

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

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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]. Post-menopausal 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.

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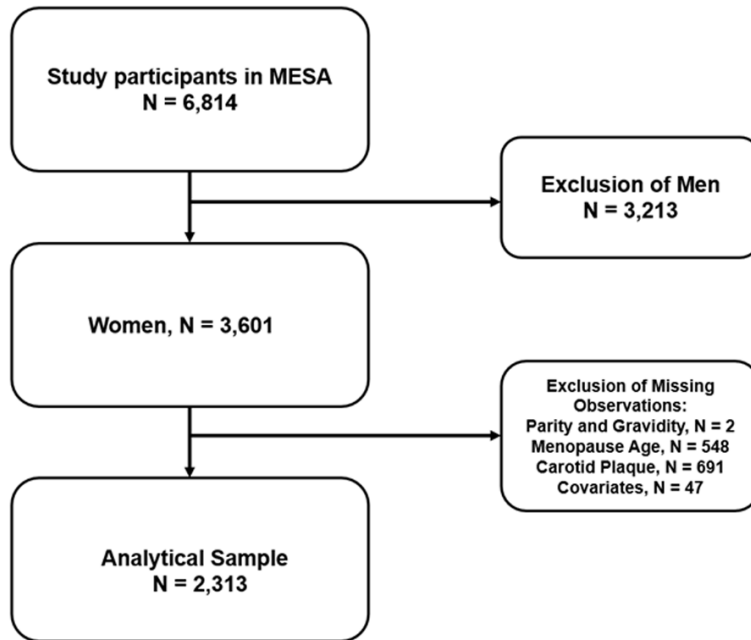


Figure 1. Flowchart of study participants.

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

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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 $\ln(\text{CPS} + 1)$, 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 $[\text{Exp}(\beta) - 1] * 100$ 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

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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

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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.

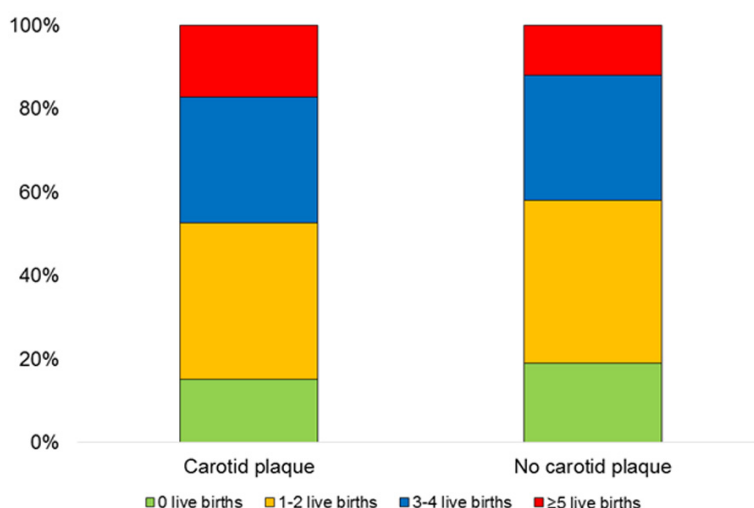


Figure 2. Distribution of the presence and absence of carotid plaque by parity categories among women of the Multi-Ethnic Study of Atherosclerosis. Parity was categorized as 0 live births, green; 1-2 live births, orange; 3-4 live births, blue and ≥5 live births, red.

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**. Multi-gravidity 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 multi-gravidity had significantly greater extent of carotid plaque when adjusted for demographics [percent difference 10% (1, 21) (model 1)], but not in further adjusted models.

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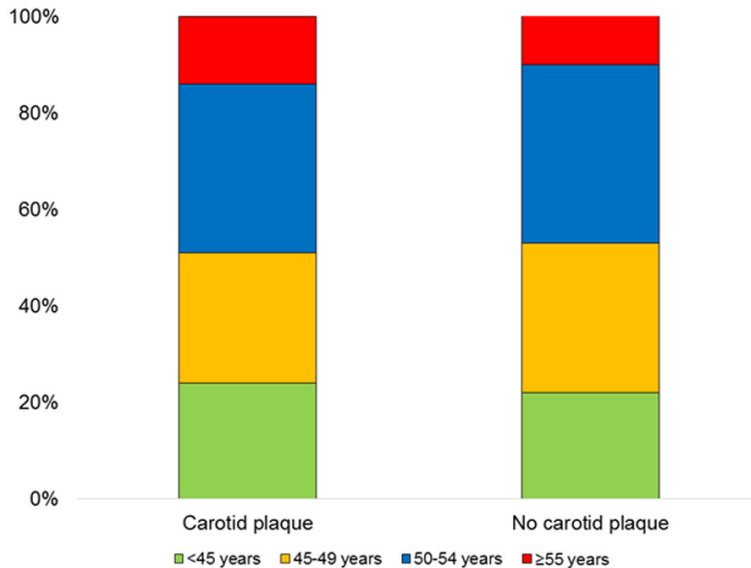


Figure 3. Distribution of the presence and absence of carotid plaque by menopausal age categories among women of the Multi-Ethnic Study of Atherosclerosis. Menopausal age was categorized as <45 years, green; 45-49 years, orange; 50-54 years, blue and ≥55 years, red.

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 $[\text{Exp}(\beta) - 1] * 100$. 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

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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 $[\text{Exp}(\beta) - 1] * 100$. 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

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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 consider-

ing 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

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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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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 $[\text{Exp}(\beta) - 1] * 100$. 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).