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Five-year exposure to $PM_{2.5}$ and ozone and subclinical atherosclerosis in late midlife women: The Study of Women's Health Across the Nation

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ABSTRACT

Introduction: Effects of more than one-year exposure to air pollution on atherosclerosis is seldom studied. This paper aims to examine the association between five-year exposure to particulate matter ≤2.5 μm ($PM_{2.5}$), ozone (O_3) and atherosclerosis observed about seven years later in late midlife women.

Material and methods: This study was conducted among 1188 women of the Study of Women's Health Across the Nation (SWAN) from five sites, Detroit, MI; Oakland, CA; Pittsburgh, PA; Chicago, IL; and Newark, NJ, with available data on both air pollutant exposure and carotid ultrasound scans. Five-year mean annualized exposure levels of two air pollutants, $PM_{2.5}$ and ozone (O_3), were collected during 5 SWAN visits (1999–2005) from monitors 20 km within the participant's residential address. Linear regression models were used to estimate the association of prior five-year mean annualized exposure to $PM_{2.5}$ and O_3 with common carotid intima-media thickness (cIMT) and inter-adventitial diameter (IAD) examined approximately seven years later (2009–2013). Logistic and multinomial logistic regressions were applied to assess the associations of air pollutants with plaque presence and plaque index, respectively.

Results: At time of carotid ultrasound scan, women were on average 59.6 (± 2.7) years old and a majority was postmenopausal (88.4%). The women were White (48.4%), Black (31.2%), Chinese (13.3%) and Hispanic (7.1%). A 1 μg/m^3 higher 5-year mean annualized exposure to $PM_{2.5}$ was associated with an 8.0 μm (95% CI: 1.0–15.1) greater maximum cIMT at a later mid-life, adjusting for cardiovascular disease risk factors; but was only related to IAD after adjusting for site. No association was found between either pollutant and plaque presence or plaque index.

Conclusions: Long-term exposure to $PM_{2.5}$ may contribute to elevated risk of atherosclerosis in the post-menopausal period.

1. Introduction

Air pollution is ubiquitous and has deleterious effects on health. The most significant health outcomes related to air pollution are pulmonary and cardiovascular disease (CVD) (Brook et al., 2010; Franchini and Mannucci, 2012). Since air pollution exists in our everyday environment, its cumulative effect may play a role in heart health (Atkinson et al., 2013; Hoek et al., 2013). Accumulating evidence from the last decade suggests that more than one-year exposure to air pollution may be particularly deleterious for CVD health. In analyses of several European cohorts, approximately 3-year exposure to particulate matter (PM) contributed to future all-cause mortality (Beelen et al., 2014) and coronary events (Cesaroni et al., 2014). Several cohort studies in the U.S. have also found a harmful effect of $PM_{2.5}$ on CVD mortality and morbidity in women (Miller et al., 2007; Puett et al., 2009; Hart et al., 2015).

Atherosclerosis, responsible for a majority of CVD events, is an inflammatory and lipids driven process, in which plaque builds up in the artery (Lu and Daugherty, 2015). Biomarkers of subclinical atherosclerosis as outcomes have been widely adopted in research to study

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Visit	00	01	02	03	04	05	06	07	08	09	10	11	12	13
Start year	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	interim	2009	2011
End year	1997	1999	2000	2001	2002	2003	2004	2005	2006	2009*	2008		2011	2013
Variables														
Age													X	X
Race/Ethnicity	X													
Education	X													
Carotid Ultrasound Scan													X	X
Air Pollution: $PM_{2.5}$ and Ozone				X	X	X	X	X						
Menopause Status													X	X
Continuous Variables#				X	X	X	X	X						
Categorical Variables†													X	X

Fig. 1. Timeline of the data collection and extraction for this analysis. * Newark, NJ site skipped visit 10, and visit 9 were collecting data overlapped with visit 10's time frame.
BMI, SBP, cholesterol, triglyceride, LDL-c, HDL-c, fasting blood glucose, insulin, hsCRP, tPA, and PAI-1.
† Other categorical variables: smoking, diabetes, HTN, financial strain, and medications.

pre-clinical CVD. Carotid artery intima-media thickness (cIMT) measured via B-mode ultrasound, a surrogate biomarker of subclinical atherosclerosis (Bots and Grobbee, 2002; Bauer et al., 2012), reflects early vascular changes and predicts CVD and stroke events independent of traditional CVD risk factors (Chambless et al., 2000; Bots et al., 2003; Polak et al., 2011; Bauer et al., 2012; van den Oord et al., 2013). Ultrasound assessment of carotid plaque is a direct measure of atherosclerotic lesions. Plaque in conjunction with cIMT may be a better biomarker for predicting CVD risk compared to cIMT alone (Inaba et al., 2012), and utilizing quantitative measures of plaque may further improve prediction (Naqvi and Lee, 2014).

The cross-sectional relationship between exposure to one-year air pollution and atherosclerosis has been examined in different populations (Künzli et al., 2005; Bauer et al., 2010; Lenters et al., 2010; Breton et al., 2012; Rivera et al., 2012; Tonne et al., 2012; Kälsch et al., 2013; Armijos et al., 2015; Perez et al., 2015). Most of these studies found that living close to major roads and exposure to higher air pollutant levels were related to atherosclerosis. There are very few studies that have examined the association between more than 1-year exposure to air pollution and atherosclerosis; two of these studies were limited to young populations, whose atherosclerotic changes were not significant (Breton et al., 2012; Armijos et al., 2015). Diez-Roux et al. observed an association between 20-years exposure to PM_{10} using the EPA monitors and cIMT after adjusting for CVD risk factors (Diez Roux et al., 2008). Rivera et al. related the 10-year exposure to NO_2, using land use regression and traffic proximity, to cIMT among a community population aged 32–86 years old in the Girona region of Spain (the REGICOR study) (Rivera et al., 2012). NO_2 and traffic proximity were related to cIMT in the unadjusted model, but only traffic proximity remained significantly associated with cIMT in the model adjusted for confounders. To our knowledge, there are no studies evaluating the effect of more than one-year cumulative exposure to air pollution on atherosclerosis in midlife women, a time of increased CVD susceptibility and accelerated progression of atherosclerosis in women (El Khoudary et al., 2013). Thus, we investigated, in a cohort of women transitioning through the menopause, the association between 5-year mean annualized exposure to $PM_{2.5}$ and O_3 and atherosclerosis burden assessed by cIMT and plaque, approximately 6.6 (range: 5.4–9.6) years later.

