Daily Variation of Particulate Air Pollution and Poor Cardiac Autonomic Control in the Elderly

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Particulate matter air pollution (PM) has been related to cardiovascular disease mortality in a number of recent studies. The pathophysiologic mechanisms for this association are under study. Low heart rate variability, a marker of poor cardiac autonomic control, is associated with higher risk of myocardial infarction and sudden cardiac death. To address the possible mechanisms for PM-cardiovascular disease mortality, we examined the cardiac autonomic response to daily variations in PM in 26 elderly (mean age 81) individuals for 3 consecutive weeks. Several standardized methods were used to measure 24-hr average PM concentrations prior to the clinical test inside (indoor $PM_{2.5}$) and immediately outside (outdoor $PM_{2.5}$ and $PM_{2.5-10}$) of participants' residences. Resting, supine, 6-min R wave to R wave (R-R) interval data were collected to estimate high frequency (0.15–0.40 Hz) and low frequency (0.04–0.15 Hz) powers and standard deviation of normal R-R intervals (SDNN) as cardiac autonomic control indices. Participant-specific lower heart rate variability days were defined as days for which the high-frequency indices fell below the first tertile of the individual's high-frequency distribution over the study period. Indoor $PM_{2.5} > 15$ μg/m^3 was used to define high pollution days. Results show that the odds ratio (95% confidence interval) of low heart rate variability high frequency for high (vs. not high) pollution days was 3.08 (1.43, 6.59). The β-coefficients (standard error) from mixed models to assess the quantitative relationship between variations in indoor $PM_{2.5}$ and the log-transformed high frequency, low frequency, and SDNN were: -0.029 (0.010), -0.027 (0.009), and -0.004 (0.003), respectively. This first study of cardiac autonomic control response to daily variations of $PM_{2.5}$ indicates that increased levels of $PM_{2.5}$ are associated with lower cardiac autonomic control, suggesting a possible mechanistic link between PM and cardiovascular disease mortality. *Key words*: ambient air pollution, autonomic system, cardiovascular disease, elderly, heart rate variability, particulate matter, $PM_{2.5}$. *Environ Health Perspect* 107:521–525 (1999). [Online 13 May 1999]
http://ehpnet1.niehs.nih.gov/docs/1999/107p521-525liao/abstract.html

Many epidemiologic studies have shown an association between exposure to particulate air pollution below the current national air quality standard and excess mortality from cardiopulmonary diseases (*1*).

Consistent with the mortality findings, epidemiologic studies in the United States (*2–4*), Canada (*5,6*), and Europe (*7–9*) also demonstrate significant associations of ambient air pollutants with hospital admissions for respiratory and cardiovascular diseases. However, the observed excess mortality and morbidity associated with relatively low particulate matter (PM; the subscript number denotes the particle size in micrometers) levels have been questioned because of an apparent lack of any biologically demonstrable mechanisms. A direct link between a pathophysiologic effect on the heart and mortality or morbidity in human populations has not yet been established. The role of air pollution in cardiovascular disease is a recent focus of attention. Several investigators reported an association between particle air pollution and hospital admissions for ischemic heart disease, congestive heart failure, or dysrhythmias (*10–13*). Watkinson et al. (*14*) produced arrhythmias after installation of combustion particles into rat lungs, resulting in a doubling of mortality rate, and Godleski et al. (*15*) observed electrocardiographic changes including T-wave alternans and arrythymias in dogs exposed to concentrated ambient air particles. The link between inhalation of particle air pollution and effects on cardiac rhythm may be the induction of an inflammatory response in the lung with a subsequent release of chemical mediators that alter the autonomic nervous system control of cardiac rhythm (*16*).

The research question for this study is: What is the physiologic link between air pollution exposure and cardiopulmonary effects in susceptible populations? Specifically, this study is designed to investigate whether the changes in the concentrations of particulate matter are associated with the changes in the cardiac autonomic control (CAC), as measured by the analysis of heart rate variability (HRV), in a group of elderly individuals.

