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ORIGINAL RESEARCH

# Persistent Asthma Is Associated With Carotid Plaque in MESA

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**BACKGROUND:** Asthma and atherosclerotic cardiovascular disease share an underlying inflammatory pathophysiology. We hypothesized that persistent asthma is associated with carotid plaque burden, a strong predictor of atherosclerotic cardiovascular disease events.

**METHODS AND RESULTS:** The MESA (Multi-Ethnic Study of Atherosclerosis) enrolled adults free of known atherosclerotic cardiovascular disease at baseline. Subtype of asthma was determined at examination 1. Persistent asthma was defined as asthma requiring use of controller medications, and intermittent asthma was defined as asthma without controller medications. B-mode carotid ultrasound was performed to detect carotid plaques (total plaque score [TPS], range 0–12). Multivariable regression modeling with robust variances evaluated the association of asthma subtype and carotid plaque burden. The 5029 participants were a mean (SD) age of 61.6 (10.0) years (53% were women, 26% were Black individuals, 23% were Hispanic individuals, and 12% were Chinese individuals). Carotid plaque was present in 50.5% of participants without asthma (TPS, 1.29 [1.80]), 49.5% of participants with intermittent asthma (TPS, 1.25 [1.76]), and 67% of participants with persistent asthma (TPS, 2.08 [2.35]) ( $P \leq 0.003$ ). Participants with persistent asthma had higher interleukin-6 (1.89 [1.61] pg/mL) than participants without asthma (1.52 [1.21] pg/mL;  $P=0.02$ ). In fully adjusted models, persistent asthma was associated with carotid plaque presence (odds ratio, 1.83 [95% confidence interval, 1.21–2.76];  $P < 0.001$ ) and TPS ( $\beta=0.66$ ;  $P < 0.01$ ), without attenuation after adjustment for baseline interleukin-6 ( $P=0.02$ ) or CRP (C-reactive protein) ( $P=0.01$ ).

**CONCLUSIONS:** Participants with persistent asthma had higher carotid plaque burden and higher levels of inflammatory biomarkers, compared with participants without asthma. Adjustment for baseline inflammatory biomarkers did not attenuate the association between carotid plaque and asthma subtype, highlighting the increased atherosclerotic cardiovascular disease risk among those with persistent asthma may be multifactorial.

**Key Words:** asthma ■ carotid plaque ■ inflammation

Asthma and atherosclerotic cardiovascular disease (ASCVD) are highly prevalent inflammatory diseases. Globally, >339 million people have asthma, and its prevalence in the United States is increasing.<sup>1</sup> ASCVD is the leading cause of death in the United States.<sup>2–5</sup> Carotid arterial plaque detected by B-mode ultrasound represents advanced, typically subclinical, atherosclerosis that is a strong, independent predictor

of incident ASCVD events.<sup>6,7</sup> Inflammation plays a key role in the initiation, progression, and triggering of clinical events in ASCVD.<sup>8</sup> Serum inflammatory biomarkers, such as CRP (C-reactive protein) and interleukin 6 (IL-6), are associated with increased ASCVD events.<sup>2,9</sup> In asthma, CRP and other inflammatory biomarkers are higher compared with individuals without asthma and increase further during exacerbations.<sup>10,11</sup> IL-6 is

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## CLINICAL PERSPECTIVE

### What Is New?

- In a multiethnic US population, persistent but not intermittent asthma was associated with carotid plaque presence and burden, both strong predictors of future atherosclerotic cardiovascular disease events.
- Participants with persistent asthma had the highest serum interleukin-6 and CRP (C-reactive protein) levels.
- Adjustment for inflammatory markers did not attenuate the association of persistent asthma and carotid plaque presence or burden, suggesting that atherosclerotic cardiovascular disease risk among individuals with asthma may be multifactorial.

### What Are the Clinical Implications?

- Persistent asthma is an inflammatory syndrome that is associated with increased atherosclerotic cardiovascular disease risk, highlighting the importance of optimizing control of atherosclerotic cardiovascular disease risk factors in patients with persistent asthma.

## Nonstandard Abbreviations and Acronyms

**TPS** total plaque score

associated with a more severe and exacerbation-prone asthma phenotype.<sup>12,13</sup>

To date, there are limited data investigating the associations of asthma, asthma severity, and atherosclerotic plaque burden. We hypothesized that in the MESA (Multi-Ethnic Study of Atherosclerosis), a multiethnic population of individuals free of prevalent ASCVD, persistent asthma would be associated with carotid plaque presence and burden, which are strong predictors of future ASCVD events. We also explored whether these associations would be attenuated after adjustment for baseline inflammatory biomarkers.

## METHODS

Anonymized data and materials have been made publicly available at BioLincc and can be accessed at <https://biolincc.nhlbi.nih.gov/home/>.

