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Long-Term Coarse Particulate Matter Exposure and Heart Rate Variability in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background—Reduced heart rate variability, a marker of impaired cardiac autonomic function, has been linked to short-term exposure to airborne particles. This research adds to the literature by examining associations with long-term exposures to coarse particles (PM_{10-2.5}).

Methods—Using electrocardiogram recordings from 2,780 participants (45-84 years) from three Multi-Ethnic Study of Atherosclerosis sites, we assessed the standard deviation of normal-to-normal intervals (SDNN) and root-mean square differences of successive normal-to-normal intervals (rMSSD) at a baseline (2000-2002) and follow-up (2010-2012) examination (mean visits/person=1.5). Annual average concentrations of PM_{10-2.5} mass, copper, zinc, phosphorus, silicon, and endotoxin were estimated using site-specific spatial prediction models. We assessed associations for baseline heart rate variability and rate of change in heart rate variability over time

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using multivariable mixed models adjusted for time, sociodemographic, lifestyle, health, and neighborhood confounders, including co-pollutants.

Results—In our primary models adjusted for demographic and lifestyle factors and site, PM_{10-2.5} mass was associated with 1.0% (95% CI: -4.1, 2.1%) lower SDNN levels per interquartile range of 2 µg/m³. Stronger associations, however, were observed prior to site adjustment and with increasing residential stability. Similar patterns were found for rMSSD. We found little evidence for associations with other chemical species and with the rate of change in heart rate variability, though endotoxin was associated with increasing heart rate variability over time.

Conclusion—We found only weak evidence that long-term PM_{10-2.5} exposures are associated with lowered heart rate variability. Stronger associations among residentially stable individuals suggest that confirmatory studies are needed.

Keywords

Air pollution; PM_{10-2.5}; cardiovascular; chronic; longitudinal; components; sources

Introduction

Particulate air pollution has been linked to numerous adverse health outcomes including cardiovascular morbidity and mortality.[1] While there is a rich epidemiologic and toxicologic literature on fine particulate matter less than 2.5 µm (PM_{2.5}),[1] far less is known about coarse particulate matter between 2.5 to 10 µm in diameter (PM_{10-2.5}).[2] These two types of particles differ with respect to source, composition, and biologic deposition.[3] PM_{2.5} is mainly generated from cars, trucks, industrial facilities, forest fires, and biogenic sources and is thus dominated by sulfates, nitrates, and carbon. In contrast, sources of PM_{10-2.5} include brake and tire wear from motor vehicles, agriculture, windblown soil, and road dust leading to a high metal content. Once inhaled, PM_{2.5} also has higher deposition rates in the alveolar regions of the lung as compared to PM_{10-2.5}. As a result of these key differences, the United States Environmental Protection Agency (EPA) has stated that PM_{2.5} and PM_{10-2.5} should be considered separately under the National Ambient Air Quality Standards (NAAQS) [3] yet a lack of epidemiologic data has limited their ability to assess a unique standard for PM_{10-2.5}.

One of the more consistent outcomes associated with PM_{10-2.5} in previous short-term and toxicologic studies is heart rate variability.[4-13] Reduced heart rate variability is a marker for impaired cardiac autonomic control that has been associated with lower survival among patients with myocardial infarctions, sudden death, chronic heart failure, and sepsis.[14] Although the exact mechanism by which particles impact heart rate variability is not completely understood, it is hypothesized that inhaled particles can directly affect afferent nerves in the lungs as well as initiate inflammation that can result in downstream alterations to cardiopulmonary rhythm.[1] PM_{10-2.5} may be especially important for this outcome given that it is often rich in endotoxin, an immune-modulating component of bacterial cell membranes that has been repeatedly linked to alterations in heart rate variability in humans and in animal models.[15, 16]