Population and Methods

Population. This study was designed as a short-term (21 days) longitudinal monitoring of daily changes in both particulate matter concentrations and in cardiac autonomic activity. Study participants were selected from a retirement center in metropolitan Baltimore, Maryland.

As described by Creason et al. (*17*), the following exclusion criteria were used to screen for eligible participants: uncontrolled hypertension (systolic blood pressure ≥ 190 or diastolic blood pressure ≥ 100 mm Hg), angina pectoris and/or heart attack in past 12 months, physician-diagnosed episodes of syncope, heart failure, current smoker, retinal disease, diabetes, dementia, dialysis treatment, acute illness (> 2 days) within the past week, need for supplemental oxygen, or having a pacemaker. After the eligibility screening and after attending small group meetings with trained recruiters, 26 of the 58 eligible individuals volunteered to participate in this study. These 26 participants were then individually informed about study content, risks and discomforts, procedure for confidentiality, right of withdrawal, daily scheduling requirements, and study incentives and benefits. Signed consent forms were then obtained.

Particulate matter pollution assessment. The following measures of particulate concentrations were obtained during the study period (*18,19*):

- Integrated 24-hr indoor mass concentrations of $PM_{2.5}$ were obtained in the hallway of the retirement facility near the rooms where physiologic testing of participants was administered. The results from this monitor were labeled "hallway."

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The participation of D. Liao and C. Shy in this study was funded through cooperative agreement CR820076 between the Division of Human Studies (National Health and Environmental Effects Research Laboratory, U.S. EPA) and the Department of Epidemiology (University of North Carolina at Chapel Hill, Chapel Hill, NC).

Received 11 August 1998; accepted 19 February 1999.

- Continuous indoor $PM_{2.5}$ concentrations were obtained with a tapered element oscillating microbalance (TEOM) instrument located in the hallway beside the stationary hallway PM monitor. The TEOM monitor was used with a $PM_{2.5}$ cyclone inlet and provided hourly measures of fine particle concentrations. Because the instrument monitored fine particles continuously, two metrics were derived from the output of this monitor. The first was a 24-hr average $PM_{2.5}$, averaged to the time when each subject began his or her daily battery of physiologic testing. This metric was labeled "indoor-24 hr" to represent the average 24-hr concentration just prior to each person's actual start of testing. The other metric was a 24-hr average as of 7 A.M. of the date of each day's physiologic testing. This metric was labeled "indoor-7 A.M."
- Integrated 24-hr outdoor concentrations of $PM_{2.5}$ and $PM_{2.5-10}$ (fine and coarse particulate matter) were obtained with a dichotomous monitor placed on the outdoor parking deck of the retirement center. Samples were collected on Teflon (E.I. Du Pont de Nemours and Company, Wilmington, DE) filters, and sampler flow rates were 15 L/min for the $PM_{2.5}$ fine fraction and 1.67 L/min for the $PM_{2.5-10}$ coarse fraction. Data from this monitor were labeled "outdoor."

Cardiac autonomic activity. Analysis of beat-to-beat HRV was used to assess cardiac autonomic control for all participants daily over the entire study period. For the measurement of HRV, three electrocardiogram (ECG) electrodes were positioned on the subject. Two electrodes were in the regular ECG V1 and V6 locations on the epigastrium and one was on the lower right extremity. Resting supine 6-min beat-to-beat heart rate data were collected after participants remained comfortably in the supine position for 10 min. A dedicated computer and specialized software (PREDICT II HRVECG, Arrhythmia Research Technology, Inc., Austin, TX) were used for continuous detecting and recording of ECG R waves. The system uses a wave form correlation technique to correlate each digitized possible electrocardiographic wave complex (QRS) with a participant-specific QRS template with the overall correlation coefficient preset to 0.75. The participant-specific QRS template was identified as a normal QRS template by trained and certified technicians through visual inspection of several QRSs. The sampling frequency was set to 1000 Hz, as recommended by the manufacturer. Each of the possible QRSs was marked as a normal QRS if the wave form correlation coefficient was > 0.75; otherwise they were marked as artifact QRS. The system then calculated beat-to-beat R wave to R wave (R-R) intervals for the entire 6-min period.