2. Material and methods

2.1. Study population

The Study of Women's Health Across the Nation (SWAN) is a community-based multi-center multi-ethnic cohort study of women's health as they transition the menopause. The SWAN study, conducted at seven sites across the U.S. began in 1996. This analysis involves the five sites that collected both air pollution and subclinical atherosclerosis outcome data, Detroit, MI; Oakland, CA; Pittsburgh, PA; Chicago, IL; and Newark, NJ. Each site recruited Whites and another minority racial group. Detroit, MI; Pittsburgh, PA and Chicago, IL recruited Black, Oakland, CA recruited Chinese; and Newark, NJ recruited Hispanics. Of the 1311 women who had a carotid ultrasound exam and readable images, 1188 (90.6%) had residential air pollutant estimates at visits 3–7 and were included. A detailed illustration of population inclusion is presented in Supplementary Fig. S1. SWAN was approved by the Institutional Review Board at each site, and written informed consent was obtained from all participants. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Exposure to $PM_{2.5}$ and O_3

Air pollution exposure was assessed by the Air Pollution Study, an ancillary study of SWAN. Detailed methods have been published elsewhere (Ostro et al., 2014; Green et al., 2016). Daily $PM_{2.5}$ and O_3 values were retrieved from US EPA Air Quality System DataMart (US EPA, 2015). Exposure to $PM_{2.5}$ and O_3 was determined by monitors within 20 km from each participant's address. Monitor readings were used to calculate average exposure over 360 days before each of the five SWAN visits 3–7, corresponding to the years 1999–2005 (Fig. 1). The mean annualized level of air pollutants over this 5-year period, from this point forward referred to as *5-year mean annualized exposure*, was then calculated using the trapezoidal rule for the area under the curve (Yeh and Collegeville, 1991) based on the yearly exposure from SWAN visits 3–7. Exposure data were limited to these SWAN visits, as visit 3 occurred in approximately 2000, when U.S. EPA first started to monitor $PM_{2.5}$ level at the national level, and data for inflammatory/hemostatic biomarkers, lipids and glucose were available up to SWAN visit 7 (Green et al., 2016). In our assessment, we included all of the monitor information related to the participants' residential addresses. The number of $PM_{2.5}$ monitors ranged from 6 to 19 and the number of ozone monitors ranged from 4 to 13 for each site. For residences with multiple monitors within 20 km, one monitor was selected to represent exposure. Selection was based on criteria balancing the number of women's clinic visits from Visit 3 to 7 with available exposure data for a monitor versus the distance to the monitor. Preference was typically given to the closer monitor. However, for example, if a monitor was located twice as far away as the closest monitor, it would be chosen if it provided more than doubled the number of clinic visits included in the study. If a participant moved (~13% of all women) during the year prior to her visit, exposure data from multiple addresses were weighted based on the time of move when assigning exposure, or evenly weighted if the move date was not available (Basu et al., 2017). The Detroit, MI site was excluded from O_3 exposure analyses since only four participants had available data.

Table 1
Characteristics by 5-year mean annualized exposure to $PM_{2.5}$ exposure quartiles (N = 1188).

