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FINE PARTICULATE AIR POLLUTION IS ASSOCIATED WITH HIGHER VULNERABILITY TO ATRIAL FIBRILLATION—THE APACR STUDY

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The acute effects and the time course of fine particulate pollution ($PM_{2.5}$) on atrial fibrillation/flutter (AF) predictors, including P-wave duration, PR interval duration, and P-wave complexity, were investigated in a community-dwelling sample of 106 nonsmokers. Individual-level 24-h beat-to-beat electrocardiogram (ECG) data were visually examined. After identifying and removing artifacts and arrhythmic beats, the 30-min averages of the AF predictors were calculated. A personal $PM_{2.5}$ monitor was used to measure individual-level, real-time $PM_{2.5}$ exposures during the same 24-h period, and corresponding 30-min average $PM_{2.5}$ concentration were calculated. Under a linear mixed-effects modeling framework, distributed lag models were used to estimate regression coefficients (βs) associating $PM_{2.5}$ with AF predictors. Most of the adverse effects on AF predictors occurred within 1.5–2 h after $PM_{2.5}$ exposure. The multivariable adjusted βs per 10-$\mu g/m^3$ rise in $PM_{2.5}$ at lag 1 and lag 2 were significantly associated with P-wave complexity. $PM_{2.5}$ exposure was also significantly associated with prolonged PR duration at lag 3 and lag 4. Higher $PM_{2.5}$ was found to be associated with increases in P-wave complexity and PR duration. Maximal effects were observed within 2 h. These findings suggest that $PM_{2.5}$ adversely affects AF predictors; thus, $PM_{2.5}$ may be indicative of greater susceptibility to AF.

Several studies suggested an association between ambient air pollution and atrial fibrillation/flutter (AF) (Rich et al., 2006), stroke, and cardiovascular disease (CVD) (Miller et al., 2007; Pope et al., 2004), but the impact of air pollution on AF risk may have been underestimated (Whitsel and Avery, 2010). Approximately 4% of U.S. adults aged 60 yr or more have been diagnosed with AF (Go et al., 2001). Moreover, AF is a well-established risk factor of ischemic stroke (Atrial Fibrillation Investigators, 1994). AF is also a potent risk factor for heart failure (Roy et al., 2009), and CVD (Atrial Fibrillation Investigators, 1994). However, it is well recognized that a large proportion of AF cases are asymptomatic and intermittent. Thus, it is difficult to investigate AF, either as a consequence of other exposures such as air pollution exposure, or as the cause of stroke and CVD in

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a healthy population (Soliman et al., 2009). Meanwhile, several studies identified electrocardiogram (ECG) P-wave based measures as predictors of AF, including paroxysmal forms of this arrhythmia (Andrikopoulos et al., 2000; Budeus et al., 2007; Dilaveris et al., 1998; Gorenek et al., 2007; Materazzo et al., 2007; Mehta et al., 2000; Ozdemir et al., 2007; Passman et al., 2001; Raitt et al., 2004; Stafford et al., 1997). Thus, these P-wave-based measures are termed AF predictors. Most importantly, Soliman and coworkers (2009) reported significant prospective associations between the AF predictors and the incidence of ischemic stroke in a large middle-aged population-based sample. Therefore, in order to investigate AF pathway as one of the potential mechanisms that link PM exposure and stroke, one can investigate the air pollution effects on the P-wave based AF predictors. Thus, this study was undertaken to examine the acute effect and time course of individual-level exposures to fine PM, defined as particles with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), on the AF predictors in a community-dwelling sample of healthy individuals.

MATERIALS AND METHODS

Population

For this report, data collected for the Air Pollution and Cardiac Risk and its Time Course (APACR) study were used; this study was designed to investigate the mechanisms and the time course of the adverse effects of $PM_{2.5}$ on cardiac electrophysiology, blood coagulation, and systemic inflammation. Recruitment methods and examination procedures for the APACR study were published elsewhere (He et al., 2010; Liao et al., 2010). Briefly, all study participants were recruited from communities in central Pennsylvania, primarily from the Harrisburg metropolitan area, in which the air pollution level was similar to, if not higher than, other major metropolitan areas on the East Coast of the United States. All participants gave written informed consent prior to their participation in the study. The inclusion criteria for the study included nonsmoking adults ≥ 45 yr old who had not been diagnosed with severe cardiac problems (defined as diagnosed valvular heart disease, congenital heart disease, acute myocardial infarction or stroke within 6 mo, or congestive heart failure). Approximately 75% of the individuals who were contacted and who met inclusion criteria were enrolled in the APACR study. Our targeted sample size was 100 individuals, and 106 individuals were enrolled and examined for the APACR study.

