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Residential Exposure to $PM_{2.5}$ and Ozone and Progression of Subclinical Atherosclerosis Among Women Transitioning Through Menopause: The Study of Women's Health Across the Nation

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Abstract

Objective: This article aims to examine the association between long-term ambient air pollution and progression of subclinical atherosclerosis with 2-year follow-up among midlife women from the Study of Women's Health Across the Nation (SWAN).

Methods: Carotid duplex ultrasonography was performed in participants from a SWAN ancillary study carried out at the Pittsburgh and Chicago sites. Mean and maximum carotid intima-media thickness (CIMT) and plaque burden were assessed throughout the common, bulb, and internal carotid artery. The yearly mean exposure to $PM_{2.5}$ (particulate matter) and ozone was generated based on monitors within 20 km of the participants' home. The effect of air pollutants during follow-up on progression of CIMT was estimated using linear mixed-effects models, and the effect on progression of plaque presence and plaque index, a measure of extent of plaque, was evaluated using logistic regression.

Results: This study included 417 (257 White and 160 Black) women with a mean age of 51 years at baseline. A 1 $\mu g/m^3$ higher yearly mean exposure to $PM_{2.5}$ during follow-up was associated with a 4.28 (95% confidence interval [CI]: 0.02–8.54) μm/year increase in maximum CIMT, after adjusting for socioeconomic and traditional cardiovascular disease (CVD) risk factors. Exposure to $PM_{2.5}$ contributed to a 30% (95% CI: 3%–65%) higher odds of plaque index progression adjusting for socioeconomic factors only.

Conclusions: $PM_{2.5}$ independently contributed to progression of subclinical atherosclerosis, among women transitioning through menopause, a time of increasing CVD risk. Yet no significant associations between ozone and subclinical atherosclerosis were observed.

Keywords: particulate matter ($PM_{2.5}$), ozone (O_3), subclinical atherosclerosis progression, women's health, menopause transition

Introduction

During the past two decades, there have been a growing number of studies demonstrating that ambient air pollution has a deleterious effect on health,[1,2] especially for cardiovascular disease (CVD).[3–6] Franklin et al.[6] estimated that air pollution may account for 10%–25% of the risk of coronary heart disease that is not explained by traditional risk factors. However, the effects of long-term exposure of air pollution and the mechanisms leading to CVD are unclear, but may be through increased inflammation, oxidative stress, increased blood pressure, and endothelial dysfunction, processes associated with atherosclerosis.[7]

The mechanisms linking air pollution to CVD may be explored by assessing progression of markers of subclinical atherosclerosis. Carotid intima-media thickness (CIMT) measured *via* B-mode ultrasound reflects the carotid artery wall thickness. It is a surrogate biomarker of atherosclerosis[8] that predicts CVD events in population-based cohorts.[8–11] Change in CIMT may be a valid predictor of vascular

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events[12–16] and a widely used surrogate measure for intervention studies.[17,18] Plaque is a direct measure of atherosclerosis, and its presence in the carotid arteries may better predict CVD risk compared with CIMT alone.[19] Few studies have considered plaque progression,[20] and have been mainly limited to patients who already had significant atherosclerosis.[21–23]

The role of air pollution in women's cardiovascular health has drawn more attention in recent years. In the Women's Health Initiative, $PM_{2.5}$ (particulate matter) exposure was associated with cardiovascular events after a median follow-up of 6 years among postmenopausal women.[24] In the Nurse's Health Study, long-term exposure to PM was related to CVD among diabetic women.[25] However, it is unclear whether greater exposure to air pollution during the menopause transition exacerbates the increased CVD susceptibility.[26]

The increasing CVD risk across the menopause stages has been observed using subclinical measures of CVD.[27] In a prior analysis of women at various stages of the menopause, late peri- and postmenopausal women had greater progression of markers of subclinical CVD, including CIMT, compared with pre- and early perimenopausal women.[26] Moreover, national data indicate that midlife women are more active than older women, and spend more time outdoors; and therefore, may have greater exposure to ambient air pollution.[28] Thus, exposure to ambient air pollution may affect progression of subclinical CVD differentially across menopause stages.

The positive association between exposure to 1-year air pollution and atherosclerosis has been examined in different populations cross-sectionally.[29–37] To date, only a few published studies have addressed the longitudinal association between air pollution and progression of atherosclerosis,[38–41] and even fewer have focused on midlife women. In the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) study,[38] exposure to $PM_{2.5}$ was associated with greater common carotid artery (CCA) CIMT progression; however, most of the women were postmenopausal.[42] One of the few studies evaluating plaque progression did not find any significant associations with air pollutants and either CIMT progression or plaque progression.[39]

These heterogeneous findings suggest that more evidence is needed to ascertain the association between air pollution and progression of atherosclerosis. Thus, in a cohort of middle-aged (45–56 years old) Black and White women, we examined the prospective association between exposure to $PM_{2.5}$ and O_3 and progression of atherosclerosis over a 2.2-year period, utilizing both CIMT and plaque as biomarkers of atherosclerosis.

Materials and Methods

Study population

The Study of Women's Health Across the Nation (SWAN) is a community-based multicenter multiethnic cohort study designed to characterize women's health as they transition through menopause. The SWAN study was conducted at seven sites across the United States beginning in 1996 and enrolled 3302 women aged 42–52 years at baseline.[43] For the current analyses, we used data from SWAN Heart, an ancillary study to SWAN focused on subclinical CVD progression, in which carotid ultrasound measures of atherosclerosis were collected from women in the Pittsburgh and Chicago sites. These two SWAN Heart study sites recruited White and Black women. The SWAN Heart baseline carotid ultrasound measurements were obtained from participants attending SWAN visits 4–7 (2001–2004); a 2-year follow-up took place at SWAN visits 6–9 (2002–2006) (Supplementary Table S1). The current analysis included SWAN Heart participants who also had air pollution exposure data available (Supplementary Figure S1). The study was approved by the Institutional Review Board at each site. Written informed consent was obtained from all of the participants.

Exposure to $PM_{2.5}$ and O_3

Ambient air pollution exposure was assessed by the Air Pollution Study, another SWAN ancillary study. This study determined the $PM_{2.5}$ and O_3 exposure levels of SWAN participants from visits 3 to 7 based on monitors located within 20 km of residential address data collected at these visits. Daily $PM_{2.5}$ and O_3 values were retrieved from US EPA Air Quality System Data Mart.[44] Annual exposure to these pollutants was defined as 360 days before the study visit. Detailed methods of exposure assessment and the address geocoding have been published elsewhere.[45,46] For each participant, an annualized mean exposure to $PM_{2.5}$ and O_3 was calculated based on each participant's prior mean yearly exposure from their SWAN Heart baseline to follow-up visit (Supplementary Table S1).