	$PM_{2.5}$ (μg/m^3)				p-trend
	9.8–13.58 (n = 297)	13.58–15.34 (n = 297)	15.34–16.14 (n = 297)	16.14–20.84 (n = 297)	
Ozone (ppb)	25.0 (6.2)	34.6 (3.3)	33.2 (3.3)	33.7 (4.2)	< .001
Age[a] (years)	60.1 (2.6)	59.3 (2.7)	59.3 (2.6)	60.0 (2.7)	.638
Race[b] (%)					< .001
White	43.1	57.6	47.1	45.1	
Black	3.4	38.1	48.5	35.7	
Chinese	53.6	0	0	0	
Hispanic	0	4.4	4.4	19.2	
Ever Smoking[a] (%)	24.0	41.9	39.0	49.5	< .001
Education[b] (%)					0.919
≤ High School	20.9	24.8	23.7	22.3	
Some College/College	51.2	55.2	49.5	53.3	
> College	28.0	20.0	26.8	24.4	
Pay for Basis[a] (%)					< .001
Consistently Hard	17.5	38.1	36.7	38.4	
Mixed	29.6	27.6	24.6	25.9	
Consistently not hard	52.9	34.3	38.7	35.7	
Menopause Status[a] (%)					.389
Pre/Peri-menopause	1.7	2.7	2.4	2.4	
Post-menopause	91.6	86.9	86.5	87.9	
Other	6.7	10.4	11.1	9.8	
Ever hormone users (%)	42.1	43.4	43.8	43.8	.675
BMI	25.6 (5.8)	31.5 (7.7)	30.2 (6.7)	30.1 (6.4)	< .001
SBP (mmHg)	111.2 (11.4)	118.7 (15.5)	122.0 (15.7)	122.6 (13.5)	< .001
DBP (mmHg)	71.0 (7.5)	72.1 (8.7)	75.6 (9.1)	77.1 (7.9)	< .001
Hypertension[a](%)	48.5	70.7	76.1	76.4	< .001
Hypertension Medication[a](%)	33.3	55.6	55.6	60.6	< .001
Cholesterol (mg/dL)	203.2 (31.8)	201.7 (33.8)	197.9 (33.7)	204.2 (32.7)	.933
LDL-c (mg/dL)	115.8 (26.3)	118.8 (29.7)	116.5 (29.8)	122.5 (30.9)	.022
HDL-c (mg/dL)	62.3 (15.0)	58.1 (14.1)	56.9 (14.2)	56.9 (14.0)	< .001
Triglyceride (mg/dL)[c]	103.9 (76.7, 151.6)	101.4 (77.9, 151.5)	104.4 (80.4, 143.5)	108.0 (85.3, 146.0)	.616
Lipids Lowering Medication (%)	21.9	36.0	38.1	37.7	< .001
Glucose (mg/dL)[c]	88.9 (83.8, 94.3)	87.6 (83.3, 95.8)	88.6 (84.1, 95.8)	88.7 (83.8, 97.0)	.281
Insulin (uIU/mL)[c]	9.3 (7.5, 12.4)	11.2 (8.3, 16.9)	11.4 (8.6, 15.9)	11.5 (8.5, 16.9)	< .001
Diabetes[a] (%)	7.4	15.8	16.5	19.2	< .001
Diabetic medication (%)	7.1	15.8	14.8	18.2	< .001
hsCRP (mg/L)[c]	1.2 (0.6, 2.9)	2.9 (1.0, 7.7)	2.9 (1.2, 5.9)	2.9 (1.3, 6.3)	< .001
tPA (ng/dL)[c]	6.5 (4.8, 8.4)	7.6 (5.5, 9.4)	7.4 (5.8, 9.6)	7.8 (6.0, 10.1)	< .001
PAI (ng/dL)[c]	14.4 (7.3, 26.1)	19.8 (10.9, 38.2)	19.1 (10.9, 35.1)	22.2 (11.9, 35.5)	< .001
Avg. cIMT[a](mm)	0.76 (0.11)	0.80 (0.11)	0.80 (0.12)	0.81 (0.13)	< .001
Max. cIMT[a](mm)	0.89 (0.13)	0.94 (0.13)	0.93 (0.14)	0.95 (0.15)	< .001
IAD[a](mm)	7.12 (0.72)	7.24 (0.72)	7.24 (0.66)	7.20 (0.67)	.175
Plaque[a] (%)	47.8	41.9	40.4	40.4	.065
Plaque index[a] (%)					.025
0	52.2	58.1	59.6	59.6	
1–2	29.3	28.7	27.6	29.6	
3+	18.5	13.2	13.8	10.8	

[a] Data corresponds to carotid visits (SWAN visit 12/13).
[b] Data corresponds to baseline; All the other information was anualized mean level of visit 3–7 corresponding to the available air pollution data.
[c] Presented median (25th and 75th percentile), all the other continuous variables presented mean (std), and categorical variables presented percentage.

2.3. Assessment of cIMT and plaque

Ultrasound scans were implemented once, either at SWAN visit 12 or 13 (years 2009–2013). At each site, centrally trained and certified sonographers obtained carotid ultrasound images using a Terason t3000 Ultrasound System (Teratech Corp, Burlington, MA). Two images were obtained of the left and right distal common carotid artery (CCA) for later reading at the Ultrasound Reading Center (University of Pittsburgh Ultrasound Research Lab) (Wendelhag et al., 1991). The inter-sonographer reliability for repeat carotid ultrasound scans was good to excellent, with intraclass correlation coefficient (ICC) for mean cIMT 0.72–0.95 and for inter-adventitial diameters (IAD) 0.80–0.98. AMS semi-automated edge detection software was used to measure the near and far wall cIMT by tracing the lumen-intima interface and the media-adventitia interface across the 1-cm CCA segment proximal to the carotid bulb. IAD were measured directly as the distance between the adventitial-medial interfaces on the near and the far wall. The reading reproducibility was excellent between and within readers, with ICC greater than 0.87. The mean of the average and maximal readings of both sides comprised mean and maximal cIMT, respectively. Sonographers at each site evaluated the presence and extent of plaque (grade) in each of 5 segments of the left and right carotid artery (distal and proximal CCA, bulb, and proximal internal and external carotid arteries). The grades from all segments of the combined left and right carotid artery were summed to create the plaque index (Sutton-Tyrrell et al., 2002). Plaque index was categorized as: 0 (no observable plaque), 1–2, and greater than 2 (Sutton-Tyrrell et al., 1998; Gepner et al., 2017).

2.4. Assessment of other CVD risk factors

Covariate data were obtained at the SWAN baseline or follow-up visits. A detailed illustration of when the data were collected and extracted for this study is presented in Fig. 1. Self-reported race/ethnicity and education were collected at baseline. The smoking status was reported as never, past and current use at baseline, and the smoking