Study participants were examined at the Pennsylvania State University General Clinical Research Center (GCRC) in the morning between 8 and 10 a.m. on day 1. All participants fasted for at least 8 h prior to the clinical examination. After completing a health history questionnaire, a trained research nurse measured seated blood pressure thrice, height, and weight, and drew 50 ml of blood for biomarker assays according to the blood sample preparation protocols. A trained investigator connected the $PM_{2.5}$ and Holter ECG recorders. Participants were given an hourly activity log to record special events that occurred over the next 24 h, including outdoor activities, exposure to traffic on the street, traveling in an automobile, and any physical activities. The entire clinical examination session lasted approximately 1 h. Participants were then released to proceed with their usual daily routines. The next morning, the participants returned to the GCRC to remove the $PM_{2.5}$ and Holter monitors, deliver the completed activity log, have another 50 ml of blood drawn, and provide a urine sample. Then an exercise echocardiography was performed on each participant according to a standardized protocol to measure the participant's ventricular function and structure. The entire day-2 session lasted for about 1 h and 45 min. Penn State University College of Medicine Institutional Review Board approved the study protocol. Each participant received $50, a certificate for breakfast in the hospital cafeteria, and compensation for the mileage associated with travel to and from the GCRC.

Personal $PM_{2.5}$ Exposures

The APACR study used a personal $PM_{2.5}$ DataRam (pDR, model 1200, Thermo Scientific, Boston) for real-time 24-h personal $PM_{2.5}$ exposure assessment. Details of the exposure assessment (He et al., 2010; Liao et al., 2010) and the instrument's performance were reported elsewhere (Howard-Reed et al., 2000; Rea et al., 2001; Wallace et al., 2006; Williams et al., 2009). Real-time $PM_{2.5}$ concentrations were initially recorded at 1-min intervals. For each participant, 30-min, segment-specific averages were calculated on the whole and half hour, as the $PM_{2.5}$ exposure variables. The $PM_{2.5}$ exposure variables therefore consisted of 48 repeated measures on each participant.

Continuous Ambulatory ECG and AF Predictors

A high-fidelity (sampling frequency 1,000 Hz) 12-lead HScribe Holter System (Mortara Instrument, Inc., Milwaukee, WI) was used to collect the 24-h Holter beat-to-beat ECG data. The high-fidelity ECG significantly increases the resolution and enhances the accuracy of various waveform measurements. The details of the Holter ECG data collection and reading were published by He et al. (2010) and Liao et al. (2010). In brief, the Holter ECG data were scanned to a designated computer for offline processing by an experienced investigator using a modified version of the Holter System software and the SuperECG software (also developed by Mortara Instrument, Inc.). The main objectives of the offline processing were to (1) verify the Holter-identified ECG waves, (2) identify and label additional electronic artifacts and arrhythmic beats in the ECG recording, and (3) perform beat-to-beat ECG analysis used to estimate various ECG waveform parameters. Relevant to this study, the following three P-wave-related measures were calculated as AF predictors:

P-wave duration (ms), as the time between the first "onset" and last "offset" deflection from the isoelectric line.

PR duration (ms), as the time between the first onset defection of the P and R wave (the latter representing the onset of ventricular depolarization), with longer PR duration indicating higher risk of AF.

P-wave complexity (unitless), as the average ratio of the second to the first eigenvalue, the value of which reflects the relative complexity of atrial depolarization (Priori et al., 1997), with more complexity in the atrial depolarization indicating the higher risk of AF.

Heart-Rate Variability (HRV) Variables

Time- and frequency-domain heart-rate variability (HRV) analyses were performed on the ECG recording, after removing artifacts with standardized visual inspection and statistical filters. HRV indices were calculated from 30-min segment-specific recordings, after removing artifacts and ectopic beats, using HRV Analysis System (Department of Applied Physics, University of Kuopio, Finland) according to current recommendations (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), and focused on the following HRV indices as measures of cardiac autonomic modulation (CAM): standard deviation of all normal RR intervals (SDNN, ms), square root of the mean of the sum of the squared differences between adjacent normal RR intervals (RMSSD, ms), power in the low frequency range (0.04–0.15 Hz, LF), power in the high frequency range (0.15–0.4 Hz, HF), and the ratio of LF to HF (LF/HF).

Weather Variables

Real-time temperature and relative humidity were obtained using the HOBO H8 logger (Onset Computer Corporation, Bourne, MA). The real-time temperature and relative humidity were recorded at 1-min intervals initially. For each participant, 30-min segment-specific averages were calculated, corresponding to the $PM_{2.5}$ and Holter measures. Each weather covariable also consisted of 48 repeated measures on every participant.

