



Original Contribution

Vascular Function, Inflammation, and Variations in Cardiac Autonomic Responses to Particulate Matter Among Welders

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Initially submitted May 30, 2008; accepted for publication December 8, 2008.

Patients with health conditions associated with impaired vascular function and inflammation may be more susceptible to the adverse health effects of fine particulate (particulate matter with a mass median aerodynamic diameter of $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$)) exposure. In 2006, the authors conducted a panel study to investigate directly whether vascular function and inflammation (assessed by C-reactive protein) modify $\text{PM}_{2.5}$ -associated reductions in heart rate variability among 23 young male workers (mean age, 40 years) from Massachusetts. Concurrent 24-hour ambulatory electrocardiogram and personal $\text{PM}_{2.5}$ exposure information was collected over a total of 36 person-days, including either or both welding and nonwelding days. Linear mixed models were used to examine the 5-minute standard deviation of normal-to-normal intervals (SDNN) in relation to the moving $\text{PM}_{2.5}$ averages in the preceding 1–4 hours. C-reactive protein levels and 3 measures of vascular function (augmentation index, mean arterial pressure, and pulse pressure) were determined at baseline. The authors observed an inverse association between the 1-hour $\text{PM}_{2.5}$ and 5-minute SDNN. Greater SDNN declines were observed among those with C-reactive protein ($P_{\text{interaction}} < 0.001$) and augmentation index ($P = 0.06$) values at or above the 75th percentile and pulse pressure values below the 75th percentile ($P < 0.001$). Systemic inflammation and poorer vascular function appear to aggravate particle-related declines in heart rate variability among workers.

augmentation; C-reactive protein; disease susceptibility; heart rate; inflammation; particulate matter; vascular diseases; welding

Abbreviations: Alx, augmentation index; CI, confidence interval; $\text{PM}_{2.5}$, particulate matter with a mass median aerodynamic diameter of $\leq 2.5 \mu\text{m}$; SDNN, standard deviation of normal-to-normal intervals.

Exposure to airborne particulate matter is a recognized risk factor for acute cardiovascular events, and the elderly and individuals with preexisting cardiovascular and respiratory diseases are especially susceptible (1). The fine fraction of particulate matter (mass median aerodynamic diameter of $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$)) is especially toxic, because it readily reaches the alveolar region of the lungs. Cardiovascular mortality, cardiac arrhythmia, myocardial infarction, myocardial ischemia, and heart failure have been associated with short-term exposure to $\text{PM}_{2.5}$ (2–6). Research has focused on identifying the biologic mechanism(s) by which particles elicit adverse cardiovascular events, and a number of potential pathways have been suggested. One such pathway involves alterations in cardiac autonomic function, which is

usually assessed by heart rate variability (7). Decreased heart rate variability is associated with increased risk of mortality in the general population and the development of nonfatal cardiac events (8, 9).

In studies of particulate matter-related health effects, changes in heart rate variability after short-term exposures have been studied in numerous elderly populations (10–16) and, to a lesser extent, in younger populations (17–19) and workers (20–23). These studies demonstrate that individuals with hypertension, diabetes, and ischemic heart disease experience greater particulate matter-associated declines in heart rate variability (10, 12, 24), although what accounts for such enhanced susceptibility remains largely unexplained. Because most people with these clinical indicators

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of susceptibility have underlying impairments in vascular health (25–27) and increased systemic inflammation (28–30), such factors may be important determinants of greater risk for particle-related declines in heart rate variability. However, to the best of our knowledge, there are no published data in the air pollution epidemiology or toxicology literature linking vascular function or inflammation with susceptibility to particulate matter-associated declines in heart rate variability.