Most research on heart rate variability has focused on temporary exposures such as time of day[17] and short-term exposures to air pollution,[1] yet there is also evidence that heart rate variability declines with increasing age, chronic diseases, and long-term exposures to medications, disturbed sleep, and lifestyle factors such as chronic active smoking. Longitudinal studies have also shown that short-term heart rate variability has prognostic value for several more chronic health endpoints including diabetes[18] and heart failure.[19] In addition, repeated measures of heart rate variability from healthy [20, 21] and diseased subjects[22] have been shown to be highly correlated over time. All together, this suggests that even short-term measures of heart rate variability may be used to capture more chronic cardiac autonomic dysfunction and alterations in homeostatic function. Although there is some toxicological evidence suggesting a role of longer-term exposures to particulate matter, [23] no epidemiologic investigation to our knowledge has yet to examine the association of long-term exposures to $PM_{10-2.5}$ and heart rate variability.

This study aims to add to the limited literature on $PM_{10-2.5}$ and health by investigating associations between heart rate variability and long-term exposures to $PM_{10-2.5}$ in a longitudinal analysis from the Multi-Ethnic Study of Atherosclerosis (MESA). We explore $PM_{10-2.5}$ mass as well as specific components as indicators of key $PM_{10-2.5}$ sources including traffic, windblown soil, agricultural activities, and biological compounds. We hypothesize that greater long-term exposures to $PM_{10-2.5}$ are associated with lower heart rate variability and more rapid age-related declines in heart rate variability over time, independent of co-pollutant exposures including $PM_{2.5}$ and nitrogen dioxide (NO_2)

Methods

Study Population

The MESA cohort consists of 6,814 men and women aged 45-84 who were free of cardiovascular disease at baseline and were recruited from the following six regions in the United States: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. As described elsewhere,[24] the cohort is diverse by design, consisting of white, African-American, Hispanic and Chinese participants. As part of the MESA Coarse Air Pollution (MESA Coarse) ancillary study, detailed measurements of $PM_{10-2.5}$ were collected in St Paul, Forsyth County, and Chicago, allowing for assessment of this exposure among the subset of participants (n=3,295) residing in these locations. Individuals with complete outcomes, exposure, and covariate data were included in this analysis. Institutional review board approval and informed consent was obtained from each site and participant.

Heart Rate Variability Measurements

Standard 12-lead electrocardiograms (ECG) were recorded on all participants after a 5-minute rest using similar ECG machines (Marquette MAC-1200; GE Healthcare, Milwaukee, WI, USA) at the MESA baseline examination (2000-2002) and again at the 5th examination (2010-2012) with an average of 9.4 years of follow-up. At each examination, three consecutive 10-second ECG recordings were collected and automatically processed

using GE Marquette 12-SL (GE Healthcare, Milwaukee, WI, USA) at a central reading center. Heart rate variability was assessed using two time-domain measures obtained from normally conducted sinus beats: the standard deviations of all normal-to-normal intervals, hereafter referred to as SDNN, and the root-mean square differences of successive normal-to-normal intervals, hereafter referred to as rMSSD. Whereas the former reflects overall autonomic tone, the latter is more dominated by parasympathetic tone.[14] For each individual and examination, we used SDNN and rMSSD levels derived from the average of the three 10-second values. Participants with non-sinus rhythm or visits with only one 10-second interval were excluded from the analysis. The mean of repeated 10-second readings has been shown to be highly correlated with 6-minute measures ($r = 0.76$, 95% CI: 0.68-0.82 for SDNN and $r = 0.82$, 95% CI: 0.75-0.86 for rMSSD)[25] and associated with poor health outcomes in MESA[19] and other populations[18, 26, 27] where long-term recording is logistically challenging. Power and frequency measures were not considered due to the short reads.