Other Participant-Level Covariables

A standardized questionnaire administered on day 1 of the study was used to collect the following individual-level information: (a) demographic variables, including age, race, gender, and highest education level; (b) use of medication, including anti-anginal, antihypertensive, and antidiabetic agents; and (c) physician-diagnosed chronic disease history of CVD (including revascularization procedures and myocardial infarction), hypertension, and diabetes. The averages of the second and third measures of seated systolic and diastolic blood pressures on day 1 were used to represent a participant's blood pressure levels. Day 1 fasting glucose was measured by the Penn State GCRC central laboratory. CVD was defined by anti-anginal medication use or a history of CVD. Hypertension was defined by antihypertensive medication use, physician-diagnosed hypertension, systolic blood pressure $\geq$140 mm Hg, or diastolic blood pressure $\geq$90 mm Hg. Diabetes was defined by antidiabetic medication use, physician-diagnosed diabetes, or fasting glucose $\geq$126 mg/dl. Body mass index (BMI) was defined as the ratio of weight to height squared (BMI, kg/m^2).

Statistical Analysis

Distributed lag models (Almon, 1965; Pope & Schwartz, 1996; Schwartz, 2000) were used under a linear mixed-effects models framework (Laird & Ware, 1982) with a first-order autoregressive covariance structure to (1) model the correlation between observations from the same participant and (2) estimate the regression coefficient between 30-min $PM_{2.5}$ and the AF predictors (the outcome variables). All independent variables were treated as fixed effects, and time, broken into 30-min segments, was included as a categorical variable. This general specification places no specific functional form of time. Residual diagnostics were used to assess the appropriateness of modeling assumption, and no sizeable departures were detected. In these models, one lag indicates a 30-min separation between the exposure and outcome. Thus, lag 0 indicates the spontaneous relationships between $PM_{2.5}$ and the AF predictors, and lag 1 indicates 30 min between the $PM_{2.5}$ and AF predictors, and so on. A constrained distributed lag model, the polynomial distributed lag model, was selected to reduce the potential collinearity of $PM_{2.5}$ between individual lags using a second-degree polynomial. The linear mixed-effects model framework was selected because it allows us to explicitly model the expected correlation between measurements taken from the same participant. As the measurements are equally spaced, the natural choice for correlation structure, autoregressive order 1, was used throughout the analyses to account for the potential autocorrelation. A second-degree polynomial for the distributed lag model was used because the amount of variability in the outcomes of interest explained by the air pollution measures is not large, so that the degree of polynomial needs to be selected parsimoniously. In our experience, second-degree polynomials perform adequately, which is supported by Schwarz (2000). Another advantage of the distributed lag model is its ability to facilitate interpretation of the cumulative effects of the lags included in the model, as well as individual lag effects. Because the $PM_{2.5}$ and ECG variables were assessed in parallel over 48 lags (24 h), the cut off was decided a priori to model no more than 10 lags was decided, which allowed us to fit the distributed lag model using at least 75% of the data. Using P-wave complexity as the primary outcome variable, models were initially fitted containing the largest number of lags (lag 0–10) determined a priori, and reduction in the total number of individual lags was made by back-eliminating the longest (e.g., lag 10) in succession until a significant cumulative effect ($p < .05$) was identified (lag 0 to lag 3 for P-wave complexity in this report). This model was then used as our final model for the other two AF predictors (PR interval and P durations). Because the cumulative effects including lag 0 to lag 3 in the model were not significant for these two AF predictors, one more lag (lag 4) was forced into the model to avoid potential underascertainment of significant cumulative effect on these two AF predictors. All results

are expressed per 10-$\mu g/m^3$ increase in $PM_{2.5}$. In the final models, all time-dependent covariables, such as weather and HRV variables, were entered in the models using the same distributed lag structure as the $PM_{2.5}$ variable. SAS version 9 (SAS Institute, Inc., Cary, NC) was used for all analyses. The criterion for significance was set at $p < .05$.

RESULTS

The demographic and CVD risk profiles of the study population are presented in Table 1. The mean age of the participants was 56 yr, with 74% non-Hispanic white, 26% minorities (including Blacks, Hispanics, and Chinese), 59% female, and 43% having chronic diseases (mostly hypertension). At the population level, the distributions of both the $PM_{2.5}$ exposure and AF predictors were approximately normal. The temporal distributions of the $PM_{2.5}$ and PR duration are presented in Figures 1 and 2, each of which plots means and standard deviations versus time of day. Both the $PM_{2.5}$ and AF predictor exhibited substantial variation within 24 h, and within 30-min averaging periods between participants. Excluding 48 (0.94%) of the 30-min segments in which the proportion of artifacts and arrhythmic beats exceeded 20% of recording time left 5040 pairs of 30-min $PM_{2.5}$ exposure and AF predictor data points collected from 106 individuals over a 24-h period.