To determine whether poorer vascular function and increased systemic inflammation impart greater risk of particle-mediated declines in heart rate variability, we conducted a panel study among a group of relatively young and healthy welders with occupational and environmental exposures to PM_{2.5}. Our previous investigations demonstrated declines in heart rate variability with particulate matter exposures among this cohort (20). We also found that obesity and higher cardiovascular disease risk aggravate particulate matter-related heart rate variability declines (31, 32). However, specific biologic markers of susceptibility have yet to be identified. We chose to evaluate determinants of susceptibility in this population, as opposed to elderly individuals or those with cardiovascular-related conditions, because younger working populations are less likely to suffer multiple comorbidities, which minimizes the difficulty of ascertaining the responsible determinants of susceptibility. We hypothesized that individuals with lower capacities of vascular function and higher baseline levels of C-reactive protein, a marker of systemic inflammation that is predictive of cardiovascular disease (30), have a stronger cardiac autonomic response to PM_{2.5} exposure.

MATERIALS AND METHODS

Study population

The study population consisted of 25 male boilermaker construction workers or “boilermakers” recruited from a union in Massachusetts. As part of their apprentice program, boilermakers are instructed in welding techniques. Welding generates high levels of fine and ultrafine particulate matter when the heated metal vaporizes and then condenses in air. We invited the workers to be monitored on a high-exposure welding day and a low-exposure nonwelding day over the winter months of 2006 at the union welding school. Workers were monitored for up to a 24-hour period on each occasion. The most common type of welding was manual metal arc welding on mild (manganese alloys) and stainless steel (chromium and nickel alloys) bases. All welding was performed in a room outfitted with 10 workstations, each with local exhaust ventilation. On nonwelding days, participants performed office work or bookwork in a large enclosed break room adjacent to the welding room.

Twenty-five boilermakers were monitored; however, 1 individual with an unreadable electrocardiogram tape and another with missing covariate information were excluded from the analyses, resulting in 23 participants. Among these, 13 participated on both days and 10 on a single day (9 on a welding day and 1 on a nonwelding day), giving a total of 36 person-days. The Harvard School of Public

Health Institutional Review Board approved the study protocol, and written, informed consent was obtained from each individual prior to participation.

Data collection

Personal continuous real-time PM_{2.5} concentrations were obtained with the DustTrak Aerosol Monitor (TSI, Inc., St. Paul, Minnesota), which was placed in a padded pouch with the inlet tubing secured to the participant's shoulder in the breathing zone area. The DustTrak was fitted with an inlet impactor designed to separate particles with a mass median aerodynamic diameter of ≤ 2.5 μm . PM_{2.5} concentration (mg/m³) readings were recorded in 1-minute averages. Moving averages over 1–4 hours were calculated for each monitoring period.

After participants were provided with their personal PM_{2.5} monitors (generally between 7:00 and 9:00 AM), each was fitted with a standard 3-channel, 5-lead electrocardiogram Holter monitor (Spacelabs 90205; Spacelabs, Redmond, Washington), which sampled at 200 samples per second. Electrodes were placed in a modified V₁ and V₅ position. The Holter monitor remained in position throughout the monitoring period, with periodic lead checks performed by study personnel at the welding school.

Cardiac recording tapes were shipped to Raytel Cardiac Services (Haddonfield, New Jersey) for processing and analysis with a Del Mar Avionics (Irvine, California) Strata Scan model 563. For each QRS complex, only beats with an RR interval (time duration between 2 consecutive R waves of the electrocardiogram) between 0.6 and 1.5 seconds and an RR ratio of 0.8–1.2 were included in the analysis. Trained technicians, blinded to the exposure status of the participants, used standard criteria to reject all abnormal findings (7). The standard deviation of normal-to-normal intervals (SDNN), which reflects overall parasympathetic and sympathetic components of the cardiac autonomic nervous system, was calculated for each 5-minute segment (measured in milliseconds). For the analysis, we used epochs for which at least 90% of the total beats were validated beats used to calculate the 5-minute SDNN.

As few participants had diastolic or systolic blood pressures above 90 or 140 mm Hg, respectively, vascular function was characterized by parameters related to blood pressure: augmentation index (AIx), mean arterial pressure, and pulse pressure. Brachial systolic and diastolic blood pressure readings were obtained in triplicate by using a validated digital blood pressure monitor (LabTron 7070A; Graham-Field, Inc., Bay Shore, New York), and the average of the 3 readings was calculated (intraclass correlation coefficient, 83.3% for systolic and 92.3% for diastolic pressure). Pulse pressure, an independent marker of subclinical cardiovascular disease (33), was calculated as the difference between the systolic and diastolic pressures. Mean arterial pressure was calculated as the diastolic pressure + (1/3 \times pulse pressure). Both pulse pressure and mean arterial pressure have been shown to be predictive of cardiovascular disease events independent of systolic or diastolic pressure (34).