The R-R interval data were processed in a central location by one trained computer programmer. During the data-processing phase, a data cleaning program was used to remove any R-R intervals having an artifact QRS from the HRV analysis. Segments with such artifacts were imputed and R-R intervals in these segments were recalculated using an algorithm developed by Arrhythmia Research Technology, Inc. Fast Fourier transformation was performed to estimate the power spectral density (PSD). An example of the PSD curve with the corresponding time–domain beat-to-beat R-R interval histogram inserted is shown in Figure 1 for one participant. From the PSD curve, the high frequency spectral power component (HF) and the low frequency spectral power component (LF), defined as the power (area) between 0.15 and 0.40 Hz and between 0.04 and 0.15 Hz bands under the PSD curve, respectively, were calculated. The standard deviation of all normal R-R intervals (SDNN) was calculated from the time–domain data after the replacement of artifacts. The average heart rate from the 6-min R-R interval data was also calculated.

In this study, any record with 15% or more of QRS artifacts in all possible QRS complexes was excluded from analysis, even though these segments could be successfully imputed, as the manufacturer suggested. These exclusion criteria were implemented to reduce the influence of data imputation on the estimates of HRV.

Other covariables. Other covariables, such as age, ethnicity, sex, and health status, were obtained using a standardized questionnaire. A participant was classified as having previous cardiovascular related conditions (labeled as the compromised group) if the medical record review and/or medication survey revealed active treatment of any of the following conditions: hypertension, coronary heart disease, episodes of arrhythmia, and thyroid abnormalities requiring thyroid medication.

Statistical methods. Random coefficient regression models were used in the analysis of the study data (*20*). Most models contained fixed effects of intercept, age, sex, cardiovascular health status, and $PM_{2.5}$ particulate level as measured by various exposure monitors, with age and $PM_{2.5}$ being continuous variables. Models with separate slopes for each of the health status groups were also fit. In addition to the population-fixed effects, each subject was allowed to have an individual incremental slope and intercept for PM. Using model-fitting information available in the SAS Mixed Model (*20*) output for each model, it was determined that intercepts for each subject were necessary,