The cumulative effects and individual lag effects of $PM_{2.5}$ on each of the AF predictors are summarized in Table 2 as multivariable adjusted regression coefficients β (SE, p value) associated with $PM_{2.5}$ exposure (per 10-$\mu g/m^3$ increment in $PM_{2.5}$). In summary, elevated $PM_{2.5}$ was positively associated with P-wave complexity and PR duration. A significant cumulative effect was observed for P-wave complexity and a quantitative cumulative effect on PR duration. $PM_{2.5}$ was not significantly associated with P-wave duration. Examining the individual lag effects, the multivariable adjusted regression coefficients for a 10-$\mu g/m^3$ rise in $PM_{2.5}$ were significant for lag 1 and lag 2 (approximately 0.5–1 h after the elevation of $PM_{2.5}$) for P-wave complexity, and lag 3 and lag 4 (approximately 1.5–2 h after $PM_{2.5}$ increase) for PR duration, respectively. In summary, both individual lag effects and cumulative effects from the data presented in Table 2 suggest an acute response of these AF predictors to $PM_{2.5}$ exposures. Additional adjustment

TABLE 1. Demographic Characteristics and Health Status of the Study Population

Characteristic	All subjects, $n = 106$	Hypertension, diabetes, or CVD	
		No, $n = 60$	Yes, $n = 46$
Age (yr)	56.23 (7.61)	55.55 (8.19)	57.12 (6.76)
Gender (% male)	40.57	40.00	41.30
Race (% white)	73.58	71.67	76.09
Glucose (mg/dl)	88.82 (25.14)	84.64 (10.04)	94.29 (35.95)
BMI (kg/m^2)	27.71 (5.86)	26.19 (4.31)	29.69 (6.98)
CVD (%)	8.49	0.00	19.57
Hypertension (%)	34.91	0.00	84.78
Diabetes (%)	7.55	0.00	17.39
Systolic BP (mm Hg)	121.88 (15.73)	117.05 (11.86)	128.18 (17.93)
Diastolic BP (mm Hg)	75.07 (9.22)	73.12 (8.34)	77.62 (9.77)
College or higher (%)	78.30	73.33	84.78
PR duration (ms)	159.06 (20.27)	157.93 (20.89)	160.53 (19.34)
P duration (ms)	108.14 (11.31)	107.72 (11.47)	108.70 (11.07)
P complexity	0.21 (0.08)	0.20 (0.09)	0.21 (0.07)
$PM_{2.5}$ ($\mu g/m^3$)	13.61 (21.59)	11.86 (14.69)	15.87 (27.95)
Temperature (°C)	21.76 (3.53)	21.84 (3.66)	21.66 (3.36)
Relative humidity (%)	39.66 (12.08)	40.18 (12.30)	38.98 (11.76)

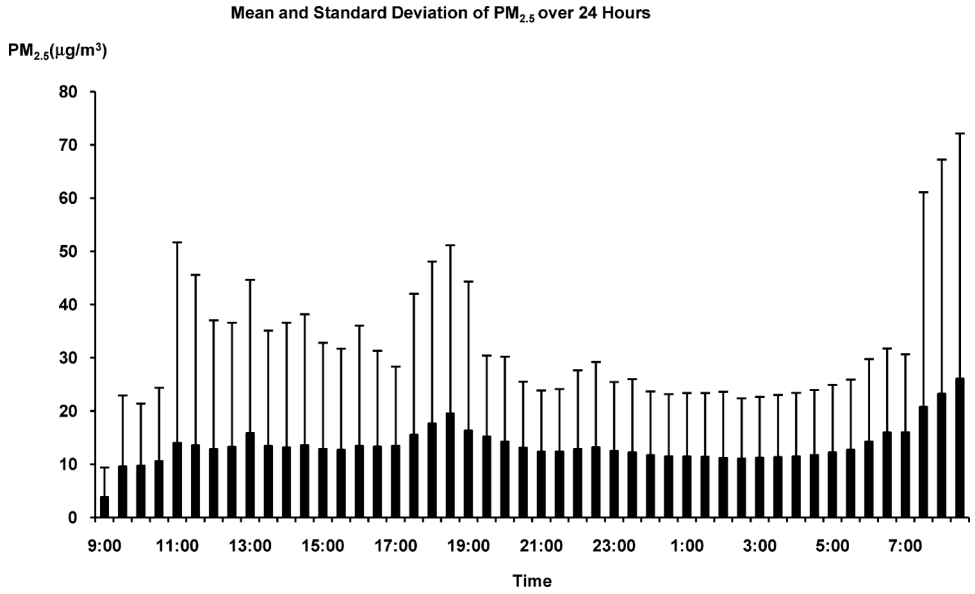

FIGURE 1. Time-specific mean $PM_{2.5}$ exposure over 24 h in the APACR study.