Exposure Assessment

Methods for estimating long-term exposures to $PM_{10-2.5}$ mass and selected chemical components in the MESA Coarse Study have been described in detail elsewhere.[28] Briefly, spatial prediction models were developed using air pollution measurements collected specific to this project and geographic factors including land use, vegetation, and emission sources. These land use regression models were developed uniquely for each study site and allowed for individual-level predictions of $PM_{10-2.5}$ mass and components at all participants' residential addresses. Using positive matrix factorization, copper, zinc, phosphorus, and silicon were selected as indicator species consistent with brake wear, tire wear, agriculture, and soil/road dust, respectively.[29] Endotoxin concentrations were also estimated as a measure of biological activity since they are an important modulator of innate immunity found in bacterial cell membranes.[30] Estimates of $PM_{2.5}$ and two indicators of tailpipe emissions from motor vehicles, light absorbing carbon, and nitrogen dioxide (NO_2), were also derived from spatio-temporal models developed for this cohort and explored as potential confounders.

We generated average concentrations for each participant based on their residential history in the year preceding each exam. At any given address, however, we assumed that the spatial patterning of pollution was constant over time such that models derived using data from 2006–2009 were considered to accurately estimate concentrations for the full study period (2000–2012). This is supported by an unpublished analysis that demonstrated general spatial stability of pollution over multiple years in the states of interest. For all scenarios, concentrations are intended to represent long-term exposures.

Covariates

We used standardized methods to collect demographic and health characteristics.[24] We used questionnaires to gather information including age, gender, race/ethnicity, education, occupation, smoking history, pack-years smoked, physical activity, and use of beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers. Measurements of height, weight, blood pressure, fasting glucose, and triglyceride levels were also collected

during the clinical exams. United States Census tract level information on education, occupation, median home values, and median household income was also employed to capture participants' contextual environments as has been published previously.[31] Diabetes and metabolic disease statuses were based on 2003 American Diabetes Association (ADA) fasting criteria algorithm and by the National Cholesterol Education Program (NCEP) guidelines, respectively. In addition, data on average outside temperature in each study site was collected from the National Oceanic and Atmospheric Administration.

Statistical Analysis

We conducted all analyses using SAS software, Version 9.3 (SAS Institute Inc. Cary, NC). First, we employed simple descriptive statistics to characterize the study population. In all models we estimated associations between heart rate variability levels with pollution concentrations based on the previous year of residential history as well as the interaction of pollution with time to examine if higher exposures were associated with a more rapid decline in heart rate variability over time (rate of change). We examined these associations within the context of linear mixed models with random intercepts and random slopes for time (years since baseline exam) for each subject. Since SDNN and rMSSD were both highly skewed, we log-transformed these variables prior to analysis. We constructed our models in stages to explore the impacts of inclusion of various potential confounders selected *a priori*. Model 1 adjusted for time trends as well as the demographic characteristics of baseline age, gender, and race/ethnicity. Model 2 added socioeconomic and lifestyle factors including education, occupation, neighborhood socioeconomic status, physical activity, smoking history, second hand smoke exposure, and pack years. Finally, our main model (Model 3) controlled for study site as a main effect as well as interacted with time and neighborhood socioeconomic status. These terms were included to capture confounding of the longitudinal relationships with air pollution by site and because past research has demonstrated different relationships between air pollution and NSES by location.[31] We also explored control for meteorological variables including season, potential causal intermediaries including body mass index (BMI), diabetes, triglycerides, hypertension, and metabolic syndrome, and interactions of demographics by time, but, since results were consistent these parameters were excluded. The following variables were allowed to vary with time: physical activity, pack-years, meteorological variables, BMI, triglycerides, hypertension, and metabolic syndrome, otherwise baseline values were used. All pollutants were modeled individually though additional models explored control for other PM_{10-2.5} components, PM_{2.5}, light-absorbing carbon, and NO₂ as other components of the pollution mixture. Linearity of associations with heart rate variability and all continuous variables were assessed with p-splines in R.[32] Finally, we explored effect modification by including interaction terms for study site, age, race/ethnicity, gender, obesity, diabetes, hypertension, metabolic syndrome, cardiac medications (including beta-adrenergic agonists, angiotensin-converting enzyme inhibitors, and calcium channel blockers) and residential stability (10 years at residence).