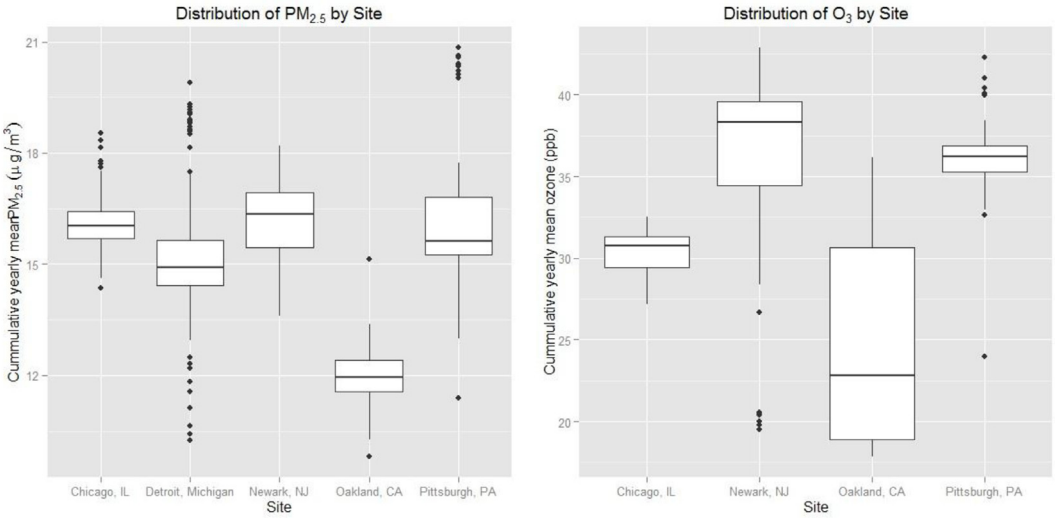

Fig. 2. 5-year mean annualized exposure levels of $PM_{2.5}$ and O_3 by site.

status of the past-year was asked again at each follow-up visit. All of the information was taken into account to determine the smoking status as past or current users at visit 12/13. We determined the medication use of antihypertensive, antidiabetic and hormone replacement therapy in the same fashion. Financial strain was assessed based on the question of how hard it was to pay for basics, which includes living expenses and medical treatment. A longitudinal category for financial strain was created and categorized into three groups, (a) consistently not hard; (b) mixed (more than 50% of time had no difficulties); (c) consistently hard (more than 50% of time had any difficulties) (Thurston et al., 2014). The status of hypertension was determined by either systolic blood pressure (SBP) ≥130 mmHg, or a diastolic blood pressure (DBP) ≥85 mmHg (American Heart Association, 2016; Sokol et al., 2016), or use of antihypertensive medication. Diabetes status was determined by a fasting glucose level ≥126 mg/dL while not on steroid for two consecutive visits and/or reporting diabetes or use of antidiabetic medications (Mayo Clinic, 2018). Physical measures of body mass index (BMI), and SBP and DBP were collected at all the visits using standard methodology. Blood samples were drawn after a 12-h fast and were sent to the Medical Research Laboratories for analyses of high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), total cholesterol, triglyceride, as well as high sensitivity C-reactive protein (hsCRP), tissue-type plasminogen activator antigen (tPA), and plasma plasminogen activator inhibitor 1 (PAI-1). Detailed methods have been published elsewhere (El Khoudary et al., 2016). These biomarker measures were available for visits baseline, 1, 3–7, 12 and 13. Corresponding to available air pollution data, 5-year mean levels of these biomarkers, as well as BMI and SBP, were calculated using SWAN visit 3–7 data. We observed that the continuous variables did not change very much over time (data not published yet).

2.5. Statistical analysis

Fasting glucose, insulin, triglyceride, hsCRP, tPA and PAI-1 were log transformed due to positive skewness. The distribution of the covariates and outcomes by $PM_{2.5}$ quartiles are presented in Table 1. We used linear or logistic regression to test the association between the participants' characteristics and $PM_{2.5}$ level in quartiles (treated as continuous). Linear regression was used to estimate the association between visits 3–7 annualized mean exposure level of per 1 $\mu g/m^3$ $PM_{2.5}$ and per 1 ppb ozone and visit 12/13 mean and maximum cIMT, and mean IAD. Logistic regression and multinomial logistic regression was used to estimate the relationship between the annualized mean exposure to air pollutants and plaque presence and plaque index, respectively. Multinomial logistic regression was used, since the assumption of proportional odds was violated (score test p = 0.035). A series of nested models were constructed to evaluate the association between air pollutant exposures and subclinical atherosclerosis adjusting for established confounders: (1) model controlling only for site, (2a) model additionally adjusting for SES/demographic factors, age, race, education, and financial strain, (2b) fully adjusted model (model 2a plus BMI, smoking, triglyceride, cholesterol, HDL-c, menopause status, hormone replacement therapy, fasting glucose, and antidiabetic and antihypertensive medication), and (3) extended model, additionally adjusting for potential intermediates, SBP, hsCRP, tPA and PAI-1. The main analyses are single pollutant models, which used $PM_{2.5}$ or O_3 as the exposure. An exploratory analysis to identify high risk population was conducted by stratifying participants' characteristics related to CVD risk. These strata have been used in several studies in the same domain (Diez Roux et al., 2008; Bauer et al., 2010; Kaufman et al., 2016). Analyses were performed with SAS (V9.3, SAS Institute, Cary, NC). All tests were two-sided with $\alpha = 0.05$.

3. Results

Among the 1188 women with air pollutant estimates at visits 3–7 and a carotid ultrasound scan at visit 12/13, 573 were White, 373 Black, 159 Chinese, and 83 Hispanic. At the time of the carotid ultrasound scan, women were a mean age of 59.6 years (SD = 2.7, range: 54–67), and approximately 90% were post-menopausal (Table S1). In contrast, at visit 5, 5.0% were pre-, 43.0% were early peri-, 11.6% were late peri, and 40.3% were post menopause. Overall, the 5-year mean annualized $PM_{2.5}$ exposure level was 14.9 (SD = 1.9) $\mu g/m^3$ (IQR: 13.6–16.1); and the annualized mean O_3 exposure level was 30.8 (SD = 6.2) ppb (IQR: 29.2–35.9). The correlation between the two pollutants $PM_{2.5}$ and O_3 was r = 0.56. Five-year mean annualized exposure to $PM_{2.5}$ and ozone are shown in Fig. 2. Oakland, CA had the lowest $PM_{2.5}$ exposure over time, with a mean of 12.0 $\mu g/m^3$ (SD = 0.6), and relatively low level of O_3 exposure (mean = 24.6 ppb and SD = 5.9), but the range was very wide. All other four sites had comparable $PM_{2.5}$ exposure levels. The mean cIMT was 0.79 mm (SD = 0.12), maximum cIMT was 0.93 mm (SD = 0.14) and the mean IAD was 7.20 mm (SD = 0.67).

