2020; 141: 592-599.
[11] Elder P, Sharma G, Gulati M and Michos ED. Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention. Am J Prev Cardiol 2020; 2: 100028.
[12] O'Kelly AC, Michos ED, Shufelt CL, Vermunt JV, Minissian MB, Quesada O, Smith GN, Rich-Edwards JW, Garovic VD, El Khoudary SR and Honigberg MC. Pregnancy and reproductive risk factors for cardiovascular disease in women. Circ Res 2022; 130: 652-672.
[13] Li W, Ruan W, Lu Z and Wang D. Parity and risk of maternal cardiovascular disease: a dose-response meta-analysis of cohort studies. Eur J Prev Cardiol 2019; 26: 592-602.
[14] Li Y, Zhao D, Wang M, Sun JY, Liu J, Qi Y, Hao YC, Deng QJ, Liu J, Liu J and Liu M. Association of menopause with risk of carotid artery atherosclerosis. Maturitas 2021; 143: 171-177.
[15] Honigberg MC, Zekavat SM, Aragam K, Finneran P, Klarin D, Bhatt DL, Januzzi JL Jr, Scott NS and Natarajan P. Association of premature natural and surgical menopause with incident cardiovascular disease. JAMA 2019; 322: 2411-2421.
[16] El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, Limacher MC, Manson JE, Stefanick ML and Allison MA; American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. Circulation 2020; 142: e506-e532.
[17] Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, Gunderson EP, Stuart JJ and Vaidya D; American Heart Association Council on Epidemiology and Prevention; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and the Stroke Council. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. Circulation 2021; 143: e902-e916.
[18] Zhao D, Guallar E, Ouyang P, Subramanya V, Vaidya D, Ndumele CE, Lima JA, Allison MA, Shah SJ, Bertoni AG, Budoff MJ, Post WS and Michos ED. Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. J Am Coll Cardiol 2018; 71: 2555-2566.
[19] El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT and Sutton-Tyrrell K. Endogenous sex hormones impact the progression of subclinical atherosclerosis in women during the menopausal transition. Atherosclerosis 2012; 225: 180-186.
[20] Madika AL, Nasserdine P, Langlet S, Lecerf C, Ledieu G, Devos P and Mounier-Vehier C. Association between reproductive factors and carotid atherosclerosis in post-menopausal women. Maturitas 2019; 126: 38-44.
[21] Peters SA and Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart 2018; 104: 1069-1075.
[22] Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, Brunner EJ, Kuh D, Hardy R, Avis NE, Gold EB, Derby CA, Matthews KA, Cade JE, Greenwood DC, Demakakos P, Brown DE, Sievert LL, Anderson D, Hayashi K, Lee JS, Mizunuma H, Tillin T, Simonsen MK, Adami HO, Weiderpass E and Mishra GD. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Health 2019; 4: e553-e564.
[23] Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, Krumholz HM and Lichtman JH. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: the VIRGO Study. J Am Coll Cardiol 2015; 66: 1949-1957.
[24] Ness RB, Harris T, Cobb J, Flegal KM, Kelsey JL, Balanger A, Stunkard AJ and D'Agostino RB. Number of pregnancies and the subsequent risk of cardiovascular disease. N Engl J Med 1993; 328: 1528-1533.
[25] Parikh NI, Cnattingius S, Dickman PW, Mittleman MA, Ludvigsson JF and Ingelsson E. Parity and risk of later-life maternal cardiovascular disease. Am Heart J 2010; 159: 215-221, e216.
[26] Peters SA, van der Schouw YT, Wood AM, Sweeting MJ, Moons KG, Weiderpass E, Arriola L, Benetou V, Boeing H, Bonnet F, Butt ST, Clavel-Chapelon F, Drake I, Gavrila D, Key TJ, Klinaki E, Krogh V, Kuhn T, Lassale C, Masala G, Matullo G, Merritt M, Molina-Portillo E, Moreno-Iribas C, Nost TH, Olsen A, Onland-Moret NC, Overvad K, Panico S, Redondo ML, Tjonneland A, Trichopoulou A, Tumino R, Turzanski-Fortner R, Tzoulaki I, Wennberg P, Winkvist A, Thompson SG, Di Angelantonio E, Riboli E, Wareham NJ, Danesh J and Butter-