Over the full study period, the cohort experienced approximately 20% loss-to-follow-up. To test the sensitivity of our results to these individuals, we conducted multiple imputation using Chained Equations to estimate follow-up values for those who received an

electrocardiogram at baseline, but were not present at the follow-up examination.[33] IVEware 0.2 package for SAS was used to produce the 12 imputed datasets, each after 10 iterations.

All associations are presented as percent change per interquartile range of each pollutant.

Results

Baseline Characteristics

After excluding participants with missing outcome (4%), covariate (1%), or exposure (10%) information, a total of 2,780 subjects (84%) were available for analysis. The Table shows the sociodemographic, clinical, and exposure characteristics of this cohort at baseline. The average age was 61 years, with slightly more females (53%) than males. The majority of participants were white (53%) with additional representation of African-Americans (23%), Chinese Americans (10%), and Hispanics (14%). Participants were generally well educated (43% were college educated or more) and non-smokers. Approximately 10% of the cohort had diabetes and 42% had hypertension. On average, subjects were followed for 9.4 years with the average participant contributing 1.5 visits. Those who were lost to follow-up were older, were more likely to be diabetic or hypertensive, and had lower baseline heart rate variability measures but similar exposure levels to those who were not lost to follow-up (eTable 1).

SDNN and rMSSD were highly correlated ($r=0.95$) with the highest levels in Winston Salem and lowest in Chicago (Table). Declines in heart rate variability over time were small (mean absolute declines of 0.2 to 0.3 msec per year for both SDNN and rMSSD; median declines of 0.8% to 1.4% per year on the natural log scale) and more consistent across study center. Pollutant levels were also generally low with only modest differences by city. The lowest average levels of PM_{10-2.5} mass, copper, and zinc were observed in Winston Salem while Chicago had the highest average levels of these pollutants. Although still low, St Paul had the highest average levels of endotoxin and silicon and Winston Salem had the highest levels of phosphorus.

Associations with Mean Heart Rate Variability

After adjustment for only demographic, socioeconomic, and lifestyle factors, we found that higher PM_{10-2.5} mass, copper, and zinc concentrations were associated with lower SDNN and rMSSD mean levels (Figure 1). For example, we observed 2.9% (95% CI: -5.5,-0.2%) lower SDNN levels per 2 µg/m³ higher levels of PM_{10-2.5} mass concentrations. However, in our main model, which further adjusts for study site, associations were only suggestive with weaker point estimates and inflated standard errors (Figure 1) resulting in a relationship of 1.0% (95% CI: -4.1, 2.1%) lower SDNN levels per interquartile range of 2 µg/m³. PM_{10-2.5} mass concentrations were most consistently associated with both SDNN and rMSSD (Figure 1) with evidence of linearity relationships before and after adjustment for study site (Figure 2), inverse associations across all study sites (ranging from -2.8%; 95% CI: -9.8, 4.8 lower SDNN in Winston Salem to 0.1%; 95% CI: -6.0, 6.3 lower SDNN in Chicago), and stronger

inverse associations with increasing residential stability (Figure 3). Associations with other species were less consistent.

Associations with Rate of Change of Heart Rate Variability

We found little evidence of a relationship between $PM_{10-2.5}$ mass and components with the rate of change of heart rate variability over time. Only endotoxin was associated with a 0.7%/yr (95% CI: 0.06, 1.3%/yr) greater increase in rMSSD over time per 0.08 EU/m^3 (Figure 4) after adjustment for study site.

Effect Modification and Sensitivity Analyses

Similarly, we found no strong support for effect modification by personal characteristics (eFigure 2). All results were robust to control for other co-pollutants including annual average $PM_{2.5}$ concentrations, which was itself not strongly associated with lower HRV after control for study site (eFigure 1). Multiple imputation to recover missing records during the follow-up examination similarly did not alter our results (results not shown).