Assessment of CIMT and plaque

The carotid arteries were scanned *via* B-mode ultrasound by centrally trained and experienced sonographers. In Chicago, a Hewlett Packard SONOS 5500 scanner (Hewlett Packard, Andover, MA) was used to collect the images, and in Pittsburgh, a Toshiba 270 A (Toshiba American Medical Systems, Tustin, CA) was used. The qualities of the images were comparable between the two machines.[47,48] Images were collected at both left and right sides of carotid artery at four locations: two at CCA, one at the bulb, and one at internal carotid artery (ICA). These images were read using semiautomated edge detection reading software (AMS). This study has yielded high reproducibility in both scanning and reading as previously reported.[47,48] The mean and maximum of these eight segments were calculated. Interadventitial diameters (ADs) were measured directly as the distance from the adventitial–media interface of the near wall to the media–adventitial interface of the far wall of the CCA segment only.[26] Plaque presence, number, and grade were assessed during the ultrasound scan in five carotid segments, proximal and distal segments of the CCA, bulb, ICA and external carotid artery. For each segment, plaque grade was categorized into four levels, with 0 representing no plaque to 3 for a plaque taking up >50% diameter of the artery. The sum of plaque grades across all segments generated our major outcome plaque index (possible range: 0–30).[49]

Assessment of other CVD risk factors

Self-reported race, education, and financial strain were collected at baseline screening. Financial strain was collected based on the question of how hard to pay for the very basics, which includes living expenses and medical treatment. It was

categorized into three classes: very hard, somewhat hard, and not hard at all. The study collected data on traditional CVD risk factors at each follow-up visit. Physical measures of body mass index (BMI), and systolic and diastolic blood pressures (SBP and DBP) were collected using standard methodology.[50] Blood samples were drawn after a 12-hour fast. The samples were sent to the Medical Research Laboratories for analysis. The analyses of high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein (LDL-c), total cholesterol, and triglycerides, as well as high-sensitivity C-reactive protein (hsCRP), tissue-type plasminogen activator antigen (tPA), and plasma plasminogen activator inhibitor 1 (PAI-1), used standard methodology that has been published elsewhere.[48,51]

Statistical analysis

Since glucose, insulin, and triglycerides were positively skewed, they were log transformed. Linear mixed-effects models were used to estimate the effect of time-varying $PM_{2.5}$ and O_3 exposures on CIMT and AD progression. The associations between the annualized mean exposure during follow-up and progression of CIMT or AD were assessed by examining the regression coefficient of the interaction term of air pollution exposure from SWAN Heart baseline to follow-up and time since baseline (Supplementary Data). Other covariates were extracted using the baseline value. Logistic regressions were applied to estimate the effect of the annual mean cumulative exposure to $PM_{2.5}$ and O_3 and progression of plaque presence and plaque index. The annualized mean of air pollutants exposure and continuous covariates from SWAN Heart baseline to SWAN Heart follow-up visits were used in these models. All of the categorical variables were extracted at SWAN Heart baseline. Three nested models were constructed to establish the association between air pollutant exposures and subclinical atherosclerosis, Model 1, model controlling for site; Model 2a, model further adjusted for socioeconomic status (SES)/demographic factors: age at baseline, race, education, and financial strain; Model 2b, fully adjusted model, further adjusted for traditional CVD risk factors: BMI, smoking, triglycerides, LDL-c, HDL-c, lipid-lowering medication, hypertension medication, menopause status, hormone replacement therapy, diabetes and family history of CVD or stroke; and Model 3, extended model, additionally adjusted for potential mediators based on the literature[7]: SBP, hsCRP, tPA, and PAI-1. Analyses were performed with SAS (V9.3; SAS Institute, Cary, NC). All tests were two sided, $\alpha = 0.05$.

Results

SWAN Heart baseline characteristics by quartiles of baseline ambient $PM_{2.5}$ exposure are presented in Table 1 for the 417 SWAN Heart women who were included in these analyses. There were 257 White and 160 Black women with a mean age of 51 years (standard deviation = 2.8). Most of our study participants were at late-peri menopausal stage ($N = 235$, 56.4%), while only 29 (7%) women were at pre/-early perimenopause, 113 (27%) at postmenopause stages, and the remaining 39 were indeterminable. At baseline, most CVD risk factors were comparable across $PM_{2.5}$ quartiles, except for race/ethnicity, insulin, and hsCRP (Table 1). Women with addresses with lower $PM_{2.5}$ levels were more likely to be White ($p = 0.038$). Women who lived in areas with higher $PM_{2.5}$ level had significantly higher median insulin and hsCRP. We also observed that, at baseline, women who lived in areas with higher $PM_{2.5}$ exposure had thinner bulb CIMT ($p = 0.023$). Cross-sectional correlations between $PM_{2.5}$ and ozone exposure and carotid CIMT and AD were weak (Supplementary Tables S2 and S3).

The median follow-up time was 2.2 years (range: 1.1–4.4). Over the course of 2 years, we observed some changes in air pollution exposure levels at the two sites. The within-site exposure levels of these two pollutants at baseline and follow-up are shown in Figure 1. The ambient $PM_{2.5}$ exposure level was 16.5 $\mu g/m^3$ (interquartile range [IQR]: 15.7–17.1) at baseline and reduced slightly to 15.5 $\mu g/m^3$ (IQR: 15.0–16.2) at follow-up; and O_3 was 31.9 ppb (IQR: 30.3–33.5) at baseline and increased to 34.4 ppb (IQR: 32.5–36.6) at follow-up. As depicted in Supplementary Figure S2, all CIMT measures demonstrated yearly progression during the study follow-up. The progression of mean CIMT was 16.3 (IQR: −1.4 to 33.6) μm/year, the progression of maximum CIMT was 20.8 (IQR: −3.6 to 45.4) μm/year, and the progression of mean AD was 41.4 (IQR: −36.7 to 113.0) μm/year. The per segment progression levels of CIMT were 15.7 (IQR: −4.4 to 27.8) μm/year, 19.5 (IQR: −10.3 to 45.1) μm/year, and 14.7 (IQR: −21.3 to 41.6) μm/year for CCA, ICA, and bulb, respectively. The prevalence of plaque was relatively low among these women, such that 66 (15.6%) women had plaque at baseline, and most of them ($n = 57$, 86%) had very small plaques with plaque index of 1 or 2. Among the 319 women who had plaque progression data, 74 (23.2%) demonstrated progression of plaque prevalence and 67 (21.0%) of plaque index.