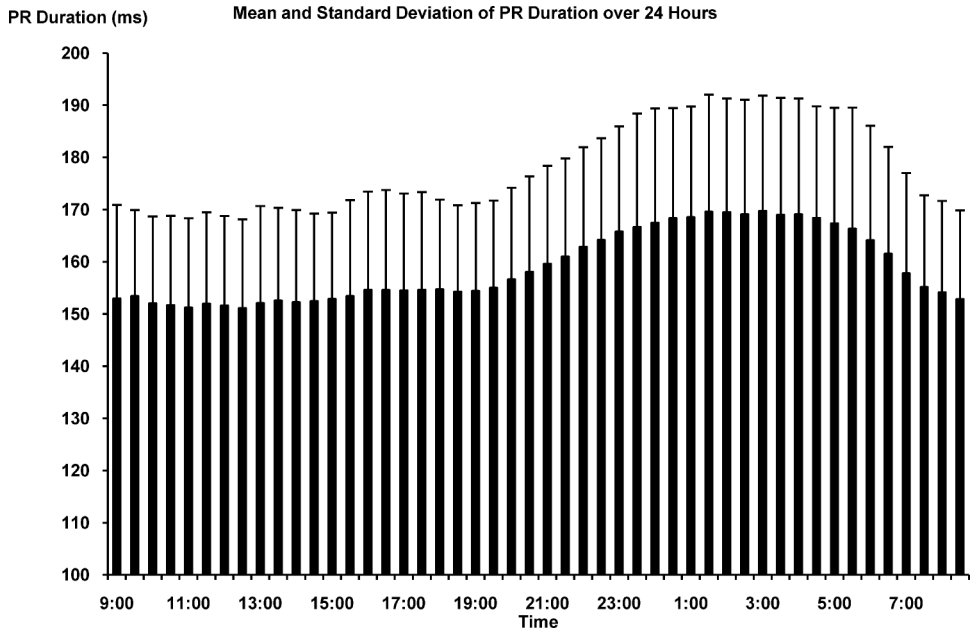

FIGURE 2. Time-specific mean PR duration over 24 h in the APACR Study.

for chronic disease (model 2 in Table 2) did not change the pattern of association from the models adjusted only for major demographic and weather-related variables (model 1 in Table 2).

To elucidate the role of CAM on the relationship between $PM_{2.5}$ exposure and AF predictors, model 2 in Table 2 was repeated for P-wave complexity and PR duration outcomes after adjusting for HRV and heart rate (HR) measures, using one HRV or HR variable at a time. The HRV and HR adjusted regression coefficients are presented in Table 3. In summary, the overall patterns of associations between $PM_{2.5}$ and these two AF predictors were greatly attenuated, but mostly remained

TABLE 2. Regression Coefficient of AF Predictors Associated With a 10-$\mu g/m^3$ Increment of $PM_{2.5}$ Concentration

P-wave variable	Lags	Regression coefficient (SE, p value) Model 1	Model 2
P complexity	Lag 0	0.0002 (0.0002, $p = .47$)	0.0002 (0.0002, $p = .49$)
	Lag 1	0.0004 (0.0002, $p = .01$)	0.0004 (0.0002, $p = .01$)
	Lag 2	0.0005 (0.0002, $p < 0.01$)	0.0005 (0.0002, $p < .01$)
	Lag 3	0.0004 (0.0004, $p = .31$)	0.0004 (0.0004, $p = .32$)
	Cumulative	0.0016 (0.0006, $p = .01$)	0.0016 (0.0006, $p = .01$)
PR duration	Lag 0	−0.022 (0.036, $p = .54$)	−0.023 (0.036, $p = .53$)
	Lag 1	−0.009 (0.025, $p = .70$)	−0.010 (0.025, $p = .68$)
	Lag 2	0.023 (0.031, $p = .46$)	0.022 (0.031, $p = .48$)
	Lag 3	0.075 (0.037, $p = .05$)	0.074 (0.037, $p = .05$)
	Lag 4	0.146 (0.068, $p = .03$)	0.145 (0.068, $p = .03$)
	Cumulative	0.213 (0.133, $p = .11$)	0.207 (0.133, $p = .12$)
P duration	Lag 0	0.014 (0.030, $p = .65$)	0.013 (0.030, $p = .67$)
	Lag 1	−0.016 (0.020, $p = .43$)	−0.017 (0.020, $p = .41$)
	Lag 2	−0.023 (0.026, $p = .36$)	−0.024 (0.026, $p = .35$)
	Lag 3	−0.008 (0.032, $p = .79$)	−0.009 (0.032, $p = .77$)
	Lag 4	0.029 (0.058, $p = .62$)	−0.028 (0.058, $p = .63$)
	Cumulative	−0.005 (0.110, $p = .96$)	−0.009 (0.111, $p = .94$)