Discussion

In this investigation we examined associations between long-term exposure to $PM_{10-2.5}$ mass and components with two measures of heart rate variability using data from a large, multi-ethnic prospective cohort study. Using individual-level estimates of long-term exposures from project-specific spatial prediction models, we documented only weak evidence of relationships between $PM_{10-2.5}$ and altered autonomic tone. Associations with both SDNN and rMSSD were strongest for $PM_{10-2.5}$ mass concentrations, especially among persons who were residentially stable, yet these associations were weak and imprecise after control for study site. Only endotoxin was associated with the rate of change in heart rate variability with evidence of increasing rMSSD over time with increasing concentrations. However, it should be noted that endotoxin exposure levels in this cohort were low. Collectively, we are unable to conclude that long-term exposure to $PM_{10-2.5}$ are associated with lowered autonomic tone among this population of middle aged and older Americans.

This work adds to the relatively scarce literature on associations between long-term exposures to air pollutants and heart rate variability. It is further unique in our focus on exposures to $PM_{10-2.5}$ mass and components. We observed some weak evidence of decreases in heart rate variability with higher levels of annual average $PM_{10-2.5}$ mass concentrations. Specifically, we found 1.0% lower heart rate variability and among persons with $2 \mu\text{g/m}^3$ higher $PM_{10-2.5}$ mass concentrations after adjustment for study site. This is approximately equivalent to the difference between individuals who were nearly 1 year apart in age. Although this analysis used 1-year exposure estimates, we found that the individuals with the greatest residential stability experienced the strongest $PM_{10-2.5}$ - heart rate variability associations. This suggests that longer-term exposures may be important since the 1-year estimates are most likely to reflect previous exposures among participants who have lived at the same location for many years.

The presence of an association with long-term exposures to $PM_{10-2.5}$ could suggest a potential mechanism leading to cardiovascular endpoints since lower heart rate variability is

associated with poor cardiac health and increased risk of cardiovascular disease related death.[14] As with our findings, however, the little research published on long-term exposures to air pollutants and heart rate variability has been somewhat inconclusive. In the Swiss SAPALDIA study, it was found that higher levels of traffic-related PM₁₀ over the previous 10-years was associated with lower measures of heart rate variability but only among individuals on ace-inhibitor therapy [34] and persons with a specific polymorphism in the interleukin-6 gene locus [35]. There was no evidence of an association among other individuals. Similarly, higher levels of NO₂ were associated with lower heart rate variability among women but not men in SAPALDIA [36]. In this work, we found more compelling evidence for an association between long-term exposure and heart rate variability than for the rate of change in heart rate variability. This could occur if air pollution has a more instantaneous impact on heart rate variability. Alternatively, it may simply reflect greater measurement error when characterizing small changes over time.

In contrast, the prior literature on short-term exposures to PM_{10-2.5} and heart rate variability have generally,[4-6, 9, 12, 13, 23] though not always [7, 8, 10] found associations with reduced heart rate variability. For instance, Chang et al. found an increase of 1 µg/m³ in PM_{10-2.5} over the previous 6-hours reduced SDNN by 1.4% (95% CI: -2.0, -0.8%).[23] Graff and colleagues conducted a case crossover study, in which they exposed volunteers to coarse concentrated ambient particles, and found that SDNN decreased 20 hours after subjects were exposed.[13] Although higher short-term concentrations of PM_{2.5} have also been associated with decreased SDNN and rMSSD,[37] we did not find associations with long-term exposures to PM_{2.5} after control for study site. Thus, control for PM_{2.5} did not alter the observed association between PM_{10-2.5} and heart rate variability suggesting that PM_{10-2.5} may independently affect cardiac autonomic control. Unfortunately, a lack of short-term measures of PM_{10-2.5} in this study limited our ability to explore shorter time-exposure windows and examine the relative strength of short- vs. long-term exposures.

This study has several important strengths, one of which is its extensive exposure assessment of fine-scale spatial differences in PM_{10-2.5} mass, components, as well as the availability of co-pollutant predictions from MESA Air. This allowed for a comprehensive exploration of long-term exposures among a large, well-defined cohort with repeated measurements of heart rate variability over time. Interestingly, PM_{10-2.5} mass rather than specific components was most strongly associated with time-varying heart rate variability. Changes in heart rate variability over time, however, were positively associated with endotoxin, which was counter to our original hypothesis.