worth AS. Parity, breastfeeding and risk of coronary heart disease: a pan-European case-cohort study. Eur J Prev Cardiol 2016; 23: 1755-1765.
[27] Ogunmoroti O, Osibogun O, Kolade OB, Ying W, Sharma G, Vaidya D and Michos ED. Multiparity is associated with poorer cardiovascular health among women from the Multi-Ethnic Study of Atherosclerosis. Am J Obstet Gynecol 2019; 221: 631.e631-631.e616.
[28] Broekmans FJ, Soules MR and Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev 2009; 30: 465-493.
[29] Mondul AM, Rodriguez C, Jacobs EJ and Calle EE. Age at natural menopause and cause-specific mortality. Am J Epidemiol 2005; 162: 1089-1097.
[30] Atsma F, Bartelink ML, Grobbee DE and van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause 2006; 13: 265-279.
[31] Singh SS, Pilkerton CS, Shrader CD Jr and Frisbee SJ. Subclinical atherosclerosis, cardiovascular health, and disease risk: is there a case for the Cardiovascular Health Index in the primary prevention population? BMC Public Health 2018; 18: 429.
[32] Polak JF and O'Leary DH. Carotid intima-media thickness as surrogate for and predictor of CVD. Glob Heart 2016; 11: 295-312, e293.
[33] Gepner AD, Young R, Delaney JA, Budoff MJ, Polak JF, Blaha MJ, Post WS, Michos ED, Kaufman J and Stein JH. Comparison of carotid plaque score and coronary artery calcium score for predicting cardiovascular disease events: the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2017; 6: e005179.
[34] Naqvi TZ and Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging 2014; 7: 1025-1038.
[35] Mehta A, Rigdon J, Tattersall MC, German CA, Barringer TA 3rd, Joshi PH, Sperling LS, Budoff MJ, Bertoni A, Michos ED, Blaha MJ, Stein JH and Shapiro MD. Association of carotid artery plaque with cardiovascular events and incident coronary artery calcium in individuals with absent coronary calcification: the MESA. Circ Cardiovasc Imaging 2021; 14: e011701.
[36] McClelland RL, Chung H, Detrano R, Post W and Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2006; 113: 30-37.
[37] Chu JH, Michos ED, Ouyang P, Vaidya D, Blumenthal RS, Budoff MJ, Blaha MJ and Whelton SP. Coronary artery calcium and atherosclerotic cardiovascular disease risk in women with early menopause: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Prev Cardiol 2022; 11: 100362.
[38] Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M and Tracy RP. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002; 156: 871-881.
[39] Vaidya D, Bennett WL, Sibley CT, Polak JF, Herrington DM and Ouyang P. Association of parity with carotid diameter and distensibility: multi-ethnic study of atherosclerosis. Hypertension 2014; 64: 253-258.
[40] Ying W, Zhao D, Ouyang P, Subramanya V, Vaidya D, Ndumele CE, Sharma K, Shah SJ, Heckbert SR, Lima JA, deFilippi CR, Budoff MJ, Post WS and Michos ED. Sex hormones and change in N-terminal Pro-B-type natriuretic peptide levels: the Multi-Ethnic Study of Atherosclerosis. J Clin Endocrinol Metab 2018; 103: 4304-4314.
[41] Mitchell C, Korcarz CE, Gepner AD, Kaufman JD, Post W, Tracy R, Gassett AJ, Ma N, McClelland RL and Stein JH. Ultrasound carotid plaque features, cardiovascular disease risk factors and events: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2018; 276: 195-202.
[42] Subramanya V, Zhao D, Ouyang P, Ying W, Vaidya D, Ndumele CE, Heckbert SR, Budoff MJ, Post WS and Michos ED. Association of endogenous sex hormone levels with coronary artery calcium progression among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA). J Cardiovasc Comput Tomogr 2019; 13: 41-47.
[43] Sharma A, Ogunmoroti O, Fashanu OE, Zhao D, Ouyang P, Budoff MJ, Thomas IC and Michos ED. Associations of endogenous sex hormone levels with the prevalence and progression of valvular and thoracic aortic calcification in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2022; 341: 71-79.
[44] Sweeney T, Ogunmoroti O, Ndumele CE, Zhao D, Varma B, Allison MA, Budoff MJ, Fashanu OE, Sharma A, Bertoni AG and Michos ED. Associations of adipokine levels with the prevalence and extent of valvular and thoracic aortic calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2021; 338: 15-22.
[45] Varma B, Ogunmoroti O, Ndumele CE, Zhao D, Szklo M, Sweeney T, Allison MA, Budoff MJ, Subramanya V, Bertoni AG and Michos ED. Higher leptin levels are associated with coronary artery calcium progression: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabet Epidemiol Manag 2022; 6: 100047.