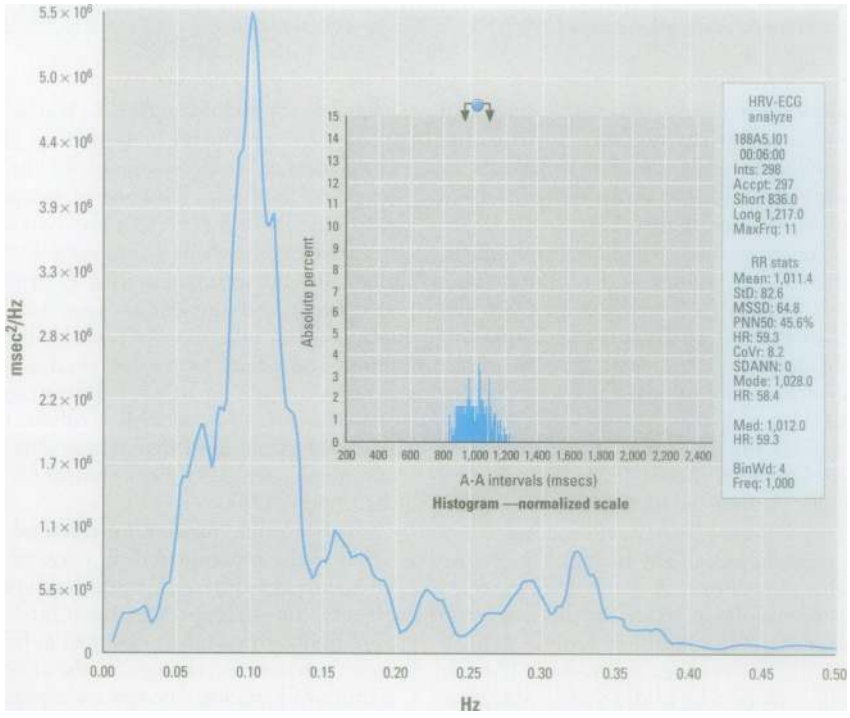

Figure 1. An example of a power spectral density curve following fast Fourier transformation, derived from time–domain heart rate data (inserted panel). Very low-frequency power (0.00–0.04 Hz) 71.8 $msec^2$; low-frequency power (0.04–0.15 Hz) 1,360 $msec^2$; high-frequency power (0.15–0.40 Hz), 575 $msec^2$; total power, 2,010 $msec^2$; standard deviation of all normal RR intervals, 82.6 msec.

but a slope for each subject was not. Two covariance structures were considered for the repeated measures of these longitudinal data. One assumed a simple model of no correlation of residuals across time. The other assumed an error covariance matrix allowing for declining correlation of residuals based on distance (time in days) between measurements. In this structure, if readings were 1 day apart the correlation was r, and for > 1 day apart the correlation was r to the power of the number of intervening days. Two final models, one fitting individual $PM_{2.5}$ slopes for each of the health status groups and one fitting only an overall slope, are presented here. The final form for each model was determined through selection of the appropriate error structure based on the model-fitting criteria as described above.

Other statistical summaries and analyses were included as appropriate in specific cases. For example, in analyzing the HRV data, a logistic model assessing normal and low HRV versus high and low $PM_{2.5}$ particulate levels was used.

Results

The reexamination rates were high, and only a few subjects failed to complete the entire 3-week study period. The greatest loss of data was attributable to the lack of functioning air monitors on some of the test days. The second greatest loss of data was attributable to exclusion of HRV records from the analysis if 15% or more of all possible QRS complexes were QRS artifacts and were consequently identified as artificial QRS complexes. Overall, the proportion of potential subjects' days for which test results were actually obtained was 74.4% in analyzing the relationship between changes of particulate matter levels and the changes in HRV.

As summarized in Table 1, the mean age of all participants was 81 years, ranging from 65 to 89; 19 subjects (73%) were female, and 25 (96%) were white. On the basis of medical records and physician's diagnosis, 18 of the participants were classified in the compromised group. Individuals with previous cardiovascular conditions (compromised group) were older; the average age was 82 years as compared to 78 years for the other eight participants. Most of the compromised participants (61%) had a history of hypertension.

Also presented in Table 1 are the mean levels of HRV indices in the study population. These values are the means of the average test results for each individual, averaged over the 3-week study period. Mean values are presented for the entire study population and separately for persons with and without compromised cardiovascular heath status. In nearly all cases, test results for persons without compromised health status were more favorable than results for those in the compromised group.

Air monitoring results are presented by Creason et al. (*17*). In summary, the means ± standard deviations (range) of $PM_{2.5}$ from the study site monitors were 17.6 ± 6.9 (9.0–30), 9.8 ± 3.7 (5.2–17.4), and 16.1 ± 6.9 (8.0–32.2) $\mu g/m^3$ for hallway, indoor-7 A.M., and outdoor monitors, respectively.