In the primary analysis, a 1 $\mu g/m^3$ higher yearly mean exposure to $PM_{2.5}$ during follow-up was associated with a 2.25 (95% confidence interval [CI]: −0.61–5.12) μm/year increase in mean CIMT; and was associated with a 4.28 (95% CI: 0.02–8.54) μm/year increase in maximum CIMT, after adjusting for traditional CVD risk factors and confounders (Table 2). In the per segment analyses, we did not observe any significant association between yearly mean exposure to $PM_{2.5}$ during follow-up and progression of CCA and ICA CIMT, but a stronger association with bulb (Table 3). Women with a 1 $\mu g/m^3$ higher yearly mean exposure to $PM_{2.5}$ during follow-up had a 6.54 (95% CI: 0.49–12.24) μm/year higher bulb CIMT progression. In the extended model, further adjustment for SBP, hsCRP, PAI-1, and tPA did not change the association between $PM_{2.5}$ and CIMT appreciably. In the model adjusting for baseline O_3, the association was slightly lower compared with the single-pollutant model (Supplementary Table S4). No association was observed between O_3 exposure and mean and the maximum CIMT (Tables 2 and 3). Neither pollutant was related to AD progression.

There was no association between $PM_{2.5}$ and O_3 and plaque presence progression in the fully adjusted single- or two-pollutant models (Table 4). Each 1 $\mu g/m^3$ higher yearly mean residential exposure to $PM_{2.5}$ during follow-up was associated with ~30% (95% CI: 3%–65%) higher chance of plaque index progression, adjusting for SES/demographic factors in both single- and two-pollutant models (Table 5). However, the relationship between $PM_{2.5}$ and progression of plaque index was not observed in the fully adjusted single-pollutant model (Table 4), and was only marginally associated in the fully adjusted two-pollutant model (Table 5) ($p = 0.080$).

Table 1. Baseline Characteristics by Baseline $PM_{2.5}$ Exposure Quartiles

	$PM_{2.5}$ ($\mu g/m^3$)				
	13.16–15.74 (n = *105*)	*15.74–16.45* (n = *104*)	*16.45–17.11* (n = *103*)	*17.11–23.04* (n = *105*)	p-*Trend*
O_3 (ppb)	32.7 (2.7)	32.8 (2.5)	30.3 (2.8)	32.0 (2.5)	**<0.001**
Age (years)	51.0 (2.7)	50.2 (2.8)	50.5 (2.8)	50.6 (2.7)	0.484
White (%)	78 (74.3)	58 (55.8)	59 (57.3)	62 (59.1)	**0.038**
Education (%)					0.245
≤ High school	22 (21.0)	25 (24.0)	8 (7.8)	12 (11.4)	
Some college/college	27 (25.7)	31 (29.8)	35 (34.0)	39 (37.1)	
> College	56 (53.3)	48 (46.2)	60 (58.3)	54 (52.4)	
Pay for basics (%)					0.613
Very hard	3 (2.9)	6 (5.8)	3 (2.9)	6 (5.7)	
Somewhat	26 (24.8)	29 (27.9)	32 (31.1)	26 (24.8)	
Not very	76 (72.4)	69 (66.3)	68 (66.0)	73 (69.5)	
Menopausal status (%)					0.481
Pre- and early perimenopause	7 (6.7)	10 (9.7)	7 (6.8)	5 (4.8)	
Late perimenopause	54 (51.4)	55 (53.4)	66 (64.1)	60 (57.1)	
Postmenopause	29 (27.6)	30 (29.1)	25 (24.3)	29 (27.6)	
Other	15 (14.3)	8 (7.8)	5 (4.9)	11 (10.5)	
Current smokers (%)	13 (12.4)	17 (16.4)	11 (10.7)	15 (14.4)	0.928
BMI	28.2 (6.3)	30.1 (6.1)	29.7 (6.8)	29.1 (6.0)	0.400
SBP (mmHg)	115.4 (17.3)	120.0 (19.2)	118.4 (14.6)	120.6 (17.4)	0.063
DBP (mmHg)	73.1 (10.4)	76.2 (10.3)	76.1 (9.0)	76.0 (10.3)	0.063
Hypertension medication (%)	16 (15.2)	37 (35.6)	21 (20.3)	30 (28.6)	0.186
Hypertension (%)	26 (25.7)	41 (40.2)	34 (34.0)	36 (34.6)	
Cholesterol (mg/dL)	203.6 (34.0)	207.0 (39.6)	194.6 (32.4)	204.5 (42.7)	0.569
LDL (mg/dL)	120.2 (29.7)	126.9 (35.0)	114.1 (27.3)	123.7 (38.7)	0.883
HDL (mg/dL)	60.1 (14.4)	56.9 (13.9)	56.9 (14.7)	56.4 (13.0)	0.065
Triglycerides (mg/dL)	97.0 (77.0–136.0)	98.8 (75.0–136.0)	100.5 (73.0–140.0)	104.0 (79.0–138.0)	0.362
Lipid-lowering medication (%)	3 (2.9)	12 (11.5)	11 (10.7)	5 (4.8)	0.673
Glucose (mg/dL)	87.0 (81.0–93.0)	88.0 (82.0–97.0)	90.0 (84.0–96.0)	86.5 (82.0–94.0)	0.279
Insulin (uIU/mL)	8.2 (6.6–12.1)	9.3 (6.9–13.4)	10.1 (7.4–14.9)	10.0 (7.3–15.1)	**0.017**
Diabetes (%)	5 (4.8)	2 (1.9)	1 (1.0)	2 (1.9)	0.164
Diabetic medication (%)	1 (1.0)	0 (0)	0 (0)	1 (1.0)	0.999
hsCRP (mg/L)	1.5 (0.5–4.1)	1.7 (0.8–6.0)	2.5 (0.8–5.6)	2.3 (1.1–5.5)	**0.015**
tPA (ng/dL)	6.5 (4.7–9.0)	6.9 (5.4–9.4)	7.2 (5.9–10.0)	7.3 (5.3–9.7)	0.159
PAI-1 (ng/dL)	13.9 (6.8–23.2)	10.0 (6.4–24.4)	16.0 (8.0–26.9)	15.6 (9.8–26.1)	0.121
Family history (%)	73 (72.3)	73 (73.7)	61 (61.0)	66 (70.2)	0.348
Mean CIMT (μm)	677.3 (90.9)	697.8 (101.9)	662.9 (95.9)	672.7 (80.7)	0.236
CCA CIMT (μm)	668.2 (76.9)	696.1 (104.9)	672.4 (95.7)	679.1 (90.8)	0.820
ICA CIMT (μm)	603.0 (132.4)	611.8 (133.3)	577.3 (134.7)	595.3 (129.0)	0.325
Bulb CIMT (μm)	772.0 (181.5)	783.2 (185.2)	725.6 (154.4)	735.8 (135.9)	**0.023**
Maximum CIMT (μm)	873.9 (135.1)	896.8 (131.8)	867.0 (130.1)	860.7 (106.6)	0.217
AD (μm)	6658.8 (641.9)	6701.6 (646.2)	6778.2 (560.4)	6755.2 (604.7)	0.182
Plaque (%)	14 (13.3)	22 (21.2)	14 (13.6)	15 (14.3)	0.771
Plaque index (%)					0.783
0	91 (86.7)	82 (78.9)	89 (86.4)	88 (85.4)	
1–2	11 (10.5)	20 (19.2)	11 (10.7)	14 (13.6)	
>2	3 (2.9)	2 (1.9)	3 (2.9)	1 (0.9)	

Data presented as mean (standard deviation) or median (25th and 75th percentile) for continuous variables, and *N* (%) for categorical variables.

p-values < 0.05 are bolded.