AIx measurements were performed with a SphygmoCor Px Pulse Wave Analysis System model SCOR-Px (Atcor

Medical, Inc., Chicago, Illinois). A detailed description of the AIx measurements for this population is given elsewhere (35). Larger values of AIx indicate increased wave reflection (i.e., earlier return of the reflected wave) and have been correlated with increased arterial stiffness (36). Increased AIx is associated with advancing age, diabetes, hyperlipidemia, and hypertension and is also a strong and independent marker of established coronary artery disease (37) and coronary artery disease risk (38, 39).

Venous blood samples were collected into a serum separator tube, allowed to clot for 15 minutes, and then placed on ice. Samples were sent to a clinical laboratory for analysis (PathLab, Inc., Portsmouth, New Hampshire). Quantitative determination of C-reactive protein in serum was performed with a Boehringer Mannheim/Hitachi 911 analyzer (Roche Diagnostics Corp., Indianapolis, Indiana) by use of a latex particle enhanced immunoturbidimetric assay.

Information on demographics, medication usage, and medical, smoking, and occupational history was obtained from a self-administered, modified American Thoracic Society questionnaire (40). Time-varying information on personal smoking, coffee drinking, and alcohol consumption over the 24 hours of monitoring was self-recorded on activity sheets, as previously done within this population (32).

Statistical methods

Linear mixed-effects models were constructed to estimate the association between the moving average $PM_{2.5}$ concentrations and 5-minute SDNN. The covariance of the repeated measurements within individuals was modeled with a spatial power covariance structure, which allows for the correlation between repeated measurements to decline as a function of time, and by including a random effect for each individual, chosen by minimizing the Akaike Information Criterion. The SDNN measurements were highly skewed and were therefore natural log transformed to improve normality of the residuals.

We included both age and time-varying covariates in the models to account for between-person and within-person factors that may be correlated with exposure and affect heart rate variability. Time-varying covariates treated as dummy variables reflected activity every 5 minutes. Indicators for time of day were included to account for the circadian variation of heart rate variability: morning (7:00 AM–11:59 AM); afternoon (12:00 PM–5:59 PM); evening (6:00 PM–10:59 PM); and nighttime (11:00 PM–6:59 AM). In addition, an indicator for welding was included to account for factors that may differ between welding and nonwelding periods, such as physical activity and ventilation. Percent changes and 95% confidence intervals were reported for an increase in the exposure equal to the interquartile range of the moving average $PM_{2.5}$ concentration.

To assess modification by vascular function, each vascular parameter was evaluated in separate models by entering an interaction term between $PM_{2.5}$ and the vascular parameter, which was dichotomized (<75th percentile and \geq 75th percentile) to maintain an adequate number of observations in the top quartile while maximizing contrast within each vascular parameter. For individuals who participated on 2

monitoring days, the average of each vascular parameter was used as the baseline value. For models with a statistically significant interaction term ($P \leq 0.05$), models stratified by the indicated levels of vascular parameters were subsequently run to obtain estimates of effects and confidence intervals. The same approach was used to evaluate modification by C-reactive protein levels.

AIx and pulse pressure are inversely related (38), and therefore we also refit models after excluding individuals with both low pulse pressure and high AIx and established new cutpoints. Further, because pulse pressure is a function of diastolic and systolic pressures, we investigated the role of each in subsequent models. Sensitivity analyses excluding individuals on antihypertensive medications were also performed. We also refit the models with the 1-hour average restricted to working hours and nonworking hours separately to evaluate potential differences in cardiac responses by source of $PM_{2.5}$ exposure (i.e., occupational vs. nonoccupational). An interaction term between an indicator variable for welding and the $PM_{2.5}$ average was also included to evaluate potential differences in the effects of $PM_{2.5}$ on heart rate variability due to differing compositions of $PM_{2.5}$ on welding and nonwelding days. This was performed in the primary analysis as well as the analysis restricted to working hours. Residual plots and the distribution of the error terms were evaluated to verify the normality of the residuals and fit of the models. All analyses were performed in SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