Baseline characteristics and 5-year mean levels of CVD risk factors by 5-year mean annualized exposure to $PM_{2.5}$ quartiles are presented in Table 1. Most of these factors were positively associated with $PM_{2.5}$. Those in lower $PM_{2.5}$ exposure areas were more frequently never smokers and women who reported no financial strains. On average,

Table 2
Association between 5-year mean annualized exposure to $PM_{2.5}$ and ozone and carotid artery intima-media thickness (cIMT) and inter-adventitial-diameter (IAD).

Models	Mean of average cIMT (μm)	Mean of maximum cIMT (μm)	Mean IAD (μm)
$PM_{2.5}$ (μg/m^3)			
Model 1	9.59 (3.19–15.98)***	12.57 (5.21–19.93)****	42.48 (6.77–78.19)**
Model 2a	7.57 (1.31–13.82)**	10.46 (3.29–17.63)***	35.28 (−0.01–70.57)[a]
Model 2b	5.59 (−0.58–11.75)[a]	8.03 (1.01–15.05)**	21.18 (−12.60–54.96)
Model 3	3.22 (−2.83–9.26)	5.02 (−1.86–11.90)	8.99 (−24.26–42.26)
Model 2b + SBP	3.48 (−2.56–9.53)	5.40 (−1.48–12.28)	
Model 2b + HTN[↑]	5.44 (−0.67–11.56)[a]	7.90 (0.94–14.86)**	
Model 2b + hsCRP	5.45 (−0.71–11.61)[a]	7.86 (0.84–14.87)**	
Model 2b + tPA	5.64 (−0.54–11.82)[a]	8.01 (0.97–15.04)**	
Model 2b + PAI-1	5.67 (−0.50–11.84)[a]	8.11 (1.08–15.14)**	
Ozone (ppb)[b]			
Model 1	−0.86 (−2.95–1.23)	−1.38 (−3.81–1.05)	−2.36 (−14.11–9.39)
Model 2a	−0.20 (−2.27–1.87)	−0.51 (−2.90–1.88)	0.16 (−11.60–11.91)
Model 2b	−0.49 (−2.51–1.53)	−0.92 (−3.23–1.38)	−0.47 (−11.67–10.72)
Model 3	−0.65 (−2.63–1.33)	−1.09 (−3.34–1.15)	−2.11 (−13.16–8.93)

Note: Model 1 adjust for site; model 2a further adjust for age, race, education, and longitudinal financial strain; model 2b additionally adjust for BMI, smoking, cholesterol, HDL-c, triglyceride, menopause status, hormone use, fasting glucose, antidiabetic medication, and antihypertensive medication; model 3 adjusting for intermediates: systolic blood pressure (SBP), C-reactive protein, tPA and PAI-1.
Data presented as effect (95% confidence interval).
[a] Marginal significant, $0.05 \leq p < 0.1$,**$p < 0.05$,***$p < 0.01$.
[b] Michigan site was excluded, since there were extensive missing values with ozone exposure, N = 826.

women who lived in more polluted areas had higher BMI, blood pressure, LDL-c, insulin, hsCRP, tPA and PAI, and lower HDL-c. We also observed that women in the higher $PM_{2.5}$ exposure quartiles had higher mean and maximum cIMT but were less likely to have plaque. In SWAN, it should be noted that Chinese women were more likely to have plaque.

In the main analyses of cIMT measures, $PM_{2.5}$ was associated with mean cIMT in the model adjusted for site and SES (Model 2a, Table 2). Women had a 7.57 μm (95% CI: 1.31–13.82) thicker cIMT for each 1 μg/m^3 5-year mean annualized exposure to $PM_{2.5}$. However, this association was only marginally significant ($p = 0.076$) after adjusting for standard CVD risk factors (model 2b). Women with an average of 1 μg/m^3 5-year mean annualized exposure to $PM_{2.5}$, had an 8.03 μm (95% CI: 1.01–15.05) thicker maximum cIMT on average (model 2b). In the models adjusted for SES plus diabetes (model 2b) and lipid (model 2c) biomarkers (Supplementary Tables S2 and S3), we noted there were small effect size reductions from model 2a to models 2b and 2c, but not as large as compared to model 3. After accounting for intermediates in the model, this association became null, which was mainly influenced by SBP (model 3). The association between $PM_{2.5}$ and IAD was significant in the model adjusting for site, but not significant in the models adjusting for standard CVD risk factors. No clear association was observed between O_3 and any carotid measures (Table 2). In the two-pollutant model, the estimates were slightly attenuated after adjusting for each other (supplementary tables S4 – S6). Neither of the two pollutants was significantly associated with plaque presence or plaque index in any model (Table 3).

We also explored the association between air pollution and cIMT by participants' characteristics and CVD risk factors. We observed that 5-year mean annualized exposure to $PM_{2.5}$ had a stronger effect on maximum cIMT in some of the subgroups (Fig. 3), which was observed among diabetic, obese and more than college educated women. However, due to the disproportionate sample sizes across strata, no significant interactions were observed.

Table 3
Association between 5-year mean annualized exposure to $PM_{2.5}$ and ozone and plaque presence and plaque index.