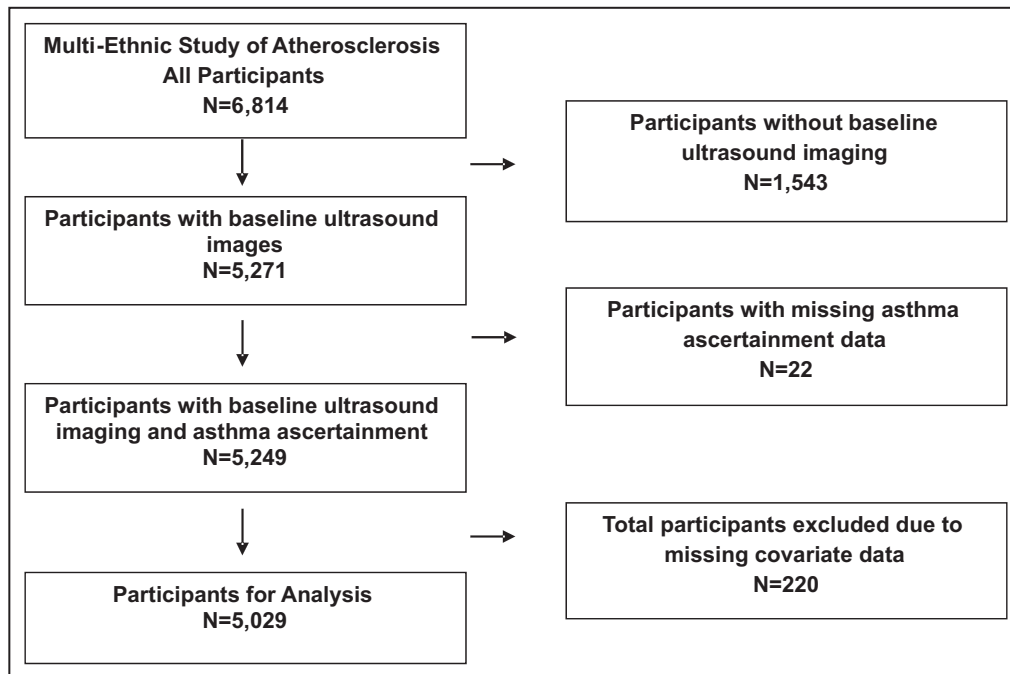
### Participants

The MESA investigates ASCVD risk factors and progression in an ethnically diverse, population-based

study of 6814 healthy participants who were aged 45 to 84 years and free of known ASCVD at baseline.<sup>14</sup> The presence of clinical cardiovascular disease was an exclusion for entry into the MESA.<sup>14</sup> Baseline participant recruitment occurred in 2000 to 2002 from 6 field centers located in Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Details of the MESA design have been published previously.<sup>14</sup> The study was approved by the institutional review boards of all participating centers. All participants provided informed consent. Our primary analysis was restricted to participants with baseline (examination 1) ASCVD risk factors and carotid ultrasound (July 2000–August 2002) data (N=5029) (Figure 1 and Table S1). Analyses involving inflammatory markers were further restricted to the subsets available for CRP (N=5001) or IL-6 (N=4910).

### ASCVD Risk Factors and Medications

Baseline laboratory samples were collected following a 12-hour fast. Lipid laboratory analyses were performed at the University of Minnesota; other laboratory measures were performed at the University of Vermont, as previously reported.<sup>14</sup> Total and high-density lipoprotein cholesterol were measured in EDTA plasma using a cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN) on a Roche COBAS FARA centrifugal analyzer. The coefficients of variation for these methods were 1.6% and 2.9%, respectively. Serum glucose was measured by rate reflectance spectrophotometry on a Vitros analyzer (Johnson and Johnson Clinical Diagnostics, Inc, Rochester, NY) with a coefficient of variation of 1.1%. IL-6 was measured by ultrasensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN) with a coefficient of variation of 6.3%. CRP was measured on the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc, Deerfield, IL). The intra-assay and interassay coefficients of variation for CRP ranged from 2.3% to 4.4% and from 2.1% to 5.7%, respectively. Diabetes was defined according to the American Diabetes Association and prior MESA investigations (use of hypoglycemic medications and/or fasting serum glucose  $\geq 126$  mg/dL at baseline).<sup>15,16</sup> Antihypertensive and statin medication use was verified at the examination visit. Right arm systolic blood pressure was measured using a Dinamap Monitor Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL) after the participant had rested for 5 minutes. Three readings were obtained, and the average of the last 2 readings was used for analysis. Smoking and alcohol consumption were classified as “never,” “former,” or “current” users. Education was classified as highest level completed.



**Figure 1.** Flow diagram of included participants.

## Carotid Ultrasonography

At baseline (examination 1), B-mode ultrasound longitudinal images of the right and left common, bifurcation, and internal carotid artery segments were recorded on Super-VHS videotape with a Logiq 700 ultrasound system using the M12L transducer (General Electric Medical Systems; common carotid artery frequency, 13 MHz). Video images were digitized at high resolution and frame rates using a Medical Digital Recording device (PACSGEAR, Pleasanton, CA) and converted into DICOM compatible digital records. Ultrasound images were reviewed and interpreted by the MESA Carotid Ultrasound Reading Center (UW AIRP, Madison, WI). Digitized images were imported into *syngo* Ultrasound Workplace 3.5B reading stations loaded with Arterial Health Package software (Siemens Medical, Malvern, PA) for carotid plaque scoring.