A description of the 23 male participants is provided in Table 1. The moving average $PM_{2.5}$ concentrations over the entire monitoring period and the 1-hour moving average over the work shift (approximately 6 hours) are presented in Table 2. In general, the mean $PM_{2.5}$ concentration slightly decreased as the averaging window increased; however, the distribution of the 5-minute concentrations was highly skewed, and the median concentration increased as the averaging window increased.

The mean 5-minute SDNN was 51.8 (standard deviation, 27.5) milliseconds and was significantly lower among participants whose vascular function parameters and C-reactive protein levels were at or above the 75th percentile, as compared with their counterparts with values below the 75th percentile (Table 3). Two individuals had high (\geq 75th percentile) C-reactive protein and AIx values; 1 had high C-reactive protein and pulse pressure values; 1 had high C-reactive protein and mean arterial pressure values; 2 had high AIx and pulse pressure values; and 2 had high AIx and mean arterial pressure values. None had high pulse pressure and mean arterial pressure values.

For all $PM_{2.5}$ averaging periods, models for crude and main effect estimates separately adjusted for AIx, mean arterial pressure, pulse pressure, and C-reactive protein yielded similar results; thus, only results from the adjusted main effect models that included the AIx are presented. Only the association with the 1-hour average was statistically significant, yielding a 0.56% (95% confidence interval (CI): -1.05 , -0.07) decline in SDNN per interquartile

Table 1. Characteristics of Male Welders in the Study Population, Massachusetts, 2006

	Value
Participants, no. (%)	23 (100)
White, no. (%)	21 (91)
Current smokers, no. (%)	9 (39)
Age, years	
Mean (SD)	40 (12)
Range	24–63
Years as a boilermaker, median (range)	5 (<1–38)
Physician-diagnosed hypertension, no. (%)	4 (17)
Antihypertensive medication usage, no. (%)	3 (13)
Augmentation index, %	
Mean (SD)	14.1 (13.7)
Median (25th, 75th)	16.7 (2.3, 22.3)
Mean arterial pressure, mm Hg	
Mean (SD)	97.4 (12.7)
Median (25th, 75th)	93.9 (92.2, 102.7)
Pulse pressure, mm Hg	
Mean (SD)	49.0 (8.67)
Median (25th, 75th)	48 (42.2, 56.2)
C-reactive protein, mg/L	
Mean (SD)	4.2 (5.9)
Median (25th, 75th)	2.0 (1.3, 4.7)

Abbreviation: SD, standard deviation.

range increase in PM_{2.5} (0.188 mg/m³) (Table 4). The 1-hour average was used as the primary exposure variable in subsequent analyses. Greater PM_{2.5}-associated SDNN declines were observed among those with C-reactive protein

($P_{\text{interaction}} < 0.001$) and AIx ($P_{\text{interaction}} = 0.06$) values in the ≥ 75 th percentile and pulse pressure values in the < 75 th percentile ($P_{\text{interaction}} < 0.0001$) (Figure 1). Models using new cutpoints after excluding 4 individuals with both low pulse pressure and high AIx values yielded similar results. Further analyses with systolic and diastolic pressures showed that higher diastolic pressure (≥ 86.3 mm Hg) aggravated the PM_{2.5}-associated declines in SDNN (3.51% per interquartile range increase in PM_{2.5}; 95% CI: $-6.03, -1.12$).

The interaction term for welding and PM_{2.5} concentration was not statistically significant, and its inclusion did not affect the statistically significant modifications. Exclusion of the 3 individuals on antihypertensive medications did not appreciably alter the main effect of PM_{2.5} on SDNN but resulted in a slightly greater decline in SDNN among those in the ≥ 75 th percentile of AIx. The results by mean arterial pressure, pulse pressure, and C-reactive protein levels remained unchanged.