AD, adventitial diameter; BMI, body mass index; CCA, common carotid artery; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; ICA, internal carotid artery; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor 1; PM, particulate matter; SBP, systolic blood pressure; tPA, tissue-type plasminogen activator antigen.

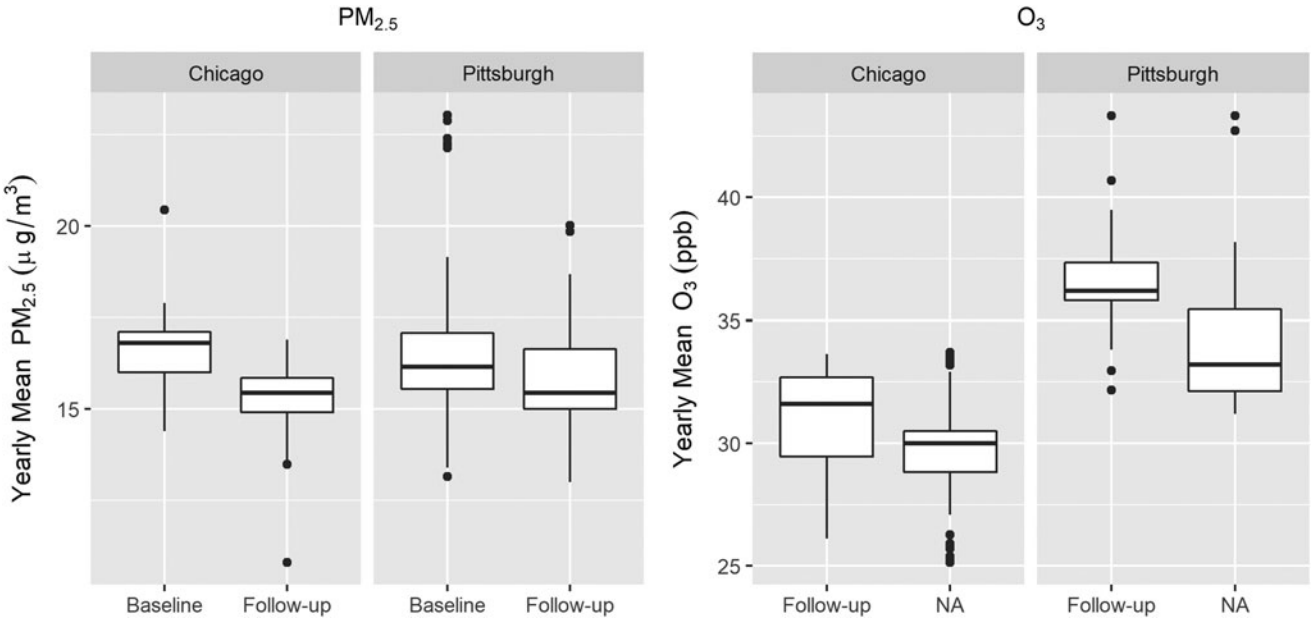

FIG. 1. Distribution of $PM_{2.5}$ and O_3 at baseline and follow-up by sites, Chicago and Pittsburgh. PM, particulate matter.

Discussion

In this prospective study, exposure to higher residential ambient $PM_{2.5}$ level was associated with accelerated atherosclerosis among early midlife women, as shown by both biomarkers, maximum CIMT and plaque index progression. However, the association between $PM_{2.5}$ and plaque index progression was not independent of traditional CVD risk factors. No effect of O_3 on subclinical atherosclerosis was observed.

This is the first study focused on air pollution and atherosclerosis among women transitioning through the menopause. The menopause is an important stage of a woman's life, which is associated with heart health. In the SWAN Heart population, El Khoudary et al. found that late peri- and postmenopausal women had a greater progression of CIMT and AD than their pre/early perimenopausal counterparts.[26] In our study, most women were at the late perimenopause stage (56.8%) at baseline. National Health and Nutrition Examination Survey (NHANES; 1999–2006) data indicate that midlife women tend to spend more time outdoors than older women; and therefore may have greater exposure to ambient air pollution.[28] We can, therefore, observe a substantial degree of atherosclerotic changes in this 2-year follow-up among midlife women, and examine the association of air pollution with these changes.

In our study, women exposed to 1 $\mu g/m^3$ higher $PM_{2.5}$ at their residential address had a 0.4 (95% CI: −2.90 to 3.69) μm/year increase in CCA CIMT, which was not statistically significant. In the MESA Air study, which also had a follow-up $\sim$2.5 years, a 2.5 $\mu g/m^3$ higher $PM_{2.5}$ exposure during follow-up was associated with a CCA CIMT progression of 5.0 (95% CI: 2.6–7.4) μm/year.[38] In a more recent 10-year

Table 2. Association Between $PM_{2.5}$ (1 $\mu g/m^3$) and Ozone (1 ppb) and Progression of Subclinical Atherosclerosis

	Mean CIMT (μm/year)	*Mean of maximum CIMT (μm/year)*	*AD (μm/year)*
$PM_{2.5}$			
Model 1	1.94 (−0.82 to 4.71)	3.77 (−0.36 to 7.90)	−6.02 (−17.98 to 5.94)
Model 2a	1.86 (−0.89 to 4.61)	3.64 (−0.48 to 7.75)	−6.20 (−18.15 to 5.74)
Model 2b	2.25 (−0.61 to 5.12)	4.28 (0.02 to 8.54)	−6.83 (−19.35 to 5.68)
Model 3	2.17 (−0.73 to 5.08)	4.06 (−0.25 to 8.37)	−5.41 (−17.93 to 7.11)
Ozone			
Model 1	0.23 (−0.82 to 1.27)	0.31 (−1.24 to 1.86)	−0.11 (−4.71 to 4.49)
Model 2a	0.24 (−0.80 to 1.29)	0.34 (−1.21 to 1.88)	−0.13 (−4.73 to 4.47)
Model 2b	0.22 (−0.90 to 1.33)	0.07 (−1.57 to 1.72)	−0.16 (−5.06 to 4.74)
Model 3	0.32 (−0.88 to 1.51)	0.05 (−1.71 to 1.82)	−0.47 (−5.77 to 4.82)

Data presented as point estimate and 95% confidence interval. Model 1 is an unadjusted model, only adjusting for measurement-related variables: site and tech; Model 2a is adjusted for socioeconomic and demographic characteristics: age, race, education, and how hard to pay for basics; Model 2b is a fully adjusted model, further adjusted for risk factors of CVD, and it is the full model: BMI, smoking, triglyceride, LDL, HDL, lipid-lowering medication, hypertension mediation, menopause status, hormone replacement therapy, diabetes, and family history of CVD or stroke; Model 3 is the extended model, additionally adjusted for potential mediators: SBP, hsCRP, tPA, and PAI-1.