Carotid plaque was defined as a discrete, focal wall thickening  $\geq 1.5$  cm or focal thickening at least 50% greater than the surrounding intima-media thickness (IMT).<sup>7</sup> Carotid plaque presence and burden were identified on B-mode ultrasound of the internal, bifurcation (bulb), and common segments of the left and right carotid arteries. The total plaque score (TPS) was defined as the number of segments with a carotid plaque (0–12) present in the near or far walls of the internal, bulb, and common segments of both carotid arteries.<sup>17</sup> For carotid plaque presence and TPS, *intrareader* reproducibility was  $\kappa=0.83$  (95% confidence interval [CI], 0.70–0.96), and *interreader* reproducibility was  $\kappa=0.89$  (95% CI, 0.72–1.00).<sup>18</sup>

## Asthma Definitions

Asthma was defined as self-reported, physician-diagnosed asthma at baseline (examination 1), as in previous studies.<sup>19–21</sup> The examiner asked the participant, “Has a doctor ever told you that you have asthma?” This definition of asthma is consistent with that of other studies that investigated asthma in the absence of pulmonary function testing.<sup>10,22</sup> Self-reported physician-diagnosed asthma questions have the highest specificity of all asthma diagnostic questions in epidemiological questionnaires for asthma diagnosis.<sup>23</sup> To account for the spectrum of asthma severity, we further stratified asthma into 2 subgroups: persistent asthma (defined as those with asthma on controller medications) and intermittent asthma (those with asthma not taking controller medications).<sup>10,24</sup> Persistent asthma was defined as those treated with step 2 to 6 therapies, such as regular use of inhaled corticosteroids, oral corticosteroids, and/or leukotriene inhibitors to modify disease activity.<sup>24</sup> Participants brought medication used in the past 2 weeks to the study clinic for verification.

## Statistical Analysis

Examination 1 descriptive statistics are reported as means (SDs) for continuous variables and as percentages for categorical variables, based on asthma severity (no asthma, intermittent asthma, and persistent asthma). Multivariable logistic and multivariable linear regression with robust variances were used to assess the associations of asthma severity and carotid plaque.

A series of models adjusting for biological confounders were constructed: model 1, unadjusted; model 2, adjusted for age, sex, race and ethnicity, and education (less than high school, high school or college, bachelor's degree, and graduate school); and model 3, additionally adjusted for body mass index, total and high-density lipoprotein cholesterol, systolic blood pressure, smoking status, statin use, hypertension medication use, and diabetes. The potential for attenuation of the estimation of the association between asthma and carotid plaque by the serum inflammatory markers IL-6 and CRP was assessed by adding these covariates to the fully adjusted multivariable models with robust variances, and the effect on coefficients in the models with and without inflammatory markers was assessed.<sup>25</sup> A sensitivity analysis was conducted using log-transformed IL-6 and CRP, which confirmed that results were similar with and without transformation. Detailed models are demonstrated in Tables S2 to S7. Analysis of variance with Tukey multiple comparisons test was used to compare the distribution of baseline inflammatory markers (IL-6 and CRP) and asthma severity. Analyses were performed in STATA version 14.2 (College Station, TX). Statistical significance was set at a 2-sided  $P < 0.05$ .

## RESULTS

### Descriptive Characteristics

The 5029 participants were a mean (SD) age of 61.6 (10.0) years (53% were women, 26% were Black individuals, 23% were Hispanic individuals, and 12% were Chinese individuals) (Table 1). Baseline risk factor distributions between the 109 participants with persistent asthma, the 388 participants with intermittent asthma, and the 4532 participants without asthma are shown in Table 1. Compared with the participants without asthma, the participants with persistent asthma were more likely to be women (70% versus 51.7%), have higher body mass index (29.9 versus 28.1 kg/m<sup>2</sup>), and have higher high-density lipoprotein cholesterol levels (56.5 versus 50.6 mg/dL) (Table 1).

### Asthma, Asthma Severity, and Carotid Plaque

Carotid plaque was present in 50.5% of the participants without asthma, with a TPS (SD) of 1.29 (1.80), 49.5% of the participants with intermittent asthma, with a TPS (SD) of 1.25 (1.76), and 67% of the participants with persistent asthma, with a TPS (SD) of 2.08 (2.35) ( $P \leq 0.003$  for comparison of proportions, and  $P = 0.002$  for comparison of means).

### Asthma Severity and Serum Markers of Inflammation

The participants with persistent asthma had the highest systemic inflammatory marker levels (Table 2).

Compared with participants without asthma, the participants with persistent asthma had significantly higher levels of CRP (mean [SD], 6.49 [11.20] mg/L versus 3.61 [5.50] mg/L;  $P = 0.008$ ) and IL-6 (mean [SD], 1.89 [1.61] pg/mL versus 1.52 [1.21] pg/mL;  $P = 0.02$ ). The participants with intermittent asthma had higher average CRP than participants without asthma (mean [SD], 4.54 [6.80] mg/L;  $P = 0.009$ ) but not higher IL-6 (mean [SD], 1.60 [1.21] pg/mL;  $P = 0.20$ ).

### Associations of Asthma Severity and Carotid Atherosclerosis

In unadjusted models, persistent asthma was associated with a higher odds of carotid plaque presence (odds ratio [OR], [95% CI], 1.97 [1.32–2.95];  $P < 0.01$ ) (Figure 1). This association persisted in models for biologic confounders (OR, 1.83 [95% CI, 1.21–2.76];  $P < 0.01$ ) (Figure 1). Persistent asthma also was associated with a higher carotid TPS (fully adjusted  $\beta = 0.62$  [95% CI, 0.24–1.00];  $P < 0.001$ ) (Table 3).

### Associations of Asthma Severity, Carotid Atherosclerosis, and Serum Inflammatory Markers

After model 3 adjustments, IL-6 was independently associated with carotid plaque presence (OR, 1.15 [95% CI, 1.05–1.26];  $P = 0.0001$ , per 1-SD increment of 1.53) and TPS ( $\beta = 0.18$  [95% CI, 0.11–0.25];  $P < 0.001$ ). CRP was slightly associated with carotid TPS ( $\beta = 0.03$  [95% CI, 0.001–0.06];  $P = 0.04$ ) but not carotid plaque presence (OR, 1.04 [95% CI, 1.00–1.02];  $P = 0.07$ ). In fully adjusted models that evaluated the associations of asthma subtype and carotid plaque presence or TPS, addition of CRP or IL-6 did not attenuate the associations of asthma severity and carotid plaque presence or TPS (Figure 2).