Note. Model 1: adjusted for age, gender, race, temperature, and relative humidity. Model 2: adjusted for age, gender, race, temperature, relative humidity, diabetes, hypertension, and CVD.

statistically significant with additional adjustment for HRV and HR variables as measures of CAM.

The interaction terms between $PM_{2.5}$ and CVD-related chronic conditions were tested; none were statistically significant (data not shown). Therefore, the effects of $PM_{2.5}$ on P-wave-related variables did not differ depending on whether an individual had previous CVD-related conditions. Stratified analysis according to chronic disease status revealed similar associations among participants with and without CVD-related conditions (data not shown).

DISCUSSION

Although epidemiologic studies consistently showed an association between exposure to increased PM air pollution and risk of CVD (Dominici et al., 2005; Franklin et al., 2007, 2008; Krewski et al., 2005; Ostro et al., 2006; Yang et al., 2004; Zanobetti & Schwartz, 2009) and stroke (Miller et al., 2007; Pope et al., 2004), the mechanisms responsible for such an association have not been fully identified. Since AF is a well-established risk factor for stroke, it is biologically plausible that PM and stroke relationship may be mediated in part by PM-related increases in AF risk. This potential mechanism is supported by data from Rich and coworkers (2006), who reported an elevated risk of paroxysmal AF after an acute gaseous air pollution exposure in patients wearing implantable cardioverter-defibrillators (ICDs). The association, however, may not be generalizable to a healthy population. Indeed, there has been no publication of such a relationship in healthy community-based samples. Given the asymptomatic and intermittent nature of AF in healthy individuals and the established relationship between AF predictors and future AF and the risk of incident stroke, this study was conducted to examine the temporal relationship and between $PM_{2.5}$ exposures and AF predictors in a healthy community-dwelling sample of nonsmokers, and through such association to elucidate the $PM_{2.5}$ effects on susceptibility to AF and stroke. The operational hypothesis is that acute exposures to $PM_{2.5}$ are associated with predictors of AF. If the association is confirmed, this would suggest that exposure to $PM_{2.5}$ is also associated with higher risk of AF development and thereby stroke.

TABLE 3. Multivariable Adjusted Regression Coefficient (SE, p Value) of AF Predictors Associated With a 10-$\mu g/m^3$ Increment of $PM_{2.5}$ With Additional Adjustment for HRV Variables

		HRV indices				
P-wave variable	Lag	Log HF	Log LF	SDNN	RMSSD	HR
P complexity	Lag 0	0.0002 (0.0002, $p = .45$)	0.0002 (0.0002, $p = .41$)	0.0002 (0.0002, $p = .44$)	0.0002 (0.0002, $p = .46$)	0.0002 (0.0002, $p = .31$)
	Lag 1	0.0004 (0.0003, $p = .01$)	0.0004 (0.0002, $p = .01$)	0.0004 (0.0002, $p = .02$)	0.0005 (0.0002, $p < .01$)	0.0004 (0.0002, $p < .01$)
	Lag 2	0.0005 (0.0002, $p < .01$)	0.0005 (0.0002, $p < .01$)	0.0005 (0.0002, $p < .01$)	0.0006 (0.0002, $p < .01$)	0.0005 (0.0002, $p < .01$)
	Lag 3	0.0006 (0.0004, $p = .20$)	0.0006 (0.0004, $p = .18$)	0.0005 (0.0004, $p = .20$)	0.0005 (0.0004, $p = .24$)	0.0004 (0.0004, $p = .30$)
	Cumulative	0.0017 (0.0006, $p < .01$)	0.0017 (0.0006, $p < .01$)	0.0016 (0.0006, $p = .01$)	0.0017 (0.0006, $p < .01$)	0.0016 (0.0006, $p = .01$)
PR duration	Lag 0	−0.024 (0.036, $p = .51$)	−0.024 (0.036, $p = .51$)	−0.019 (0.036, $p = .60$)	−0.024 (0.036, $p = .50$)	0.004 (0.033, $p = .90$)
	Lag 1	−0.011 (0.025, $p = .65$)	−0.011 (0.025, $p = .66$)	−0.011 (0.025, $p = .65$)	−0.010 (0.025, $p = .67$)	−0.007 (0.023, $p = .76$)
	Lag 2	0.020 (0.031, $p = .52$)	0.020 (0.031, $p = .51$)	0.017 (0.031, $p = .58$)	0.021 (0.031, $p = .49$)	0.007 (0.028, $p = .81$)
	Lag 3	0.070 (0.038, $p = .07$)	0.069 (0.038, $p = .07$)	0.066 (0.038, $p = .08$)	0.071 (0.038, $p = .06$)	0.046 (0.035, $p = .19$)
	Lag 4	0.138 (0.069, $p = .05$)	0.137 (0.069, $p = .05$)	0.137 (0.069, $p = .05$)	0.138 (0.069, $p = .05$)	0.109 (0.064, $p = .09$)
	Cumulative	0.192 (0.134, $p = .15$)	0.192 (0.134, $p = .15$)	0.190 (0.134, $p = .16$)	0.195 (0.134, $p = .15$)	0.159 (0.124, $p = .20$)