Following the convention in the HRV literature, all HRV indices were transformed with logarithms. The primary hypothesis in this study was that with an increase in $PM_{2.5}$ levels there would be a trend of decrease in HRV indices. Because the study only lasted 3 weeks and because the daily variations of the exposure and the HRV indices were measured concurrently, the observed association between the concentration of air pollutants and the levels of HRV indices was reflective of the acute effects of air pollutants on cardiac autonomic control beyond the lifetime accumulation of all other exposures that may have a chronic effect on HRV. Tests for autocorrelation were performed for all models, and none were statistically significant at the $p < 0.10$ level. Thus, an unrestricted correlation matrix was assumed for all models. From the mixed models, the age and sex-adjusted

Table 1. Characteristics (mean ± standard deviation, proportion, or range) of study participants.

Characteristic	All subjects combined ($n = 26$)	Without cardiovascular conditions ($n = 8$)	With cardiovascular conditions ($n = 18$)
Number of subjects	26	8	18
Age			
Mean (years)	81	78	82
Range (years)	65–89	65–84	69–89
Sex (% female)	73	63	78
Race (% whites)	96	88	100
History of hypertension (%)	42	0	61
Heart rate variability			
Log 10 high freq power ($msec^2$)	2.61 ± 0.38	2.40 ± 0.31	2.70 ± 0.37
Log 10 low freq power ($msec^2$)	2.71 ± 0.32	2.61 ± 0.15	2.76 ± 0.36
Log 10 SDNN (msec)	1.74 ± 0.15	1.67 ± 0.09	1.77 ± 0.16
Heart rate (5-min mean, beat/min)	73 ± 7.8	74 ± 5.8	72 ± 8.6
Seated blood pressure (mm Hg)			
Systolic	132 ± 16	124 ± 11	135 ± 17
Diastolic	78 ± 8	75 ± 7	79 ± 9

SDNN, standard deviation of all normal R-wave to R-wave intervals.

Table 2. Adjusted β-coefficients and 95% confidence intervals from mixed model analysis of the associations between the levels of particulate matter and cardiac autonomic control, as measured by heart rate variability.

Variable	Exposure metric	Without cardiovascular conditions ($n = 8$)[a]	With cardiovascular conditions ($n = 18$)[a]	All subjects combined ($n = 26$)[b]
High-frequency power (log 10)[c]	Hallway	-0.015 (-0.043, 0.013)	-0.027* (-0.045, -0.010)	-0.024* (-0.038, -0.009)
	Indoor, 24-hr	0.006 (-0.035, 0.046)	-0.028* (-0.052, -0.005)	-0.019 (-0.040, 0.001)
	Indoor, 7 A.M.	0.005 (-0.036, 0.045)	-0.031* (-0.055, -0.007)	-0.022* (-0.042, -0.001)
	Outdoor	-0.006 (-0.029, 0.017)	-0.014* (-0.028, -0.001)	-0.012* (-0.024, 0.000)
Low-frequency power (log 10)[d]	Hallway	-0.012 (-0.037, 0.013)	-0.025* (-0.040, -0.009)	-0.021* (-0.034, -0.008)
	Indoor, 24-hr	0.001 (-0.036, 0.038)	-0.014 (-0.036, 0.008)	-0.010 (-0.029, 0.009)
	Indoor, 7 A.M.	-0.001 (-0.038, 0.036)	-0.018 (-0.040, 0.004)	-0.013 (-0.032, 0.006)
	Outdoor	-0.008 (-0.029, 0.013)	-0.012 (-0.025, 0.001)	-0.011* (-0.022, 0.000)
SDNN (log 10)	Hallway	-0.007 (-0.016, 0.003)	-0.004 (-0.010, 0.002)	-0.005* (-0.010, 0.000)
	Indoor, 24-hr	0.002 (-0.011, 0.015)	-0.007* (-0.015, 0.000)	-0.005 (-0.012, 0.002)
	Indoor, 7 A.M.	0.001 (-0.012, 0.014)	-0.008* (-0.016, -0.001)	-0.006 (-0.013, 0.001)
	Outdoor	-0.002 (-0.010, 0.005)	-0.004* (-0.008, 0.000)	-0.004* (-0.007, 0.000)

SDNN, standard deviation of all normal R-wave to R-wave intervals.
[a]Adjusted for age and sex. [b]Adjusted for age, sex, and cardiovascular health status. [c]0.15–0.40 Hz. [d]0.04–0.15 Hz. *$p < 0.05$.