## DISCUSSION

In a large, multiethnic cohort, persistent asthma but not intermittent asthma was associated with carotid plaque presence and TPS, even in models that adjusted for potential confounders and serum levels of either CRP or IL-6.

There are limited population-level data that have assessed the associations of asthma and carotid arterial injury. In the ARMY (Atherosclerosis Risk Factors in Male Youngsters) and Bruneck studies, allergic conditions, such as allergic rhinitis and asthma, were associated with more carotid plaque and/or thicker carotid IMT; however, the ARMY study excluded people with asthma, and in the Bruneck study, asthma prevalence was low (2.4%;  $N = 20$ )<sup>26</sup> In the Atherosclerosis Risk in Communities study, women but not men with

**Table 1. Baseline Descriptive Statistics**

Variables	No asthma (n=4532)	Intermittent asthma (n=388)	Persistent asthma (n=109)	P value
Age, y	61.8 (10.0)	59.7 (10.1)	63.4 (9.9)	<0.001
Body mass index, kg/m <sup>2</sup>	28.1 (5.3)	29.9 (6.3)	29.9 (6.7)	<0.001
Female sex, n (%)	2345 (51.7)	236 (60.8)	76 (70.0)	<0.001
Race or ethnicity, n (%)				
Black	1156 (25.5)	113 (29.1)	37 (33.9)	0.005
Chinese American	586 (12.9)	33 (8.5)	6 (5.5)	
Hispanic	1028 (22.7)	94 (24.2)	17 (15.6)	
White	1762 (38.9)	148 (38.1)	49 (45.0)	
Smoking, n (%)				
Never smoker	2304 (50.8)	193 (49.7)	49 (45.0)	0.77
Former smoker	1653 (36.5)	142 (36.6)	45 (41.3)	
Current smoker	575 (12.7)	53 (13.7)	15 (13.8)	
Total cholesterol, mg/dL	194.1 (35.2)	195.5 (40.6)	197.2 (36.1)	0.52
HDL cholesterol, mg/dL	50.6 (14.8)	50.5 (14.5)	56.5 (16.0)	<0.001
Systolic blood pressure, mmHg	126.0 (21.3)	126.0 (22.5)	129.3 (20.3)	0.29
Diabetes, n (%)	756 (12.4)	76 (14.9)	21 (13.5)	0.23
Medication use, n (%)				
Antihypertensive	1637 (36.1)	146 (37.6)	51 (46.8)	0.07
Statins	673 (14.8)	55 (14.2)	25 (22.9)	0.05
Oral corticosteroids	56 (1.2)	0 (0)	25 (22.7)	N/A
Leukotriene receptor antagonists	4 (0.1)	0 (0)	31 (28.2)	N/A
Inhaled corticosteroids	17 (0.4)	0 (0)	81 (73.6)	N/A
Carotid plaque present, n (%)	2290 (50.5)	192 (49.5)	73 (67)	0.003
Carotid total plaque score	1.29 (1.80)	1.25 (1.76)	2.08 (2.35)	0.002

HDL indicates high-density lipoprotein.  
Unless noted, values are means (SDs).

**Table 2. Serum Inflammatory Markers and Coagulation Markers by Asthma Subtype**

Variables	No asthma	Intermittent asthma	Persistent asthma
IL-6, pg/mL	1.52 (1.21)	1.60 (1.21)	1.89 (1.61)*
CRP, mg/L	3.61 (5.53)	4.54 (6.84)*	6.49 (11.22)*

Data are given as mean (SD). CRP indicates C-reactive protein; and IL-6, interleukin 6.

\*Significantly different from no asthma group at the  $P < 0.05$  level.

adult-onset asthma had higher carotid intima-media thickness; however, this analysis was from the 1980s and did not evaluate associations with carotid plaque, a stronger predictor of incident ASCVD events.<sup>27</sup> Additional studies investigated arterial injury among adolescents with asthma and demonstrated increased carotid-intima media thickness, but given the young ages of these cohorts, carotid atherosclerosis was not an expected finding.<sup>28,29</sup>

Our study offers new insights. First, we investigated carotid plaque presence and burden, whereas previous studies mainly investigated carotid intima-media

thickness and asthma. Carotid intima-media thickness and plaque are related but represent different pathophysiological processes. Carotid intima-media thickening can be secondary to intimal thickening and/or medial hypertrophy, with the latter reflective of hemodynamic stressors, such as hypertension.<sup>30,31</sup> Carotid plaque, in contrast, is a specific manifestation of atherosclerotic process, including intimal thickening, foam cell infiltration, inflammatory cell infiltration, and fibrous cap formation.<sup>32</sup> Carotid plaque is a stronger predictor of future ASCVD events compared with carotid IMT.<sup>33</sup> Carotid plaque assessment allows detection of both noncalcified and calcified plaques and can identify the atherosclerotic process early, providing important prognostic data before the later stages of atherosclerosis identified as calcified plaque on computed tomography imaging.