Models	Odd Ratio of Plaque Presence	Odds Ratio of Plaque index		
		0	1–2	> 2
$PM_{2.5}$ (μg/m^3)				
Model 1	0.98 (0.88–1.09)	Reference	0.99 (0.88–1.12)	0.96 (0.82–1.12)
Model 2a	1.00 (0.89–1.11)	Reference	1.01 (0.89–1.14)	0.99 (0.85–1.16)
Model 2b	0.98 (0.87–1.10)	Reference	1.01 (0.89–1.15)	0.93 (0.79–1.10)
Model 3	0.97 (0.86–1.09)	Reference	1.01 (0.88–1.15)	0.91 (0.76–1.08)
Ozone (ppb)[a]				
Model 1	1.01 (0.97–1.05)	Reference	1.03 (0.99–1.07)	0.98 (0.93–1.03)
Model 2a	1.01 (0.97–1.05)	Reference	1.03 (0.98–1.07)	0.98 (0.93–1.03)
Model 2b	1.01 (0.97–1.05)	Reference	1.02 (0.98–1.07)	0.98 (0.93–1.04)
Model 3	1.01 (0.97–1.05)	Reference	1.03 (0.98–1.07)	0.98 (0.92–1.03)

Note: Model 1 adjust for site; model 2a further adjust for age, race, education, and longitudinal financial strain; model 2b additionally adjust for BMI, smoking, menopause status, hormone use, cholesterol, HDL-c, fasting glucose, antidiabetic medication use, and antihypertensive medication use; model 3 adjusting for intermediates: systolic blood pressure (SBP), C-reactive protein, tPA and PAI-1.
Data presented as odds ratio (95% confidence interval).
[a] Michigan site was excluded, since there were extensive missing values with ozone exposure, N = 826.

4. Discussion

In this 11-year observational study, we found that women who had a higher 5-year mean annualized $PM_{2.5}$ over approximately 5 years during early midlife had a higher maximum cIMT in late midlife, controlling for traditional CVD risk factors. Significant associations were observed between $PM_{2.5}$ and mean cIMT, independent of SES factors, and IAD after adjusting for site, but both these associations could be explained by standard CVD risk factors. No meaningful associations were found between $PM_{2.5}$ and plaque and with O_3 and subclinical atherosclerosis.

This is the first study focused on the effects of 5-year mean annualized exposure to air pollution on atherosclerosis among women transitioning from peri-menopause to post-menopause with more than 10-year effects of observation. Our study observed women during the period of life when CVD risk accelerates rapidly. An earlier SWAN analysis indicated that late peri-menopausal women have increased risk of CVD and the fastest progression of cIMT compared to women at an