CVD, cardiovascular disease; HDL, high-density lipoprotein.

Table 3. Association Between $PM_{2.5}$ (1 $\mu g/m^3$) and Ozone (1 ppb) and per Segment Progression of Carotid Intima-Media Thickness

	Common CIMT (μm/year)	*Internal CIMT (μm/year)*	*Bulb CIMT (μm/year)*
$PM_{2.5}$			
Model 1	0.25 (−2.94 to 3.44)	2.82 (−2.34 to 7.99)	5.90 (0.06 to 11.74)
Model 2a	0.19 (−2.99 to 3.37)	2.80 (−2.37 to 7.97)	5.60 (−0.23 to 11.43)
Model 2b	0.40 (−2.90 to 3.69)	2.87 (−2.54 to 8.27)	6.54 (0.49 to 12.60)
Model 3	0.54 (−2.81 to 3.88)	2.48 (−3.03 to 8.00)	6.19 (0.13 to 12.24)
Ozone			
Model 1	−0.18 (−1.40 to 1.04)	0.41 (−1.54 to 2.37)	1.11 (−1.70 to 2.65)
Model 2a	−0.18 (−1.39 to 1.04)	0.42 (−1.53 to 2.38)	0.48 (−1.69 to 2.65)
Model 2b	0.04 (−1.26 to 1.34)	0.39 (−1.71 to 2.48)	−0.07 (−2.38 to 2.24)
Model 3	0.10 (−1.29 to 1.49)	0.29 (−1.96 to 2.54)	0.20 (−2.29 to 2.69)

Data presented as point estimate and 95% confidence interval. Model 1 is an unadjusted model, only adjusting for measurement-related variables: site and tech; Model 2a is adjusted for socioeconomic and demographic characteristics: age, race, education, and how hard to pay for basics; Model 2b is a fully adjusted model, further adjusted for risk factors of CVD, and it is the full model: BMI, smoking, triglyceride, LDL, HDL, lipid-lowering medication, hypertension mediation, menopause status, hormone replacement therapy, diabetes, and family history of CVD or stroke; Model 3 is the extended model, additionally adjusted for potential mediators: SBP, hsCRP, tPA, and PAI-1.

follow-up of the MESA Air study, no significant association was found between $PM_{2.5}$ and CCA CIMT[40]; however, these updated analyses only included 70% of the original sample size of their 2.5-year follow-up study.[38] Our study population was very young (age: 46–56 years) compared with MESA Air study population (age: 45–82 years). Furthermore, CCA CIMT may not be the best endpoint as carotid artery thickening and plaque development are more likely to occur in segments exposed to greater turbulent blood flow and sheer stress such as the bulb and ICA.[52] In another study, Kunzli reported that living within 100 m of highway or within 50 m of a major road, not $PM_{2.5}$, was a predictor of CIMT progression, which may reflect a combination of pollutants as traffic.

Among these SWAN Heart women, we found that 1 $\mu g/m^3$ higher $PM_{2.5}$ during follow-up was associated with 4.28 (95% CI: 0.02–8.54) μm/year increase in the maximum CIMT. We chose our main endpoints, the maximum CIMT of CCA, bulb, and ICA segments, which can reflect a higher burden of subclinical atherosclerosis, as it is likely to capture plaque when it is present. Maximum CIMT progression is

Table 4. Association Between Exposure to $PM_{2.5}$ (1 $\mu g/m^3$) and Ozone (1 ppb) and Plaque Presence and Plaque Index Progression in Single-Pollutant Model ($N=319$)

	Plaque presence progression[a]	*Plaque index progression*[b]
$PM_{2.5}$		
Model 1	1.21 (0.98–1.51)	1.31 (1.04–1.65)
Model 2a	1.21 (0.97–1.50)	1.29 (1.02–1.64)
Model 2b	1.16 (0.92–1.46)	1.22 (0.95–1.56)
Model 3	1.14 (0.89–1.44)	1.18 (0.92–1.53)
O_3		
Model 1	1.00 (0.98–1.01)	0.99 (0.98–1.01)
Model 2a	1.00 (0.98–1.01)	1.00 (0.98–1.01)
Model 2b	1.00 (0.98–1.01)	0.99 (0.97–1.01)
Model 3	1.00 (0.98–1.01)	0.99 (0.97–1.01)

Data presented as odds ratio and 95% confidence interval. Model 1 is an unadjusted model, only control for site; Model 2a is adjusted for the SES/demographic factors, which includes age, race, education, how hard to pay for basics; Model 2b is further adjusted for the CVD risk factors, which includes BMI, smoking, cholesterol, LDL, HDL, blood glucose level, and menopause status; Model 3 is additionally adjusted for potential mediators, which includes SBP, hsCRP, tPA, and PAI-1.

[a]Reference group: participants remained plaque free, or participants who had plaque at baseline but not plaque at follow-up ($N=245$).

[b]Reference group: participants remained plaque free, or participants whose plaque index decreases at follow-up ($N=252$).

SES, socioeconomic status.

Table 5. Association Between Exposure to $PM_{2.5}$ (1 $\mu g/m^3$) and Ozone (1 ppb) and Plaque Presence and Plaque Index Progression in Two-Pollutant Model ($N=319$)

	Plaque presence progression[a]	*Plaque index progression*[b]
Model 1		
$PM_{2.5}$	1.22 (0.98–1.51)	1.31 (1.04–1.66)
O_3	1.00 (0.98–1.01)	0.99 (0.98–1.01)
Model 2a		
$PM_{2.5}$	1.21 (0.97–1.50)	1.30 (1.03–1.65)
O_3	1.00 (0.98–1.01)	0.99 (0.98–1.01)
Model 2b		
$PM_{2.5}$	1.18 (0.93–1.50)	1.25 (0.97–1.61)
O_3	0.99 (0.97–1.01)	0.99 (0.97–1.01)
Model 3		
$PM_{2.5}$	1.15 (0.91–1.47)	1.22 (0.94–1.58)
O3	0.99 (0.97–1.01)	0.99 (0.97–1.01)

Data presented as odds ratio and 95% confidence interval. Model 1 is an unadjusted model, only control for site; Model 2a is adjusted for the SES/demographic factors, which includes age, race, education, how hard to pay for basics; Model 2b is further adjusted for the CVD risk factors, which includes BMI, smoking, cholesterol, LDL, HDL, blood glucose level, and menopause status; Model 3 is additionally adjusted for potential mediators, which includes SBP, hsCRP, tPA, and PAI-1.