β-coefficients and their 95% confidence interval (CI) by baseline cardiovascular health status (compromised status), and coefficients adjusted for cardiovascular health status in the combined model, are presented in Table 2.

In the combined models (termed Beta Overall), the high-frequency (HF) power component of HRV, the low-frequency (LF) component, and the time–domain component [the standard deviation of all normal R-R intervals (SDNN)] are each inversely associated with all four $PM_{2.5}$ measures. However, conventional statistical significance ($p < 0.05$) is reached for only three of the four $PM_{2.5}$ metrics in HRV-HF, for two of the metrics for HRV-LF, and marginally with two of the $PM_{2.5}$ metrics for SDNN. The largest and statistically significant inverse associations were among individuals with previous cardiovascular-related conditions (termed Beta Compromised), whereas none of the associations among participants without previous cardiovascular-related conditions (termed Beta Healthy) were statistically significant.

When each of these analyses was repeated with a 1-day lag between $PM_{2.5}$ concentrations and HRV, none of the associations were significantly different (data not shown). Because of the lack of a biologically plausible hypothesis to justify further investigations of lag functions, no further lags were considered.

A categorical analysis was performed to evaluate the risk of having a low HRV-HF day on days when $PM_{2.5}$ concentrations were at or above 15 $\mu g/m^3$. A participant was classified as having a low HRV day if his or her HRV-HF level fell below the first tertile of the individual's HRV-HF distribution over the entire study period. The level of $PM_{2.5} \geq 15$ $\mu g/m^3$ was used to define high pollution days. On average, a low HRV-HF day occurred on 44% of high pollution days. In contrast, a low HRV-HF day occurred on only 20% of days when $PM_{2.5}$ concentrations were below 15 $\mu g/m^3$. Logistic regression models were used to estimate the age and previous cardiovascular conditions adjusted odds ratio (95% CI) expressing the relationship between low HRV-HF and high pollution days; the resulting adjusted odds ratio of 3.08 (1.43, 6.59) can be interpreted as finding the risk of having an HRV-HF value in the lowest tertile of each individual's distribution to be three times greater on days when the $PM_{2.5}$ concentration was 15 $\mu g/m^3$ or greater compared with days below this concentration.

Discussion

The data from this study suggest that elevated concentrations of $PM_{2.5}$ within an environmentally relevant range are associated with lower HRV in the elderly, and that the association is more pronounced in elderly individuals with previous cardiovascular-related conditions.

Caution should be exercised when interpreting these results. The study participants were selected from only one retirement center in a geographically defined area; thus, the results may not be representative of other populations. Also, within the retirement center, we only studied 26 volunteers who agreed to participate. We did not have data to compare the eligible individuals who did not participate with those who did. Another limitation of this study was that the measurements of $PM_{2.5}$ exposure were mostly based on a common microenvironment shared by the participants rather than on personal exposure monitoring. Although fine PM is highly penetrable and may be evenly diffused in a defined microenvironment and although the study site is located in a residential area away from major roadways, misclassification of PM exposure at individual levels cannot be ruled out. However, a recent study comparing personal sampling of PM at the individual levels with indoor and outdoor ambient PM confirmed the usefulness of ambient PM measured outdoor and indoor to assess personal PM exposure over time (*21*). Our data from five individuals who wore a personal monitor for the entire study period indicated a high correlation between personal monitoring of PM concentrations and the microenvironmental PM concentrations determined by a stationary monitor. Regardless of these limitations, to our knowledge, this is the first study to relate day-to-day variations of PM concentration with cardiac autonomic control in a susceptible population and thus demonstrating potential pathophysiologic mechanisms linking environmentally relevant PM exposure and excessive cardiovascular morbidity and mortality.