Second, this is the largest study to investigate carotid plaque presence and burden in a multiethnic cohort. In the MESA, the prevalence of asthma was  $\approx 10\%$  (N=647), which is similar to the national prevalence of asthma in the United States.<sup>1</sup> The lack of association of intermittent asthma and carotid plaque measures

**Table 3. Association of Asthma Subtype With Carotid Plaque Score**

Model	Persistent asthma*		Intermittent asthma*	
	$\beta$ (95% CI) <sup>†</sup>	P value	$\beta$ (95% CI) <sup>†</sup>	P value
1	0.79 (0.35 to 1.24)	<0.001	-0.04 (-0.22 to 0.15)	0.7
2	0.71 (0.31 to 1.11)	<0.001	0.12 (-0.05 to 0.30)	0.1
3	0.66 (0.27 to 1.04)	0.001	0.11 (-0.06 to 0.27)	0.2

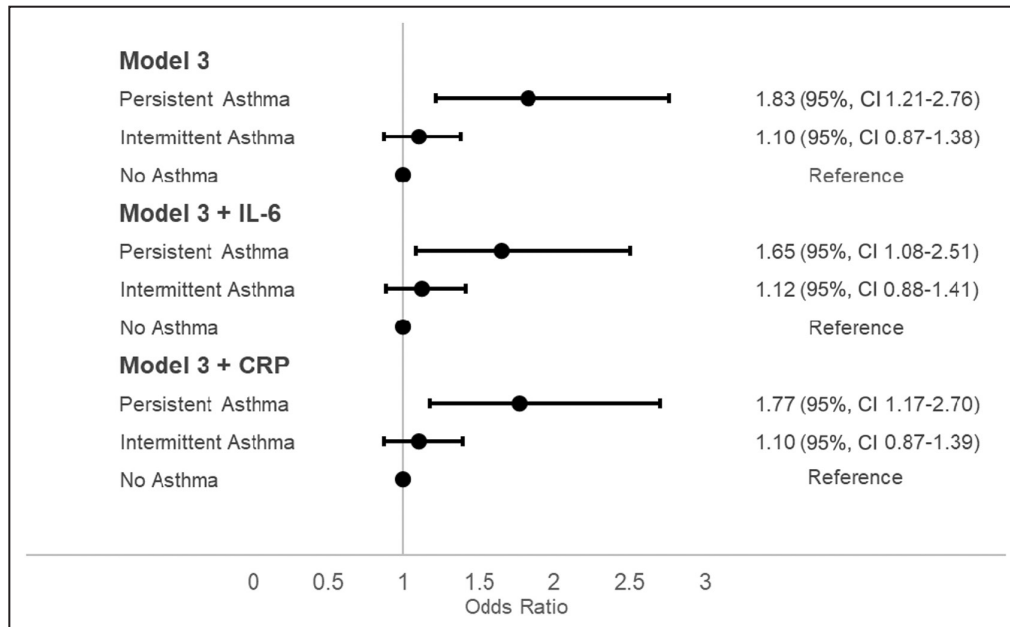
\*"No asthma" group as reference.

<sup>†</sup> $\beta$  coefficients represent adjusted plaque score difference for each asthma subtype compared with "no asthma" group. Model 1, unadjusted. Model 2, adjusted for age, race and ethnicity, sex, and education. Model 3, model 2 plus body mass index, total and high-density lipoprotein cholesterol, systolic blood pressure, smoking, statin use, hypertension medications, and diabetes.

is not unexpected, highlights the heterogeneity of the asthma syndrome, and supports our hypothesis that more severe forms of the disease may have more carotid arterial injury manifestations. Participants with intermittent asthma included those with a prior asthma diagnosis who may be in remission, in whom asthma resolved, or who did not have active asthma severe enough to require controller medications. Finally, we evaluated serum markers of inflammation among asthma subtypes. Participants with persistent asthma had the highest level of serum inflammatory markers despite use of controller medications, followed by

participants with intermittent asthma and no asthma. Previous reports demonstrated that elevated plasma IL-6 is a biomarker in asthma that is associated with asthma severity, more exacerbations, and impaired lung function.<sup>12,13,34</sup> Participants with persistent asthma in the MESA had the highest serum levels of IL-6; however, the mean IL-6 serum levels of the participants with persistent asthma in the MESA still were lower than the mean IL-6 levels of participants with asthma with exacerbation-prone asthma and the high IL-6 participants with asthma in the Severe Asthma Research Program.<sup>12,13</sup> We found that higher serum measures of IL-6 and CRP independently predicted carotid plaque presence and burden; other studies have demonstrated increased ASCVD events with higher serum IL-6 levels.<sup>9,10</sup> These findings suggest that the high IL-6 asthma phenotype may be at higher risk for carotid plaque development and future ASCVD events.

The association of persistent asthma and carotid plaque may have several potential mechanistic underpinnings. Asthma is a heterogeneous syndrome with unique endotypes and clinical phenotypes; thus, there may be multiple overlapping inflammatory pathways.<sup>35</sup> Shared aberrations in the adaptive immune system between asthma and atherosclerosis may contribute, resulting in upregulation of effector cells and cytokines contributing to systemic inflammation. Asthma and ASCVD share a disturbed balance in T-helper cell polarization.<sup>35-38</sup> High T<sub>2</sub> inflammation counterregulates T<sub>1</sub> inflammation, and interleukin-4, a T<sub>2</sub>-secreted



**Figure 2. Association of carotid plaque presence and asthma subtype with and without adjustment for baseline inflammatory markers.**

Model 3, adjusted for age, sex, race, body mass index, systolic blood pressure, tobacco use, total cholesterol, high-density lipoprotein cholesterol, education, statin medication use, antihypertensive medication use, and diabetes. CRP indicates C-reactive protein; and IL-6, interleukin-6.