[1]Reference group: participants remained plaque free, or participants who had plaque at baseline but not plaque at follow-up ($N=245$).

[2]Reference group: participants remained plaque free, or participants whose plaque index decreases at follow-up ($N=252$).

generally higher than the mean CIMT progression. Moreover, studies examining associations between exposure and maximum CIMT progression are more in line with those of exposure and clinical events than studies that only measure mean CCA CIMT.[52]

We did not observe that either pollutant was related to AD. None of the other studies examining the association between air pollution and atherosclerosis used AD as a biomarker of atherosclerosis. AD is a marker of vascular remodeling and aging, which is a predictor of CVD events. Among a high-prevalent diabetic and hypertensive population in Italy, Kozakova et al. found that AD was associated with the prevalence of CVD events, independent of CIMT and the Framingham risk score.[53] In our study, as AD is only measured in the CCA segment, it may not reflect the atherosclerosis burden and vascular remodeling in all the carotid segments. Saba et al. found that the correlation between AD and plaque score throughout the CCA, ICA, and bulb segments was 0.38 in a Japanese population.[54] The mechanisms affecting this measure of vascular remodeling during the menopause transition may be due to other factors such as endogenous hormones E2 and FSH, which dramatically change in the years surrounding the final menstrual period.[55]

In the extended models in which we considered potential intermediate factors, we further adjusted for SBP, hsCRP, tPA, and PAI-1, and the effect size did not change appreciably. These results were consistent with the findings from the MESA Air study.[38] It has been proposed that one potential mechanism linking PM to CVD is PM-induced amplification of the systemic inflammation and oxidative stress response.[6] We did not observe evidence of this effect when evaluating these biomarkers in the extended models. One explanation for this may be that these biomarkers were collected at the time of the outcomes and thus, we cannot capture the temporal effect of the potential mediators.

Among our participants, we found that women exposed to higher levels of $PM_{2.5}$ were more likely to have a higher plaque index at follow-up after adjusting for SES factors, but not with plaque presence progression. We used plaque index as a measure of plaque severity, which is a semiquantitative measure of the subclinical atherosclerosis burden and may be a more sensitive way to look at plaque progression than using only plaque presence (yes/no). Gan et al. reported the association between air pollution ($PM_{2.5}$ and traffic proximity) and plaque area, plaque number and total area progression.[39] They found that only among Chinese in Canada, people who lived within 150 m to highway or within 50 m to a major road had an increased plaque area (1.12 mm^2, CI: 0.21–2.03) but not among other racial groups or in the overall sample; and no statistically significant association was found with $PM_{2.5}$, where the air pollution level is very low resulting in a very low contrast among the participants.

We did not find a statistically significant association between O_3 and CIMT or plaque progression. In a recently published abstract using the 10-year follow-up data from the MESA Air study, they found that a 3 ppb higher long-term exposure to O_3 was associated with a 5.6 μm (95%: 1.4–9.7) per 10-year increase in CCA CIMT.[56] Translating this into 1 ppb O_3 exposure to 1-year CCA CIMT progression, the effect size is only 0.19 μm/year. This effect size is very small, and may not reflect a clinical meaningful progression of atherosclerosis. They also reported that a 3 ppb higher long-term exposure to O_3 was associated with a 20% (95% CI: 10%–40%) higher chance to develop carotid plaque by plaque score, which is a similar concept to plaque index used in our study.[56] The prevalence of plaque in our women was very low, 15%; therefore, we may not have had enough power to detect an association between O_3 and plaque progression. Also, our follow-up time is much shorter, and O_3 may require a longer time to affect significant vascular changes. The production of O_3 requires ultraviolet,[57] which is higher in the warm season and lower in the cold season. Moreover, the damage from short-term episodes of high-level O_3 exposure is reversible.[58] Thus, to observe the cumulative effect of O_3 continuous exposure to high-level O_3 may be required. A retrospective study among college students, mostly from California, found that exposure to O_3 at childhood predicted a higher CIMT level in their college years, not the years immediately preceding their college.[36] A longer follow-up may be required in the SWAN study to observe an association between O_3 and progression of CIMT.

Limitations

One of the limitations of our study is that we used a less refined estimate of air pollution levels compared with other studies that used spatial-temporal modeling.[41] Spatial-temporal modeling creates a more comprehensive exposure metrics of the study area under the assumption that the spatial variation was the same throughout the study period based on the 2-week measure. However, one of the cross-sectional papers from MESA Air study demonstrated that the nearest monitors may present a higher contrast among the study population.[59] We used the continuous monitoring data from EPA monitors throughout the entire study period with no modeling uncertainty or assumptions. Our exposure assessment was also limited to the residential address and did not directly include other information of their day-to-day activities. However, a monitor near the home may reflect the air pollutant level of the residential address, as well as the area where the participant may engage in activities. Other air components, such as NO_2, SO_2, and volatile organic compounds, can be residual confounding factors; thus, we cannot conclusively claim that $PM_{2.5}$ is causally related to subclinical atherosclerosis. However, all of these chemicals are precursors to $PM_{2.5}$ and/or ozone.[60] They can contribute to $PM_{2.5}$ components. A cross-sectional study of MESA Air found that sulfur had a relatively stronger association with CIMT than $PM_{2.5}$, and the association was in the same direction.[61] The 10-year follow-up study from MESA Air found a similar association between NOx and coronary artery calcification (CAC) but no statistically significant association between NO_2 and CAC.[40] From these studies, $PM_{2.5}$ may still be the most important air pollutant related to CVD and subclinical atherosclerosis risk. Moreover, $PM_{2.5}$ and O_3 were considered to carry the greatest risk related to human health.[62] For these reasons, we selected these two air pollutants for our study. Although our study found a significant association between $PM_{2.5}$ and subclinical atherosclerosis among women at a stage in their life when CVD risk is increasing, it was in a sample of only 400 women. Furthermore, follow-up was $\sim$2.2 years. Considering that atherosclerosis is a life-threatening progressive process,[63] a longer follow-up with a larger sample of women will be required in the future. However, we captured

the women's atherosclerosis progression during menopause transitioning, which may represent a time of accelerated vascular remodeling in women. Although our findings are limited to midlife women, it is likely, based on findings from other studies and existing literature, that exposure to air pollution is harmful to other age and sex groups than those examined in SWAN.