On one hand, it has been consistently demonstrated that exposure to particulate air pollution is associated with increased mortality and morbidity, especially cardiovascular morbidity and mortality (*1–9*). On the other hand, there has been a lack of biologically demonstrable mechanisms for such an association, particularly at environmentally relevant PM concentrations. In recent years, analysis of beat-to-beat HRV has emerged as a clinically and epidemiologically useful noninvasive method to quantitatively assess cardiac autonomic activity (*22–38*). As a result of interaction between sympathetic and parasympathetic activity, HRV shows periodicity over time. This periodicity can be identified through spectral analysis as the sum of a series of sine and cosine functions of varying amplitudes and frequencies (frequency domain analysis). Previous work (*22–30*) has shown that heart rate oscillations at low frequencies (0.04–0.15 Hz) are under the influence of both the sympathetic and parasympathetic nervous systems, whereas oscillations at high frequencies (0.15–0.40 Hz) are under the influence of the parasympathetic system only and have been regarded as a marker of cardiac parasympathetic activity. Clinically based studies have consistently demonstrated that lower HRV values were associated with higher risk of all-cause mortality among survivors of myocardial infarction (*31–34*). Lower HRV has also been related to sudden cardiac death (*35*). Results from population-based cohort studies suggested that lower HRV is associated with an increased risk of developing coronary heart disease (*36,37*). It has been proposed that HRV be used as a prognostic factor for myocardial infarction (*38*). Because of the richness of HRV literature and its consistently demonstrated association with cardiovascular disease, we originally hypothesized that PM pollution leads to increased cardiovascular morbidity and mortality partially through PM exposure altering the balance of cardiac autonomic control, thus increasing the susceptibility to adverse cardiac events. Our results of an inverse association between daily levels of PM concentration and HRV provide a suggestive link between particulate air pollution and cardiovascular mortality, especially in the elderly with preexisting cardiovascular conditions. The difference in the magnitude of association by baseline cardiovascular health status is indicative of differential susceptibility to PM exposure. However, this finding needs to be confirmed by other studies with larger sample sizes. A somewhat larger HRV effect was seen in the HF power spectrum than for the other HRV metrics, suggesting that the decrease in heart rate variability with higher concentrations of $PM_{2.5}$ may be a consequence of a relatively greater loss of parasympathetic control of heart rate. As summarized previously, lower HRV is predictive of higher risk of cardiovascular disease in clinically and population-based studies. However, we cannot find any published literature demonstrating that day-to-day change in HRV is associated with day-to-day change in risk of cardiovascular disease. Thus, we consider our study somewhat exploratory. Our findings do not rule out the involvement of other potential pathophysiologic mechanisms. We did not have data on other potential important cardiovascular responses, such as ventricular ectopy, ST-wave segment depression, T-wave alternans, and other electrocardiograph changes.

Although antihypertensive medications influence cardiac autonomic control, we consider it less likely that our results were biased by medication usage because our daily medication-usage survey did not reveal any significant day-to-day variations in the use of medications by the study participants during the study period. Our data did not show a consistent pattern of association between PM and HRV in a small group of relatively healthy individuals. The small sample size (n = 8) in this group precludes drawing any firm conclusions about the absence of an HRV effect in this group. Our data cannot completely rule out the contribution of other co-pollutants, such as carbon monoxide (CO) and ozone (O_3). However, this is less likely because the study was conducted during the winter (minimum O_3 exposure) and at a center located away from major traffic (minimum day-to-day CO exposure variations).

Whether the magnitude of decline in HRV seen in our participants has any predictive value is unknown. However, because a decline in HRV has been associated with adverse cardiovascular events, it can be hypothesized that the lower HRV associated with increased $PM_{2.5}$ concentrations increases the risk for an acute cardiovascular occurrence in elderly persons with compromised cardiovascular health status via altered cardiac autonomic control of heart rate.

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