Note. All models adjusted for age, gender, race, temperature, relative humidity, diabetes, hypertension, CVD, and each HRV index.

In this study, acute exposure to $PM_{2.5}$ significantly affected P-wave complexity and PR duration, but not P-wave duration. Overall, these findings support our a priori hypothesis. Specifically, data suggested that elevated $PM_{2.5}$ was associated with more complex P-wave morphology and longer PR duration, and both are indicative of disturbed atrial depolarization. Similar to our previous findings, in the same population, of $PM_{2.5}$ effects on HRV (He et al., 2010) or QT intervals (Liao et al., 2010), the effect size of $PM_{2.5}$ on AF predictors is relatively small. From the etiologic perspective, the small effect indicates a weak influence of $PM_{2.5}$ on risk of AF. Therefore, the changes of AF predictors due to PM exposure in this population-based healthy sample may not be clinically relevant. However, considering the fact that the entire U.S. population is exposed to ambient, indoor, and personal sources of $PM_{2.5}$, on a continuous, daily basis, minor $PM_{2.5}$ elevation may possess a greater impact on the cardiovascular health of the public than is generally appreciated. Moreover, the effects on AF predictors in this study were measured in generally healthy individuals. It is possible that $PM_{2.5}$ effects on AF predictors may be greater among those with underlying structural heart disease, ischemic heart disease, or heart failure, although the lower power tests of such interactions in this context did not support this possibility. Future studies could target clinical subgroups likely to be more PM-susceptible, especially those rendered more vulnerable by residential proximity to important $PM_{2.5}$ sources, e.g., highways.

Although several animal-based studies showed that PM (Gordon et al., 2000), diesel exhaust (Campen et al., 2003), cigarette smoking (Rai et al., 1983), and highly toxic fly ash PM (Hazari et al., 2009) exposure were associated with PR prolongation, the mechanisms responsible for PM induced changes in P-wave based ECG measures are not fully understood. The results presented in Table 3 indicate that the magnitude of association between $PM_{2.5}$ and P-complexity and PR duration were greatly attenuated but mostly remained statistically significant after adjusting for cardiac autonomic modulation as potential intermediating factors. To our knowledge, this is the first study to demonstrate the above summarized findings in a healthy community-dwelling sample. If such an attenuation effect can be confirmed by other human- and animal-based studies, this would suggest that PM exposure first produces an acute imbalance of autonomic modulation, characteristic of increased sympathetic and decreased parasympathetic modulations. Through the autonomic modulation mechanism, PM might lead to disturbances of P-wave-based ECG parameters that are indicative of higher susceptibility to AF. Other potential mechanisms may include, first, PM induced coronary artery constriction, which is supported by the observation by Brook and coworkers (2002), who reported a sudden conduit vasoconstriction after a short-term $PM_{2.5}$ and O_3 exposure in a sample of healthy volunteers. Mills and coworkers (2005) also demonstrated similar patterns. Second, PM may also decrease the oxygen–carrying capacity of the blood, as supported by studies reported by several investigators (Clarke et al., 2000; Savage et al., 2002; Seaton et al., 1999). Lastly, it is also plausible that PM exerts a direct adverse effect on cardiac electrophysiological parameters, such as AF predictors examined in this study. More mechanistic studies are needed to investigate the exact pathways from PM exposure to the adverse cardiac electrophysiological effects. Considering the large attenuation of PM effects on P-wave complexity and PR duration, after adjustment of HRV and HR, cardiac autonomic modulation was considered as the predominant mechanism.