cytokine, directly inhibits  $T_1$  cells, whereas interferon- $\beta$ , a proatherogenic  $T_1$  cytokine, directly inhibits  $T_2$  cells.<sup>39,40</sup> ASCVD appears to be a  $T_1$  (low  $T_2$ ) driven process.<sup>41–43</sup> A candidate effector cytokine in the  $T_1$  atherosclerotic process is the IL-6 pathway, which promotes atherosclerosis in part by directly inhibiting T-regulatory cells, permitting the proatherogenic  $T_1$  response to proceed.<sup>44</sup> IL-6 also induces endothelial dysfunction, the earliest stage in arterial injury and atherosclerotic plaque formation, propagates inflammation, and predicts future ASCVD events.<sup>9,45,46</sup> Each stage of atherosclerosis is impacted by IL-6 signaling from plaque inception to plaque instability and rupture.<sup>46</sup> Blockade of interleukin-1 $\beta$ , an upstream cytokine of IL-6, by canakinumab in the Antiinflammatory Therapy With Canakinumab for Atherosclerotic Disease trial reduced ASCVD events, without altering lipids or blood pressure.<sup>47</sup>

Asthma with elevated serum IL-6 levels is a type of low  $T_2$  asthma endotype, and the IL-6 pathway is a putative candidate pathway of inflammatory overlap between asthma and ASCVD. Indeed, we observed higher levels of baseline IL-6 and CRP among the participants with persistent asthma, consistent with a higher systemic inflammatory state, and these serum markers were strongly associated with carotid plaque presence and TPS; however, adjustment for these serum inflammatory markers did not attenuate the association of persistent asthma and carotid plaque; therefore, a mediation effect cannot be implied. Further investigations are needed to better define this association and explore if similar associations exist for upstream (interleukin-1 $\beta$ ) effectors in asthma and carotid atherosclerosis.

## Limitations

This is an observational study, and the associations identified may not be causal. Because asthma was diagnosed as self-reported, “physician-diagnosed asthma,” there could be misclassification bias; however, this diagnostic strategy has previously demonstrated a high sensitivity (91%) and specificity (97%) in other epidemiologic studies.<sup>10,21,22,48</sup> Also, we improved the specificity of the asthma definition by categorizing participants with asthma according to current use of step 2 to 6 asthma therapies. In the absence of characterization of asthma severity in the MESA, we observed a gradient of inflammatory markers between the participants without asthma, participants with intermittent asthma, and participants with persistent asthma, which further supports our definition and classification of asthma and its subtypes. Because asthma severity was defined in part by the need for daily controller medications, this study is unable to assess the effects of asthma medications on carotid plaque presence

and TPS. This study is a cross-sectional analysis of the association of asthma subtype and carotid plaque presence and TPS and is unable to establish temporality in this association. Our a priori models were adjusted for available biologic confounders; however, we cannot exclude residual confounding. Finally, the MESA is a US cohort of participants free of ASCVD at baseline, and the generalizability to the population at large may be limited.

## CONCLUSIONS

Participants with persistent asthma, but not those with intermittent asthma, had a higher carotid plaque burden compared with participants without asthma. Participants with persistent asthma also had higher levels of inflammatory biomarkers; however, adjustment for baseline inflammatory biomarkers did not attenuate the association between carotid plaque and asthma subtype, indicating the increased ASCVD risk among individuals with persistent asthma may be multifactorial. Because asthma prevalence continues to increase and ASCVD remains the leading cause of death in the United States, these diseases create a significant public health burden and emphasize the importance of additional studies to define their shared mechanistic underpinnings.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Table S1–S7



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# SUPPLEMENTAL MATERIAL

**Table S1. Baseline Characteristics: Included Participants Compared to Participants with Missing Data**

Variables	Included (n=5,029)	Missing Data (n=1,785)	p Value
Age, years	61.6 (10.0)	63.6 (10.6)	<0.001
Body-mass index, kg/m <sup>2</sup>	28.3 (5.4)	28.5 (5.6)	0.16
Female sex, n (%)	2657 (52.8)	944 (52.9)	0.97
Race/Ethnicity % (N)			
African-American, n (%)	1306 (26.0)	586 (32.8)	<0.0001
Chinese-American, n (%)	625 (12.4)	179 (10.0)	
Hispanic, n (%)	1139 (22.6)	357 (20.0)	
White, Caucasian n (%)	1959 (39.0)	663 (37.1)	
Smoking			
Never smoker, n (%)	2546 (50.6)	872 (49.5)	0.48
Former smoker, n (%)	1840 (36.6)	647 (36.7)	
Current smoker, n (%)	643 (12.8)	244 (13.8)	
Total cholesterol, mg/dL	194.3 (35.7)	193.8 (35.9)	0.64
HDL cholesterol, mg/dL	50.7 (14.8)	51.6 (14.9)	0.05
Systolic blood pressure, mmHg	126.1 (21.4)	128.0 (21.7)	0.001
Diabetes Mellitus, n (%)	604 (12.0)	255 (14.5)	0.007
Anti-hypertensives	1834 (36.5)	702 (39.4)	0.03
Statins	753 (15.0)	257 (14.5)	0.64
Oral corticosteroids	77 (1.5)	257 (1.6)	0.88
Leukotriene receptor antagonists	35 (0.7)	17 (1.0)	0.27
Inhaled corticosteroids	98 (1.9)	49 (2.8)	0.04
Carotid Plaque Present, n (%)	2555 (50.8)	154 (63.6)	<0.001
Mean Carotid Plaque Score (SD)	1.3 (1.8)	1.9 (2.3)	<0.001