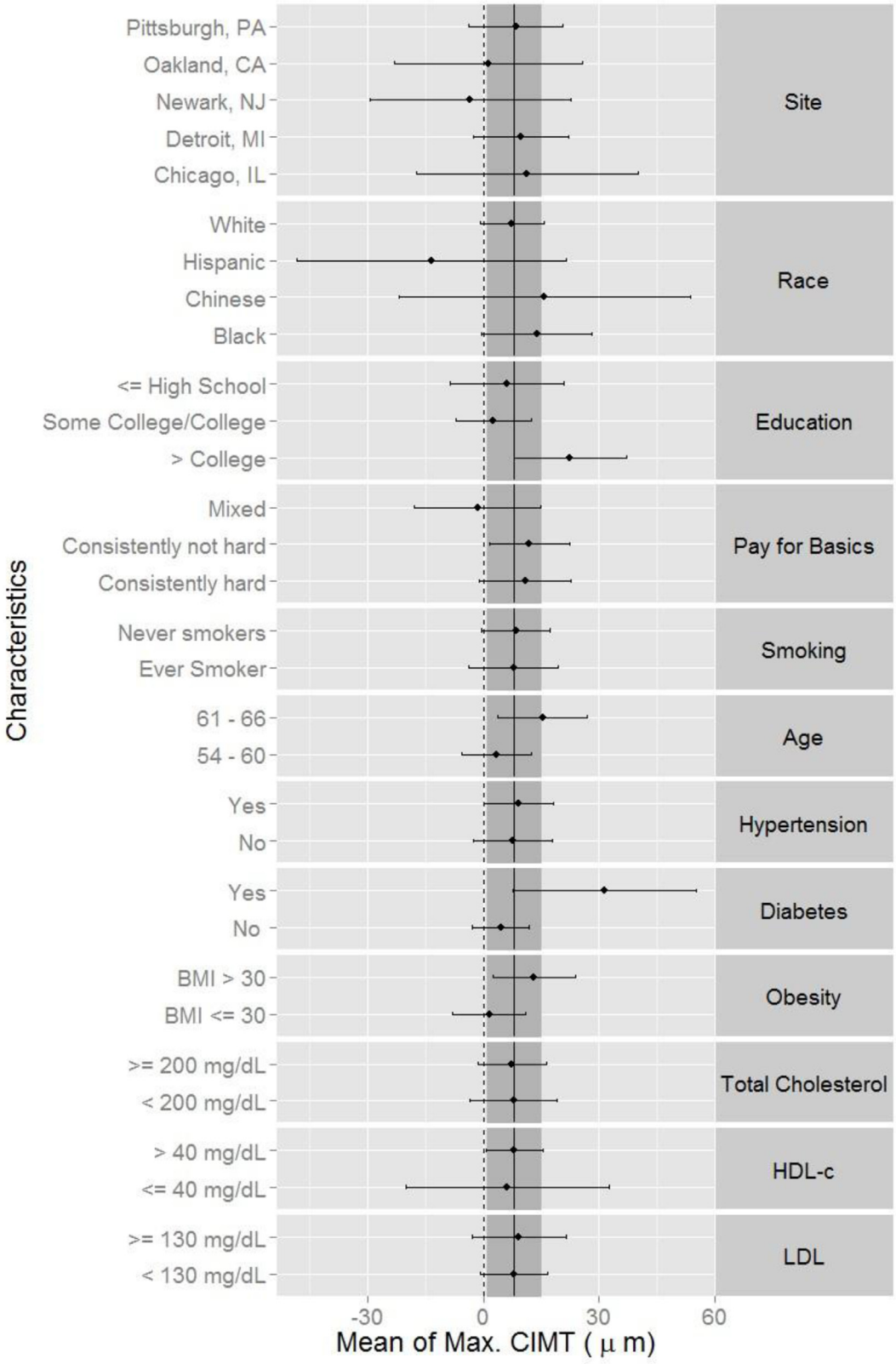

Fig. 3. Association between 5-year mean annualized exposure to $PM_{2.5}$ and mean of the maximum common carotid artery intima-media thickness (cIMT), by participant characteristics.Note: The solid line shows the point estimate of $PM_{2.5}$ and maximum cIMT in the fully adjusted model (2b), with the shaded area indicates 95% CI. The dash line indicates 0, which is the null effect.

earlier stage of menopause (El Khoudary et al., 2013). $PM_{2.5}$ exposure was assessed in our study when most women were transitioning through the menopause. Thus, the exposure data was collected at the stage of life when it may have the greatest impact on atherosclerotic progression, vascular remodeling and CVD risk.

In this study, we revealed that women had an 8.03 μm (95% CI: 1.01–15.05) thicker maximum cIMT for each 1 $\mu g/m^3$ greater 5-year mean annualized exposure to $PM_{2.5}$, adjusting for traditional CVD risk factors. Consistent with our findings, Diez-Roux et al. found that 20-years exposure to observed PM_{10} and imputed $PM_{2.5}$ were associated with cIMT independently of CVD risk factors. As $PM_{2.5}$ exposure levels were not available before 1999, they imputed the value using the spatial temporal model. Our study, using observed data, reached the same conclusion. Rivera and colleagues found that traffic intensity was associated with cIMT (Rivera et al., 2012). Traffic is one of the major sources of $PM_{2.5}$ in urban areas (U.S. Environmental Protection Agency, 2014). Although studies of more than one-year exposure to air pollutants and sub-clinical atherosclerosis are limited, the relationship between one-year $PM_{2.5}$ exposure and cIMT has been observed in several cross-sectional and longitudinal studies (Bauer et al., 2010; Künzli et al., 2010; Adar et al., 2013; Kaufman et al., 2016).

In many of the air pollution studies cited in the literature, one-year air pollution exposure is classified as long-term exposure. However, atherosclerosis is a life-long process likely resulting from long-term cumulative risk factor exposure, and its progression leading to clinical CVD events (Künzli et al., 2011). Thus, our primary aim was to assess the effects of greater than one-year exposure to $PM_{2.5}$ and O_3 on atherosclerosis. However, we also evaluated the effect of a shorter-term exposure of one year closer to the outcome measures and found that the associations between one-year exposure to $PM_{2.5}$ at visit 7 and mean and maximum cIMT were slightly attenuated compared to 5-year mean annualized exposure levels (supplementary tables S7 – S9). The associations with $PM_{2.5}$ and other subclinical atherosclerosis biomarkers, and ozone and all of the biomarkers were not changed very much. These findings confirm our hypothesis that more than one-year exposure to air pollution and longer follow-up time can contribute to atherosclerosis more meaningfully. Evidence from several large cohort studies reporting an association between more than one-year exposure to air pollution and future CVD morbidity and mortality also support our hypothesis. (Miller et al., 2007; Puett et al., 2009; Beelen et al., 2014; Cesaroni et al., 2014; Hart et al., 2015). All of these studies evaluated air pollution for one-year or across several years, and then followed up the participants for decades to clinical CVD events. From the Women's Health Initiative, Miller et al. found that $PM_{2.5}$ exposure in year 2000 was associated with cardiovascular events with a median follow-up of 6 years (Miller et al., 2007). In the Nurse's Health Study, the authors noted that up to 18-year exposure to PM was related to elevated CVD risk among diabetic women (Hart et al., 2015). These findings align with our hypothesis and results that several years of cumulative air pollution exposure may lead to elevated atherosclerosis risk as measured by maximum cIMT several years later.

The effect of air pollution on CVD risk has been extensively reviewed in several papers (Brook et al., 2010; Franklin et al., 2015). PM can trigger systemic oxidative stress and inflammation, increase adipokines and cytokines expression level, oxidize lipids, inflamed fat cells and thus, lead to atherosclerosis (Franklin et al., 2015). However, in this population-based study, we did not see an effect size change after adding hsCRP, tPA and PAI-1 in the fully adjusted model, which is consistent with findings from MESA Air study (Adar et al., 2013; Kaufman et al., 2016). We found that elevated systolic blood pressure and hypertension may be a factor mediating the effect of $PM_{2.5}$ on cIMT, reducing the effect size by about 37%. There is ample evidence for the effects of $PM_{2.5}$ on hypertension and elevation of blood pressure (Franklin et al., 2015), which are risk factors for atherosclerosis and CVD events (Allen et al., 2014). Thus, it is plausible that elevated blood pressure may be a mediator of the effect of $PM_{2.5}$ on atherosclerosis. Alternatively, the $PM_{2.5}$ effect on carotid wall thickening, especially in the CCA and in the absence of plaque, may reflect adaptive vascular remodeling driven by hemodynamic stressors such as increased arterial pressure (Heusch et al., 2014).