[46] Vu K, Nguyen K, Evans J, Fan W, Mongraw-Chaffin M, Budoff MJ, Wong ND and Michos ED. Abstract 13418: inter-relation of parity and coronary artery calcium with cardiovascular disease events: the Multi-ethnic Study of Atherosclerosis. Circulation 2020; 142: A13418.
[47] Johnsen SH and Mathiesen EB. Carotid plaque compared with intima-media thickness as a predictor of coronary and cerebrovascular disease. Curr Cardiol Rep 2009; 11: 21-27.
[48] Wang XY, Ye F, Zeng LX, Tu S, Luo WZ, Deng X and Zhang ZH. Parity and carotid atherosclerosis in elderly Chinese women. J Geriatr Cardiol 2020; 17: 759-765.
[49] Kazzi B, Ogunmoroti O, Rodriguez CP, Zhao D, Minhas AS, Osibogun O, Subramanya V, Allison MA, Ouyang P and Michos ED. Parity history and later life sex hormone levels in the Multi-Ethnic Study of Atherosclerosis (MESA). Can J Cardiol 2022; 38: 1893-1900.
[50] Rocha VZ and Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol 2009; 6: 399-409.
[51] Rodriguez CP, Ogunmoroti O, Quispe R, Osibogun O, Ndumele CE, Echouffo Tcheugui J, Minhas AS, Bertoni AG, Allison MA and Michos ED. The association between multiparity and adipokine levels: the Multi-Ethnic Study of Atherosclerosis. J Womens Health 2022; 31: 741-749.
[52] Mathews L, Subramanya V, Zhao D, Ouyang P, Vaidya D, Guallar E, Yeboah J, Herrington D, Hays AG, Budoff MJ and Michos ED. Endogenous sex hormones and endothelial function in postmenopausal women and men: the Multi-Ethnic Study of Atherosclerosis. J Womens Health 2019; 28: 900-909.
[53] Woodard GA, Brooks MM, Barinas-Mitchell E, Mackey RH, Matthews KA and Sutton-Tyrrell K. Lipids, menopause, and early atherosclerosis in study of women's health across the nation heart women. Menopause 2011; 18: 376-384.
[54] Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M and Franco OH. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. JAMA Cardiol 2016; 1: 767-776.
[55] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Munoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J and Ziaeian B. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of-Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 74: 1376-1414.

Table S1. Association between gravidity and carotid plaque at baseline, N = 2,313

	Model 1	Model 2	Model 3
Prevalence ratio (95% CI)			
Gravidity			
0	Reference	Reference	Reference
1-2	1.13 (0.99, 1.29)	1.09 (0.95, 1.25)	1.07 (0.94, 1.23)
3-4	1.08 (0.94, 1.24)	1.06 (0.92, 1.21)	1.05 (0.91, 1.20)
≥5	1.16 (1.01, 1.33)	1.11 (0.97, 1.28)	1.12 (0.97, 1.29)

Prevalence ratios were derived from Poisson regression models with robust variance estimation. Statistically significant results at P<0.05 are in bold font. Model 1: demographics (age, race/ethnicity) and study site. Model 2: model 1 + lifestyle and physiologic factors (education, smoking, physical activity, BMI, menopause and current use of hormone therapy). Model 3: model 2 + CVD risk factors and medications (total cholesterol, HDL-C, use of lipid-lowering medication, systolic blood pressure, use of anti-hypertensive medication and diabetes).

Table S2. Association between gravidity and carotid plaque extent at baseline, N = 2,313

	Model 1	Model 2	Model 3
Percent difference (95% CI)			
Gravidity			
0	Reference	Reference	Reference
1-2	8 (-1, 17)	4 (-4, 13)	3 (-5, 12)
3-4	8 (-1, 17)	5 (-3, 14)	5 (-3, 14)
≥5	10 (1, 21)	7 (-3, 17)	7 (-2, 17)

Results were presented as percent difference of carotid plaque score at baseline derived from linear mixed effects regression models and calculated from [Exp (β) - 1] *100. Statistically significant results at P<0.05 are in bold font. Model 1: demographics (age, race/ethnicity) and study site. Model 2: model 1 + lifestyle and physiologic factors (education, smoking, physical activity, BMI, menopause and current use of hormone therapy). Model 3: model 2 + CVD risk factors and medications (total cholesterol, HDL-C, use of lipid-lowering medication, systolic blood pressure, use of anti-hypertensive medication and diabetes).