The strengths of our study include that both the $PM_{2.5}$ exposure and the AF predictors were measured from individual levels on a real-time basis over 24 h. The exposure and the outcome data were treated as 30-min repeated measures, and thus benefited from increased statistical power in associating the exposure and outcomes. This type of data also enabled us to control for many individual-level unmeasured factors that may influence the AF predictors. Although the results generated from this study are compelling, there are still several

limitations. First, smokers and people who had severe cardiac events in the past 6 mo were excluded. Therefore, one may not be able to generalize the association seen in these data to individuals with more severe CVD. It is possible that $PM_{2.5}$ effects on AF predictors might be greater in individuals with underlying structural heart disease, ischemic heart disease, or heart failure. Second, most of the participants reported that they stayed indoors the majority of the time during the 24-h study period, except when they had to travel by automobile. This behavior pattern is reflected in the relatively low levels of exposure to $PM_{2.5}$. In general, our participants had limited indoor exposures, e.g., secondhand smoke. Thus, it was not possible to assess whether exposures at much higher levels would exhibit similar associations. However, the personal monitors and real-time Holter system were purposely used to collect the true individual-level exposure and routine ECG data, respectively. The associations observed in these individuals may be more reflective of their routine exposure and outcome associations. Third, it is well known that HR increases during physical activity, which could be related to higher $PM_{2.5}$ exposure if it occurs outdoors. It is also well known that PR duration is HR dependent. Thus it is possible that the $PM_{2.5}$ and AF predictors association in this study is confounded by physical activity that occurred during some segment of the 24-h study period. However, since most of participants reported that they stay indoors for the vast majority of the time during 24-h period, it is unlikely that the association is solely due to physical activity outside of their homes, which is also supported by the findings of significant associations between $PM_{2.5}$ and AF predictors after adjustment of lag-specific HR in Table 3. Fourth, the Holter ECG data were not collected in a controlled setting or the conventional supine position. Thus, the short-term variation of other factors that may impact the ECG measures can not be fully accounted for. However, it is not feasible to keep a healthy participant in a supine indoor position for 24 h. Even if this were achieved, the results from such a study design would likely have limited variation in $PM_{2.5}$ exposure levels, and would have limited utility for generalization to a real world situation. In contrast, our study captures the range of activities occurring in real life, including time spent outdoors, time spent commuting in an automobile, and various other activities undertaken by typical community-dwelling individuals free of chronic disease. Fifth, the sample size of this study is small, and individuals with chronic conditions consisted mostly of well-controlled hypertensives. As a result, the statistical power was limited to detect significant effect modification by chronic disease status. Lastly, pDR estimated $PM_{2.5}$ concentrations over 24 h were used in this study as an estimation of personal exposures. This nephelometric device responds to the optical as opposed to the true gravimetric properties of the particles it encounters. It should be recognized that the optical properties (calibrated using Arizona road dust) might not be highly representative of the actual $PM_{2.5}$ aerosol the study participants encountered. Previous studies reported that the Arizona road dust calibrated pDR, identical to the one used in this study, provides mass concentration estimates in reliable agreement with that from gravimetric mass-based measures (correlation coefficients >0.8), but 10–50% higher than those from gravimetric mass-based measures (Howard-Reed et al., 2000; Rea et al., 2001; Williams et al., 2009). Based on these validation studies, the personal exposures used in this study might systematically overestimate the true environmental conditions that existed. However, this systematic overestimation of the true exposures to $PM_{2.5}$ should not have biased the pattern of the observed associations. Under the assumption that the pDR systematically overestimates the true exposure by 10–50%, it can be argued that the reported effect sizes per 10-$\mu g/m^3$ increase in the pDR estimated $PM_{2.5}$ reported here actually represents effects per 6.67–9 $\mu g/m^3$ increase in the true $PM_{2.5}$ exposure. By extension, this implies that the reported effect in this study may be systematically underestimated.

In summary, acute exposure to $PM_{2.5}$ at the individual level is directly associated with

longer PR duration and more complexity of atrial depolarization, and the time to such an effect is approximately 1.5–2 h. The adverse effect of $PM_{2.5}$ on these AF predictors is independent of major confounding factors and cannot be attributed solely to its autonomic effects. Overall, these findings support the possibility that $PM_{2.5}$ may affect vulnerability to atrial fibrillation/flutter, and partly through such a mechanism, higher exposures to $PM_{2.5}$ increase the risk of AF and ischemic stroke.

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