During working hours, larger main effects were observed: SDNN declined approximately 0.74% (95% CI: $-0.92, -0.03$) per interquartile range increase in PM_{2.5}. Among the potential effect modifiers, only a marginally statistically significant interaction between PM_{2.5} and AIx remained ($P = 0.06$), with greater PM_{2.5}-associated SDNN declines among participants in the ≥ 75 th percentile (-2.93% per 0.188 mg/m³; 95% CI: $-5.04, -0.90$) versus those in the < 75 th percentile (-1.49% per 0.188 mg/m³; 95% CI: $-2.18, -0.82$) of AIx. Including an indicator term for welding did not appreciably alter the effect estimates nor did adding an interaction term between welding and PM_{2.5}. Statistically significant associations were not observed during nonworking hours.

DISCUSSION

In this panel study of healthy young workers exposed to occupational and environmental sources of PM_{2.5}, we

Table 2. Distribution of Work Shift and Moving Average 5-Minute PM_{2.5} Exposure Concentrations (mg/m³) Over the Study Period, Massachusetts, 2006

	No. ^a	Mean (SD)	Percentile		
			25th	50th	75th
Total monitoring period ^b					
1-hour average	7,708	0.286 (0.850)	0.012	0.039	0.200
2-hour average	7,337	0.284 (0.822)	0.013	0.045	0.240
3-hour average	6,975	0.279 (0.804)	0.014	0.048	0.261
4-hour average	6,600	0.276 (0.789)	0.015	0.053	0.269
Work shift ^c					
1-hour average	1,754	0.586 (0.718)	0.060	0.279	0.920
Welding shift	22	0.887 (0.542)	0.517	0.643	1.10
Nonwelding shift	14	0.202 (0.379)	0.046	0.089	0.138

Abbreviations: PM_{2.5}, particulate matter with a mass median aerodynamic diameter of ≤ 2.5 μm ; SD, standard deviation.

^a Number refers to *participants* for the work-shift concentrations and *observations* for the moving-average concentrations.

^b The number of hours monitored on each person-day ranged from 7 to 26 hours.

^c The mean work shift was 6.8 (SD, 1.4) hours.

Table 3. Standard Deviation of Normal-to-Normal Intervals (Milliseconds) by Level of Augmentation Index, Mean Arterial Pressure, Pulse Pressure, and C-reactive Protein, Massachusetts, 2006

	No. of Participants	No. of Observations	Mean (SD)	Median (Range)	P Value ^a
Augmentation index					
<75th percentile	17	6,143	56.4 (26.4)	52 (8–202)	<0.0001
≥75th percentile	6	1,933	37.2 (25.7)	31 (4–173)	
Mean arterial pressure					
<75th percentile	18	5,956	53.6 (28.1)	50 (4–202)	<0.0001
≥75th percentile	5	2,120	46.8 (24.8)	41 (11–200)	
Pulse pressure					
<75th percentile	18	6,630	52.8 (27.9)	49 (4–202)	<0.0001
≥75th percentile	5	1,446	46.9 (25.0)	41 (11–200)	
C-reactive protein					
<75th percentile	17	6,089	53.7 (26.0)	48 (8–200)	<0.0001
≥75th percentile	6	1,987	46.0 (30.8)	44 (4–202)	

Abbreviation: SD, standard deviation.

^a From linear mixed models.

identified specific physiologic markers of enhanced susceptibility to particulate matter-associated declines in heart rate variability. Specifically, the heart rate variability effects observed in this population were aggravated by higher AIx and C-reactive protein values and lower pulse pressure values. There was little overlap among individuals with C-reactive protein and AIx values at or above the 75th percentile. However, the majority of the participants with AIx values at or above the 75th percentile had pulse pressure values below the 75th percentile, which is consistent with the fact that AIx is an inverse function of central aortic pulse pressure (38). Notably, however, during working hours only AIx appeared to modify the PM_{2.5}–SDNN association, suggesting a distinct role for AIx in susceptibility, although a lack of modification by pulse pressure during working hours due

to insufficient power or chance cannot be ruled out. Further analyses with systolic and diastolic pressures suggest that the aggravating role of pulse pressure may be due to higher diastolic blood pressure.