In this study, we did not find evidence of an association between O_3 exposure and any biomarkers of subclinical atherosclerosis. There are very few studies examining the long-term exposure effect of O_3, since ambient O_3 level is largely dependent on ultra-violate intensity (U.S. Environmental Protection Agency, 2015). Moreover, the acute effect of O_3 can be reversible in healthy individuals (Allen, 2002) making the long-term effect of O_3 difficult to observe in areas with higher levels during the summer, and lower levels during the winter. In our sample, 5-year mean annualized exposure level of O_3 was about 30.8 (range: 17.8–46.1) ppb, much lower than the national ambient air quality standards (U.S. Environmental Protection Agency, 2014). The only study examining O_3 exposure was among college students in Los Angeles, CA (Breton et al., 2012). They noted that early childhood exposure, when students were 6–12-years old, impacted cIMT at age 19. Most of the participants in this study were originally from southern California, which may indicate that they were exposed to higher levels of O_3 all year round.

Our stratification analyses suggest that obese and diabetic women may be more susceptible to $PM_{2.5}$, as each 1 $\mu g/m^3$ higher 5-year mean annualized exposure to $PM_{2.5}$, predicted a thicker maximum cIMT in these groups compared to the reference group. In contrast to the study by Rivera et al. (Rivera et al., 2012), we did no treat these factors as potential intermediates, but adjusting for these factors decreased the effect size about 20% compared to the minimally adjusted model. We did not observe a substantial effect size change from the models adjusting for diabetes and lipid biomarkers (Supplementary Tables S2 and S3). These biomarkers may not present strong mediation effects, however this would need to be tested formally in a large study population. In line with increased susceptibility in obese populations, several animal studies using APOE or LDLR knock-out mice, that are more susceptible to fat, showed an increase in plaque volume by 50% after exposing them to $PM_{2.5}$ (Sun et al., 2005; Soares et al., 2009), although in our study $PM_{2.5}$ was not associated with plaque measures. Diabetes may also interplay with oxidative stress and increase the risk in developing atherosclerosis (Bullon et al., 2014). In the Nurses' Health Study, they observed that women with diabetes exposed to higher levels of $PM_{2.5}$ had an increased risk of incidence CVD, coronary heart disease and stroke (Hart et al., 2015).

We did not observe any association between either pollutant with plaque presence or plaque index. So far, there has been only one published study using plaque as an outcome (Gan et al., 2014). Consistent with our findings, in the M-CHAT study, the authors did not find significant associations between any of the pollutants, e.g. traffic, $PM_{2.5}$, NOx, and noise, with plaque in the overall population. There is very weak evidence between $PM_{2.5}$ and plaque in the current literature. Our study population may be still young to observe significant plaque burden. Although there were about 45% women who had plaque, most of them had only one or a few small plaques with plaque index of 1–2. The subclinical phase of atherosclerosis is very long (Künzli et al., 2011; Juhola et al., 2013). Thus, at this stage, plaque assessment may not yet reflect extensive subclinical atherosclerosis among these women.

5. Limitations

One of the limitations in our study is the gap between exposure assessment and outcomes collection, which was about 5 years. However, the data we have during year 2000–2005 corresponds to the higher exposure levels according to U.S. EPA (U.S. Environmental Protection Agency, 2016). Moreover, several studies demonstrated that earlier long-term exposure to air pollution was related to CVD outcomes in a later time (Miller et al., 2007; Beelen et al., 2014; Cesaroni et al., 2014; Hart et al., 2015). Additionally, there likely is some overlap and

gaps in the five years of exposure data since the study visits were not exactly 360 days apart. Another potential limitation is that the monitors used measured exposure estimation without any modeling. The modelled data can overcome limitations due to missing values, and may add exposure variation if the spatial variance was well modelled. However, most of the modeling methods have limitations and uncertainties (Rao et al., 2011; Venkatram, 2015). Moreover, if the extrapolation of the exposure modeling is to a period with extensive missing data from the monitors, the estimation may not be valid. Our outcome of cIMT only measured the CCA segment, which may not fully capture carotid arterial segments more prone to atherosclerosis. Rivera et al. reported a stronger association between 10-year NO_2 exposure and cIMT measured as the mean of 6 segments rather than the CCA segment only (Rivera et al., 2012). Lastly, prior cIMT information was not available to address pre-existing risk or conditions related to subclinical atherosclerosis.

6. Strengths

We have the advantage of studying air pollution exposure during the menopausal transition in women as a predictor of their post-menopausal subclinical atherosclerosis. SWAN collected extensive data of CVD risk factors of these women during the menopausal transition, allowing us to assess the independent association of five-year $PM_{2.5}$ exposure with cIMT thickening in post-menopause. We uniquely established the association between 5-year mean annualized $PM_{2.5}$ exposure and subclinical atherosclerosis about 7 years later. As atherosclerosis is a life-long process (Künzli et al., 2011), longer exposure is more meaningful in establishing the relationship with atherosclerosis.

7. Conclusions

In conclusion, 5-year mean annualized exposure to $PM_{2.5}$ in early mid-life independently contributes to atherosclerosis as measured by maximum CCA IMT at later mid-life in a multi-ethnic population-based cohort of women. The findings from this study extend the evidence in the current literature that long-term exposure to $PM_{2.5}$ is harmful to heart health.

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Conflicts of interest

All authors declared no actual or potential conflict of interest.

Data access

SWAN provides access to public use datasets that extend through the tenth annual follow-up visit. Some, but not all, of the data used for this manuscript are contained in the public use data sets. Links to each of the public use data sets are located on the SWAN web site: http://www.swanstudy.org/swan-research/data-access/. Investigators who require assistance accessing the public use data set may contact the SWAN Coordinating Center at the following email address: swanaccess@edc.pitt.edu.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijheh.2018.09.001.

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