Abbreviations HDL= High-Density-Lipoprotein

**Table S2. Association of Asthma Subtype with Carotid Plaque Score in Fully Adjusted Model 3**

Covariates	$\beta$ (95% CI)	p Value
Asthma Subtype		
Intermittent Asthma	0.11 (-0.58, 0.27)	0.21
Persistent Asthma	0.66 (0.27, 1.04)	0.001
Age, per 10 years	0.52 (0.47, 0.57)	<0.0001
Body-mass index, kg/m <sup>2</sup>	-0.02 (-0.03, -0.01)	<0.0001
Male sex	0.30 (0.20, 0.41)	<0.0001
Race/Ethnicity		
African American	-0.41 (-0.53, -0.29)	<0.0001
Chinese American	-0.64 (-0.79, -0.49)	<0.0001
Hispanic	-0.45 (-0.58, -0.31)	<0.0001
Smoking Status		
Former smoker	0.24 (0.14, 0.34)	<0.0001
Current smoker	0.72 (0.57, 0.87)	<0.0001
Total cholesterol, per 10 mg/dL	0.04 (0.03, 0.06)	<0.0001
HDL cholesterol, per 10 mg/dL	-0.04 (-0.08, -0.003)	0.03
Systolic blood pressure, per 10 mmHg	0.09 (0.06, 0.11)	<0.0001
Diabetes Mellitus	0.32 (0.16, 0.49)	<0.0001
Medication		
Antihypertensive	0.24 (0.13, 0.35)	<0.0001
Statin	0.48 (0.33, 0.63)	<0.0001
Education Highest Completed		
High School	-0.03 (-0.18, 0.11)	0.65
College	-0.17 (-0.34, 0.01)	0.06
Graduate School	-0.31 (-0.48, -0.13)	0.001

Abbreviations HDL= High-Density-Lipoprotein

**Table S3. Association of Asthma Subtype with Carotid Plaque Score Fully Adjusted Model 3 + Interleukin-6**

Covariates	$\beta$ (95% CI)	p Value
Asthma Subtype		
Intermittent Asthma	0.13 (-0.04, 0.30)	0.12
Persistent Asthma	0.62 (0.21, 1.02)	0.003
Age, per 10 years	0.51 (0.45, 0.56)	<0.0001
Body-mass index, kg/m <sup>2</sup>	-0.03 (-0.04, -0.02)	<0.0001
Male sex	0.32 (0.22, 0.43)	<0.0001
Race/Ethnicity		
African American	-0.43 (-0.55, -0.30)	<0.0001
Chinese American	-0.62 (-0.77, -0.47)	<0.0001
Hispanic	-0.45 (-0.59, -0.31)	<0.0001
Smoking Status		
Former smoker	0.24 (0.14, 0.34)	<0.0001
Current smoker	0.65 (0.50, 0.80)	<0.0001
Total cholesterol, per 10 mg/dL	0.05 (0.04, 0.06)	<0.0001
HDL cholesterol, per 10 mg/dL	-0.04 (-0.08, -0.01)	0.02
Systolic blood pressure, per 10 mmHg	0.08 (0.05, 0.11)	<0.0001
Diabetes Mellitus	0.29 (0.12, 0.45)	0.001
Medication		
Antihypertensive	0.22 (0.10, 0.33)	<0.0001
Statin	0.51 (0.35, 0.66)	<0.0001
Education Highest Completed		
High School	-0.03 (-0.18, 0.12)	0.70
College	-0.18 (-0.35, -0.001)	0.05
Graduate School	-0.29 (-0.47, -0.12)	0.001
Interleukin-6	0.18 (0.11-0.25)	<0.0001

Abbreviations HDL= High-Density-Lipoprotein

**Table S4. Association of Asthma Subtype with Carotid Plaque Score Fully Adjusted Model 3 + C-Reactive Protein**

Covariates	$\beta$ (95% CI)	p Value
Asthma Subtype		
Intermittent Asthma	0.11 (-0.05, 0.28)	0.20
Persistent Asthma	0.65 (0.25, 1.04)	0.001
Age, per 10 years	0.53 (0.47, 0.58)	<0.0001
Body-mass index, kg/m <sup>2</sup>	-0.02 (-0.03, -0.01)	<0.0001
Male sex	0.31 (0.20, 0.42)	<0.0001
Race/Ethnicity		
African American	-0.40 (-0.52, -0.28)	<0.0001
Chinese American	-0.63 (-0.78, -0.48)	<0.0001
Hispanic	-0.43 (-0.57, -0.30)	<0.0001
Smoking Status		
Former smoker	0.24 (0.14, 0.34)	<0.0001
Current smoker	0.72 (0.57, 0.87)	<0.0001
Total cholesterol, per 10 mg/dL	0.04 (0.03, 0.06)	<0.0001
HDL cholesterol, per 10 mg/dL	-0.04 (-0.08, -0.01)	0.02
Systolic blood pressure, per 10 mmHg	0.08 (0.06, 0.11)	<0.0001
Diabetes Mellitus	0.31 (0.15, 0.48)	0.001
Medication		
Antihypertensive	0.23 (0.12, 0.35)	<0.0001
Statin	0.49 (0.33, 0.64)	<0.0001
Education Highest Completed		
High School	-0.03 (-0.17, 0.12)	0.73
College	-0.15 (-0.33, 0.02)	0.09
Graduate School	-0.28 (-0.46, -0.11)	0.002
C-Reactive Protein	0.03 (0.001-0.06)	0.04