Strengths

The biggest strength of this article is that it is the first study conducted among women transitioning through menopause, a stage in women's life when CVD risk accelerates. Another strength in our study is the ability to measure atherosclerotic burden by CIMT more precisely. Most of the existing multisite studies measured CIMT in the CCA segment only. We were able to measure CIMT in the ICA and bulb, which may better reflect atherosclerotic burden, and even a better recommended biomarker maximum CIMT.[52] We also examined plaque presence, a validated biomarker of atherosclerosis.[64] The other outcome plaque index, which has not been previously studied with air pollution, was a semiquantitative measure of plaque burden.

Conclusions

Our study found that $PM_{2.5}$ independently contributed to progression of some, but not all, markers of subclinical atherosclerosis among women transitioning through menopause, a time of increasing CVD risk for women. These findings indicate that certain components of air pollution, $PM_{2.5}$, may be particularly deleterious to the vasculature of early midlife women during a time of increased CVD susceptibility. These findings add to the current knowledge that ambient air pollution is deleterious to health. The accumulating evidence suggests that further measures may need to be taken to reduce the ambient air pollution level to protect health. Although policies such as alternative commuting hours and avoiding peak commuting times may be of benefit, such policies would most likely be very difficult to implement in today's society. Alternatively, if further study bears out this finding, greater awareness of the potential short- and long-term impact of $PM_{2.5}$ and other air pollutants will be needed. Automobile traffic and commuting in today's world is still a ''fact of life''; greater awareness of idling in traffic with the car windows down, making sure that the car's air filter has been changed regularly, and considering commuting time in heavy traffic are among personal choices that can affect air pollution exposure.

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Author Disclosure Statement

There is no conflict of interest for any of the authors.

Supplementary Material

Supplementary Data
Supplementary Figure S1
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References

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224–2260.
2. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: An analysis of data from the Global Burden of Diseases Study 2015. Lancet 2017;389:1907–1918.
3. Brook RD, Rajagopalan S, Pope CA, et al. Particulate matter air pollution and cardiovascular disease an update to the scientific statement from the American Heart Association. Circulation 2010;121:2331–2378.
4. Atkinson RW, Carey IM, Kent AJ, van Staa TP, Anderson HR, Cook DG. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 2013;24:44–53.
5. Franchini M, Mannucci PM. Air pollution and cardiovascular disease. Thromb Res 2012;129:230–234.
6. Franklin BA, Brook R, Pope CA. Air pollution and cardiovascular disease. Curr Probl Cardiol 2015;40:207–238.
7. Brook RD, Rajagopalan S. Particulate matter air pollution and atherosclerosis. Curr Atheroscler Rep 2010;12:291–300.
8. Bauer M, Caviezel S, Teynor A, Erbel R, Mahabadi AA, Schmidt-Trucksäss A. Carotid intima-media thickness as a biomarker of subclinical atherosclerosis. Swiss Med Wkly 2012;142:13705.
9. Bots ML, Evans GW, Riley WA, Grobbee DE. Carotid intima-media thickness measurements in intervention studies design options, progression rates, and sample size considerations: A point of view. Stroke 2003;34:2985–2994.
10. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: The Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 2000;151:478–487.
11. van den Oord SC, Sijbrands EJ, Gerrit L, et al. Carotid intima-media thickness for cardiovascular risk assessment: Systematic review and meta-analysis. Atherosclerosis 2013;228:1–11.
12. Baldassarre D, Veglia F, Hamsten A, et al. Progression of carotid intima-media thickness as predictor of vascular events results from the IMPROVE study. Arterioscler Thromb Vasc Biol 2013;33:2273–2279.

13. Okayama KI, Mita T, Gosho M, et al. Carotid intima-media thickness progression predicts cardiovascular events in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract 2013;101:286–292.
14. Naqvi TZ, Lee M-S. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging 2014;7:1025–1038.
15. Geerts CC, Bots ML, Grobbee DE, Uiterwaal CS. Parental smoking and vascular damage in young adult offspring: Is early life exposure critical? The atherosclerosis risk in young adults study. Arterioscler Thromb Vasc Biol 2008; 28:2296–2302.
16. Polak JF, Pencina MJ, O'Leary DH, D'Agostino RB. Common carotid artery intima-media thickness progression as a predictor of stroke in multi-ethnic study of atherosclerosis. Stroke 2011;42:3017–3021.
17. Hodis HN, Mack WJ, Henderson VW, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med 2016;374:1221–1231.
18. Bots ML, Evans GW, Riley WA, Grobbee DE. Carotid intima-media thickness measurements in intervention studies. Design options, progression rates, and sample size considerations: A point of view. Stroke 2003;34:2985–2994.
19. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: A meta-analysis. Atherosclerosis 2012;220:128–133.
20. Chen PC, Jeng JS, Hsu HC, Su TC, Chien KL, Lee YT. Carotid atherosclerosis progression and risk of cardiovascular events in a community in Taiwan. Sci Rep 2016;6: 25733.
21. Wannarong T, Parraga G, Buchanan D, et al. Progression of carotid plaque volume predicts cardiovascular events. Stroke 2013;44:1859–1865.
22. van Engelen A, Wannarong T, Parraga G, et al. Three-dimensional carotid ultrasound plaque texture predicts vascular events. Stroke 2014;45:2695–2701.
23. Spence JD, Eliasziw M, DiCicco M, Hackam DG, Galil R, Lohmann T. Carotid plaque area: A tool for targeting and evaluating vascular preventive therapy. Stroke 2002;33: 2916–2922.
24. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 2007;356:447–458.
25. Hart JE, Puett RC, Rexrode KM, Albert CM, Laden F. Effect modification of long-term air pollution exposures and the risk of incident cardiovascular disease in US women. J Am Heart Assoc 2015;4:e002301.
26. El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT, Sutton-Tyrrell K. Progression rates of carotid intima-media thickness and adventitial diameter during the menopausal transition. Menopause 2013;20:8–14.
27. Maas A, Appelman Y. Gender differences in coronary heart disease. Neth Heart J 2010;18:598–603.
28. Dai S, Carroll DD, Watson KB, Paul P, Carlson SA, Fulton JE. Participation in types of physical activities among US adults—National Health and Nutrition Examination Survey 1999–2006. J Phys Act Health 2015;12(Suppl 1):S128–S140.
29. Bauer M, Moebus S, Mohlenkamp S, et al. Urban particulate matter air pollution is associated with subclinical atherosclerosis: Results from the HNR (Heinz Nixdorf Recall) study. J Am Coll Cardiol 2010;56:1803–1808.
30. Kim S-Y, Sheppard L, Kaufman JD, et al. Individual-level concentrations of fine particulate matter chemical components and subclinical atherosclerosis: A cross-sectional analysis based on 2 advanced exposure prediction models in the multi-ethnic study of atherosclerosis. Am J Epidemiol 2014;180:718–728.
31. Künzli N, Jerrett M, Mack WJ, et al. Ambient air pollution and atherosclerosis in Los Angeles. Environ Health Perspect 2005;113:201–206.
32. Lenters V, Uiterwaal CS, Beelen R, et al. Long-term exposure to air pollution and vascular damage in young adults. Epidemiology 2010;21:512–520.
33. Perez L, Wolf K, Hennig F, et al. Air pollution and atherosclerosis: A cross-sectional analysis of four European cohort studies in the ESCAPE study. Environ Health Perspect;123:597–605.
34. Su T-C, Hwang J-J, Shen Y-C, Chan C-C. Carotid intima–media thickness and long-term exposure to traffic-related air pollution in middle-aged residents of Taiwan: A cross-sectional study. Environ Health Perspect 2015; 123:773–8.
35. Tonne C, Yanosky JD, Beevers S, Wilkinson P, Kelly FJ. PM mass concentration and PM oxidative potential in relation to carotid intima-media thickness. Epidemiology 2012;23:486–494.
36. Breton CV, Wang X, Mack WJ, et al. Childhood air pollutant exposure and carotid artery intima-media thickness in young adults. Circulation 2012;126:1614–1620.
37. Rivera M, Basagaña X, Aguilera I, et al. Association between long-term exposure to traffic-related air pollution and subclinical atherosclerosis: The REGICOR study. Environ Health Perspect 2012;121:223–230. 2012.
38. Adar SD, Sheppard L, Vedal S, et al. Fine particulate air pollution and the progression of carotid intima-medial thickness: A prospective cohort study from the Multi-Ethnic Study of Atherosclerosis and Air Pollution. PLoS Med 2013; 10:e1001430.
39. Gan WQ, Allen RW, Brauer M, Davies HW, Mancini GJ, Lear SA. Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: A prospective cohort study. BMJ Open 2014;4:e004743.
40. Kaufman JD, Adar SD, Barr RG, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): A longitudinal cohort study. Lancet 2016;388:696–704.
41. Künzli N, Jerrett M, Garcia-Esteban R, et al. Ambient air pollution and the progression of atherosclerosis in adults. PloS One 2010;5:e9096.
42. Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: The Multi-Ethnic Study of Atherosclerosis (MESA). Menopause 2012;19:1081.
43. Sowers MFR, Crawford SL, Sternfeld B, et al. SWAN: A multicenter, multiethnic, community-based cohort study of women and the menopausal transition. San Diego, CA: Academic Press, 2000.
44. US EPA. AQS Data Mart, 2015. Available at: https://aqs.epa.gov/aqsweb/documents/data_mart_welcome.html Accessed October 25, 2016.
45. Ostro B, Malig B, Broadwin R, et al. Chronic $PM_{2.5}$ exposure and inflammation: Determining sensitive subgroups in mid-life women. Environ Res 2014;132:168–175.
46. Green R, Broadwin R, Malig B, et al. Long- and short-term exposure to air pollution and inflammatory/hemostatic markers in midlife women. Epidemiology 2016;27:211–220.