One possible explanation for our relatively weak findings and counter-to-hypothesis findings for endotoxin was the relatively low levels of PM_{10-2.5} and endotoxin observed across our three cities. For example, average levels of PM_{10-2.5} in this study (4-6 µg/m³) were comparable to those reported in residential neighborhoods in Detroit (6-7 µg/m³) [38], but lower than a variety of sites reported for Los Angeles (5-14 µg/m³) [39], Philadelphia (5-9 µg/m³) [40], Denver (9-16 µg/m³) [41], Research Triangle Park (1-13 µg/m³) [42], and Central and Eastern European countries (6-40 µg/m³) [43, 44]. It is possible that, at these low levels, higher endotoxin levels lead to more active phagocytosis by alveolar macrophages without a concurrent recruitment of neutrophils thus reducing any potential

impact of PM exposures.[45] Although a major strength of this work was our ability to predict fine-scale spatial variations in coarse particles, it remains possible that the inherent lower variability of long-term concentrations limited our power to detect any true associations. A lack of indoor or personal data may also have limited our ability to detect associations due to enhanced measurement error. Spatial and temporal misalignment of the exposure and outcome data may have similarly introduced error into our analyses. It is further possible that our findings with endotoxin are purely the result of chance due to multiple testing. Finally, the MESA cohort experienced some loss of participants over the 10 years of follow-up. Although selection bias could have distorted our findings if the probability of returning for the final exam was related to both health and exposure, our multiple imputation approach to minimize the impacts of selection bias did not alter our conclusions.

In summary, we found only weak evidence that long-term exposure to PM_{10-2.5} was associated with lower heart rate variability among repeated measures from a diverse, multicity population-based sample. Suggestive associations between long-term concentrations of PM_{10-2.5} mass and altered autonomic control of the heart indicate that future research is warranted to address this question.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Associations between Annual Average $PM_{10-2.5}$ Mass and Components and Mean Heart Rate Variability Level (Percent Change, 95% CI) After Adjustment for Confounding Factors

Demographic models (D) adjusted for time, age, race/ethnicity, gender. SES/Lifestyle models (SE/L) added occupation, education, neighborhood SES, education, physical activity, smoking history, secondhand smoke exposure, pack-years smoked. Our main models (Site) added site and site by time interaction, site by neighborhood SES, site by neighborhood SES by time. Associations are scaled to interquartile range of $PM_{10-2.5}$ mass, copper (Cu), zinc (Zn), phosphorus (P), silicon (Si), and endotoxin were $2 \mu g/m^3$, $4 ng/m^3$, $11 ng/m^3$, $6 ng/m^3$, and $0.1 \mu g/m^3$, and $0.08 EU/m^3$ respectively.

Figure 2. Linearity of Association between $PM_{10-2.5}$ Mass and Mean Levels of SDNN Before (Left Panel) and After (Right Panel) Adjustment for Study Site

Models adjusted for time, age, race/ethnicity, gender, occupation, education, neighborhood SES, education, physical activity, smoking history, secondhand smoke exposure, and pack-years smoked. Model on right also adjusted for site, site by time interaction, site by neighborhood SES, and site by neighborhood SES by time. Because $PM_{10-2.5}$ concentrations were derived based on colocated PM_{10} and $PM_{2.5}$ filters, occasionally we would observe negative values. These were retained in the dataset and construction of our spatial prediction models in order not to bias our results, sensitivity analyses demonstrated robust findings to excluding these few data points.