The inverse association between heart rate variability and PM_{2.5} observed in this study is consistent with previous studies (11, 16, 17, 41), including studies of boilermakers drawn from the same population as the current study (20, 32, 42). Of note, stronger declines in heart rate variability were associated with the 4-hour average in past boilermaker studies. Conflicting findings from the present study may be due in part to differences in PM_{2.5} exposure composition (i.e., the earlier study included exposure to residual oil fly ash in addition to welding fume), as well as exposure intensity and duration. In addition, average PM_{2.5} exposures at the

Table 4. Percent Change in 5-Minute Standard Deviation of Normal-to-Normal Intervals per Interquartile Range Increase in Moving Average PM_{2.5} Concentration, Massachusetts, 2006

PM _{2.5}	Interquartile Range, mg/m ³	Univariate Model			Model Adjusted for Baseline Augmentation Index ^a		
		Effect ^b	95% Confidence Interval	P Value	Effect ^b	95% Confidence Interval	P Value
1 hour	0.188	−0.62	−1.12, −0.12	0.01	−0.56	−1.05, −0.07	0.03
2 hours	0.227	−0.42	−1.09, 0.26	0.22	−0.35	−1.02, 0.31	0.30
3 hours	0.247	−0.34	−1.17, 0.48	0.41	−0.27	−1.08, 0.54	0.52
4 hours	0.254	−0.23	−1.19, 0.72	0.63	−0.08	−1.03, 0.86	0.87

Abbreviation: PM_{2.5}, particulate matter with a mass median aerodynamic diameter of ≤2.5 μm.^a Additionally adjusted for fixed covariates: age, weld, and time-varying covariates—smoking, coffee consumption, alcohol consumption, and time of day (morning, afternoon, evening, and night).^b Effect represents a percent change in 5-minute standard deviation of normal-to-normal intervals associated with an interquartile range increase in the moving average PM_{2.5} concentration.