Abbreviations HDL= High-Density-Lipoprotein

**Table S5. Association of Asthma Subtype with Carotid Plaque Presence in Fully Adjusted Model 3**

<b>Covariates</b>	<b>Odds Ratio (95% CI)</b>	<b>p Value</b>
Asthma Subtype		
Intermittent Asthma	1.08 (0.86,1.37)	0.50
Persistent Asthma	1.84 (1.22, 2.78)	0.004
Age, in years	1.06 (1.05,1.07)	<0.0001
Body-mass index, kg/m <sup>2</sup>	0.99 (0.97,1.00)	0.06
Male sex	1.31 (1.14,1.50)	<0.0001
Race/Ethnicity		
African American	0.70 (0.59, 0.82)	<0.0001
Chinese American	0.44 (0.35, 0.55)	<0.0001
Hispanic	0.59 (0.50, 0.71)	<0.0001
Smoking Status		
Former smoker	1.36 (1.19,1.55)	<0.0001
Current smoker	2.15 (1.77, 2.61)	<0.0001
Total cholesterol, mg/dL	1.01 (1.00, 1.01)	<0.0001
HDL cholesterol, mg/dL	1.00 (0.99,1.00)	0.08
Systolic blood pressure, mmHg	1.01 (1.01, 1.01)	<0.0001
Diabetes Mellitus	1.69 (1.38, 2.08)	<0.0001
Medication		
Antihypertensive	1.25 (1.09,1.44)	0.002
Statin	1.72 (1.43, 2.06)	<0.0001
Education Highest Completed		
High School	1.03 (0.86,1.25)	0.72
College	0.95 (0.75,1.20)	0.66
Graduate School	0.75 (0.60, 0.95)	0.02

Abbreviations HDL= High-Density-Lipoprotein



**Table S6. Association of Asthma Subtype with Carotid Plaque Presence in Fully Adjusted Model 3 + Interleukin-6**

Covariates	Odds Ratio (95% CI)	p Value
Asthma Subtype		
Intermittent Asthma	1.11 (0.87,1.40)	0.40
Persistent Asthma	1.67 (1.09, 2.53)	0.017
Age, in years	1.06 (1.05,1.07)	<0.0001
Body-mass index, kg/m <sup>2</sup>	0.98 (0.97,1.00)	0.017
Male sex	1.33 (1.15,1.52)	<0.0001
Race/Ethnicity		
African American	0.69 (0.59, 0.81)	<0.0001
Chinese American	0.45 (0.36, 0.56)	<0.0001
Hispanic	0.57 (0.48, 0.69)	<0.0001
Smoking Status		
Former smoker	1.37 (1.19,1.57)	<0.0001
Current smoker	2.10 (1.72, 2.56)	<0.0001
Total cholesterol, mg/dL	1.01 (1.01, 1.01)	<0.0001
HDL cholesterol, mg/dL	1.00 (0.99,1.00)	0.097
Systolic blood pressure, mmHg	1.01 (1.01, 1.01)	<0.0001
Diabetes Mellitus	1.68 (1.37, 2.07)	<0.0001
Medication		
Antihypertensive	1.23 (1.07,1.41)	0.005
Statin	1.75 (1.45, 2.10)	<0.0001
Education Highest Completed		
High School	1.03 (0.85,1.24)	0.76
College	0.92 (0.72,1.17)	0.51
Graduate School	0.74 (0.59, 0.94)	0.012
Interleukin-6	1.15 (1.06, 1.26)	0.001

Abbreviations HDL= High-Density-Lipoprotein

**Table S7. Association of Asthma Subtype with Carotid Plaque Presence in Fully Adjusted Model 3 + C-Reactive Protein**

Covariates	$\beta$ (95% CI)	p Value
Asthma Subtype		
Intermittent Asthma	1.09 (0.86,1.38)	0.46
Persistent Asthma	1.79 (1.18, 2.71)	0.007
Age, in years	1.06 (1.05,1.07)	<0.0001
Body-mass index, kg/m <sup>2</sup>	0.99 (0.97,1.00)	0.03
Male sex	1.33 (1.15,1.53)	<0.0001
Race/Ethnicity		
African American	0.70 (0.59, 0.82)	<0.0001
Chinese American, n (%)	0.45 (0.36, 0.56)	<0.0001
Hispanic, n (%)	0.60 (0.50, 0.71)	<0.0001
Smoking Status		
Former smoker, n (%)	1.36 (1.19,1.56)	<0.0001
Current smoker, n (%)	2.15 (1.77, 2.61)	<0.0001
Total cholesterol, mg/dL	1.01 (1.00, 1.01)	<0.0001
HDL cholesterol, mg/dL	1.00 (0.99,1.00)	0.06
Systolic blood pressure, mmHg	1.01 (1.01, 1.01)	<0.0001
Diabetes Mellitus	1.68 (1.37, 2.06)	<0.0001
Medication		
Antihypertensive	1.24 (1.08,1.43)	0.002
Statin	1.73 (1.45, 2.08)	<0.0001
Education Highest Completed		
High School	1.03 (0.86,1.24)	0.73
College	0.95 (0.75,1.20)	0.65
Graduate School	0.76 (0.61, 0.96)	0.02
C-Reactive Protein	1.04 (1.00-1.08)	0.08

Abbreviations HDL= High-Density-Lipoprotein