Figure 3. Associations (95% CI) between Annual Average PM_{10-2.5} Mass and Mean Heart Rate Variability Levels (Panel A) and Rate of Change (Panel B) Stratified by Residential Stability Models adjusted for time, age, race/ethnicity, gender, occupation, education, neighborhood SES, education, physical activity, smoking history, secondhand smoke exposure, and pack-years smoked. Model on right also adjusted for site, site by time interaction, site by neighborhood SES, and site by neighborhood SES by time. Associations are scaled to interquartile range of PM_{10-2.5} mass, copper (Cu), zinc (Zn), phosphorus (P), silicon (Si), and endotoxin were 2 µg/m³, 4 ng/m³, 11 ng/m³, 6 ng/m³, and 0.1 µg/m³, and 0.08 EU/m³

respectively. Results stratified by duration that someone had lived at their residence before the examination.

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Figure 4. Annual Average PM_{10-2.5} Mass and Components and Rate of Change in Heart Rate Variability (95% CI) After Adjustment for Confounding Factors

Demographic models adjusted for time, age, race/ethnicity, gender. SES/Lifestyle models added occupation, education, neighborhood SES, education, physical activity, smoking history, secondhand smoke exposure, pack-years smoked. Our main models added site and site by time interaction, site by neighborhood SES, site by neighborhood SES by time.

Associations are scaled to interquartile range of PM_{10-2.5} mass, copper (Cu), zinc (Zn), phosphorus (P), silicon (Si), and endotoxin were 2 µg/m³, 4 ng/m³, 11 ng/m³, 6 ng/m³, and 0.1 µg/m³, and 0.08 EU/m³ respectively.

Table

Population Characteristics Overall and by Study Site at Baseline.

	Full Cohort (n=2780)	Winston Salem (n=822)	St Paul (n=916)	Chicago (n=1042)
Age (years)	61 (10)	62 (10)	60 (10)	62.1 (10.0)
Followup (years)	9.4 (0.5)	9.4 (0.4)	9.4 (0.4)	9.4 (0.6)
Percent female	53%	54%	52%	54%
Race/ethnicity (%)				
White	53%	55%	59%	47%
Chinese	10%	0%	0%	27%
African-American	23%	45%	0%	26%
Hispanic	14%	0%	41%	0%
Education (%)				
High school diploma	28%	28%	41%	15%
Some college	30%	31%	35%	24%
4-year college	43%	41%	24%	60%
Smoking status (%)				
Never smoker	48%	44%	44%	52%
Former smoker	40%	42%	39%	37%
Current smoker	13%	13%	16%	10%
Diabetes (%)	10%	11%	11%	9%
BMI (kg/m ²)	28	29	30	27
Triglyceride (mg/dL)	133	122	154	124
Hypertension (%)	42%	54%	35%	38%
Pollutants, [median (IQR)]				
PM _{10-2.5} (µg/m ³)	5.0 (3.9-6.0)	3.8 (2.9-4.5)	5.4 (4.2-6.4)	5.6 (4.9-6.2)
Copper (ng/m ³)	4.6 (2.8-6.2)	2.5 (1.9-3.0)	3.5 (3.0-3.8)	7.4 (5.7-9.0)
Zinc (ng/m ³)	10 (4.0-15)	3.2 (2.2-4.3)	5.3 (4.4-6.0)	19.9 (13-20)
Silicon (µg/m ³)	0.4 (0.4-0.5)	0.4 (0.3-0.4)	0.5 (0.5-0.6)	0.4 (0.3-0.5)
Phosphorous (ng/m ³)	16 (13-19)	20 (18-21)	13 (12-14)	16 (14-18)
Endotoxin (EU/m ³)	0.07 (0.02-0.11)	0.05 (0.02-0.07)	0.12 (0.10-0.14)	0.04 (0.00-0.07)
HRV [Geometric mean ± SD]				
SDNN, msec	19.1 (1.8)	20.9 (1.8)	18.9 (1.8)	18.2 (1.8)
change per year	-0.3 (1.8)	-0.2 (2.1)	-0.3 (1.7)	-0.2 (1.7)
rMSSD, msec	21.1 (1.9)	22.6 (1.9)	21.1 (2.0)	19.9 (2.0)
change per year	-0.2 (2.3)	-0.2 (2.6)	-0.3 (2.2)	-0.2 (2.1)