47. Whipple MO, Lewis TT, Sutton-Tyrrell K, et al. Hopelessness, depressive symptoms, and carotid atherosclerosis in women: The Study of Women's Health Across the Nation (SWAN) heart study. Stroke 2009;40:3166–3172.
48. Thurston RC, Sutton-Tyrrell K, Everson-Rose SA, Hess R, Powell LH, Matthews KA. Hot flashes and carotid intima media thickness among midlife women. Menopause 2011; 18:352–358.
49. Sutton-Tyrrell K, Kuller LH, Matthews KA, et al. Subclinical atherosclerosis in multiple vascular beds: An index of atherosclerotic burden evaluated in postmenopausal women. Atherosclerosis 2002;160:407–416.
50. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009;54:2366–2373.
51. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al. Are vasomotor symptoms associated with alterations in hemostatic and inflammatory markers? Findings from the Study of Women's Health Across the Nation. Menopause 2011; 18:1044–1051.
52. Peters SA, Bots ML. Carotid intima-media thickness studies: Study design and data analysis. J Stroke 2013;15:38–48.
53. Kozakova M, Morizzo C, La Carrubba S, et al. Associations between common carotid artery diameter, Framingham risk score and cardiovascular events. Nutr Metab Cardiovasc Dis 2017;27:329–334.
54. Saba L, Araki T, Kumar PK, et al. Carotid inter-adventitial diameter is more strongly related to plaque score than lumen diameter: An automated tool for stroke analysis. J Clin Ultrasound 2016;44:210–220.
55. El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT, Sutton-Tyrrell K. Endogenous sex hormones impact the progression of subclinical atherosclerosis in women during the menopausal transition. Atherosclerosis 2012;225:180–186.
56. Wang M, Sheppard L, Sampson P, Stein J, Vedal S, Kaufman J. Long-term exposure to ambient ozone and progression of subclinical atherosclerosis: The Multi-Ethnic Study of Atherosclerosis and Air Pollution. In: Abstracts of the 2016I Epidemiology (ISEE). Abstract [O-002]. Research Triangle Park, NC: Environmental Health Perspective, 2016.
57. U.S. Environmental Protection Agency. Ground level ozone, 2015. Available at: www.epa.gov/air/ozonepollution Accessed May 17, 2015.
58. Allen J. The ozone we breath. NASA, 2002. Available at: http://earthobservatory.nasa.gov/Features/OzoneWeBreathe/ozone_we_breathe2.php Accessed January 24, 2017.
59. Sun M, Kaufman JD, Kim S-Y, et al. Particulate matter components and subclinical atherosclerosis: Common approaches to estimating exposure in a Multi-Ethnic Study of Atherosclerosis cross-sectional study. Environ Health 2013;12:39–41.
60. Hodan WM, Barnard WR. Evaluating the contribution of $PM_{2.5}$ precursor gases and re-entrained road emissions to mobile source $PM_{2.5}$ particulate matter emissions. Research Triangle Park, NC: MACTEC Federal Programs, 2004.
61. Sun Q, Wang A, Jin X, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA 2005;294:3003–3010.
62. U.S. Environmental Protection Agency. Air quality index—A guide to air quality and your health, 2014. Available at: http://airnow.gov/index.cfm?action=aqi_brochure.index Accessed May 21, 2015.
63. Künzli N, Perez L, von Klot S, et al. Investigating air pollution and atherosclerosis in humans: Concepts and outlook. Prog Cardiovasc Dis 2011;53:334–343.
64. W van Lammeren G, L Moll F, Borst GJD, de Kleijn DPV, P M de Vries JP, Pasterkamp G. Atherosclerotic plaque biomarkers: Beyond the horizon of the vulnerable plaque. Curr Cardiol Rev 2011;7:22–27.

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