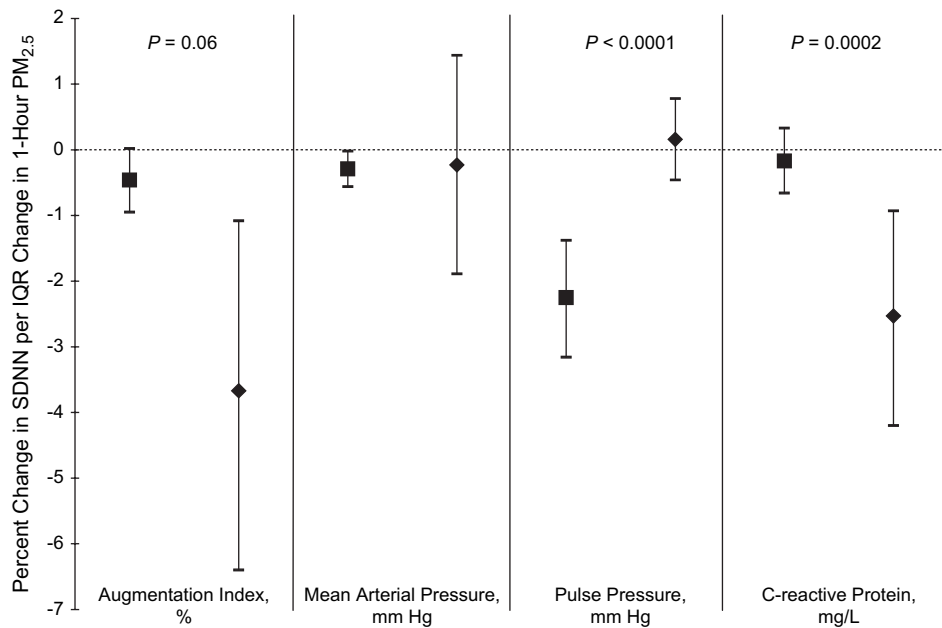


Figure 1. Multivariable association between 5-minute SDNN and PM_{2.5}, by level of baseline augmentation index, mean arterial pressure, pulse pressure, and C-reactive protein, Massachusetts, 2006. Models were adjusted for age, welding, smoking, coffee consumption, alcohol consumption, and time of day (morning, afternoon, evening, and night). Declines in SDNN associated with the preceding 1-hour average PM_{2.5} exposure were greater for individuals in the ≥75th percentile of augmentation index (≥22.3%), the <75th percentile of pulse pressure (<56.2 mm Hg), and the ≥75th percentile of C-reactive protein (≥4.74 mg/L). Percent change in SDNN is for an IQR change in PM_{2.5} (0.188 mg/m³). Square symbols indicate the effect estimate for the <75th percentile; diamond symbols indicate the effect estimate for the ≥75th percentile. SDNN, standard deviation of normal-to-normal intervals; IQR, interquartile range; PM_{2.5}, particulate matter with a mass median aerodynamic diameter of ≤2.5 μm.

welding school have decreased over sampling years with the improvement of local exhaust ventilation. However, the association between SDNN and the 1-hour PM_{2.5} concentration in this study is comparable to previous estimates that evaluated the 1-hour PM_{2.5} average (20).

Few studies have examined modifiers of particulate matter-related declines in heart rate variability. Findings from the current study, in which increased C-reactive protein and AIx were found to be aggravators, are consistent with the previous findings of enhanced particulate matter-related heart rate variability declines among a different group of boilermakers who were obese and who had a high risk of cardiovascular disease, as assessed by the Framingham Risk Score (31, 32). As inflammation and poorer vascular health are associated with obesity and increased cardiovascular risk, findings from the current study are not surprising. Importantly, however, our current study expands upon our previous studies by offering insight into specific biologic markers of susceptibility that bear implications for the mechanisms of particulate matter-associated declines in heart rate variability. Lending support to our findings that suggest that inflammation aggravates particulate matter-related heart rate variability declines, one experimental study demonstrated that dietary supplementation with omega-3 fatty acids, which are known to decrease inflammation (43), prevented heart rate variability declines in elderly individuals exposed to PM_{2.5} (44). The findings from

this study are also consistent with those from studies among elderly populations in which larger heart rate variability declines associated with increasing particulate matter exposure occurred in individuals with hypertension in cross-sectional (12, 24) and panel (10) studies. Elderly individuals with diabetes have also been reported to experience greater declines in heart rate variability in association with PM_{2.5} (12).

Since heart rate variability is an overall measure of autonomic function, the observed SDNN reduction associated with PM_{2.5} exposure may indicate increased sympathetic activity over parasympathetic activity. This may be mediated by oxidative stress pathways occurring directly upon inhalation of particles or subsequent to acute pulmonary inflammation (45). Oxidative stress in the lungs can lead to the release of proinflammatory cytokines (46), which in turn can lead to an increase in sympathetic tone and a reduction in parasympathetic tone (47). Alternatively, direct activation of pulmonary neural reflex arcs or the effects of pollutants on cardiac ion channels may be involved (1). The associations observed in this study with the 1-hour PM_{2.5} average are consistent with more rapid effects that may occur via direct mechanisms. The potential mechanisms by which poorer vascular function and increased inflammation may aggravate PM_{2.5}-associated declines in heart rate variability are unclear; however, a plausible explanation may be that lower baseline heart rate variability elicits stronger cardiac autonomic responses. Lower baseline heart rate

variability has been shown in individuals with hypertension (48), diabetes (49), and coronary artery disease (50). Likewise, lower baseline heart rate variability is demonstrated among individuals with poorer vascular function (51) and increased systemic inflammatory states (52, 53). Further research is needed to clarify the underlying mechanisms by which particles alter cardiac autonomic function and by which vascular function and inflammation impart differential responses.

Our study design was strengthened by the use of continuous and simultaneous electrocardiogram and particle monitoring over an extended period of time. A potential concern was confounding by daily activities, although we attempted to control for this by recording personal activities and adjusting for them in the models. Residual confounding by these factors and potential confounding by second-hand smoke and other unmeasured confounders cannot be ruled out in accounting for some of the observed effects of PM_{2.5} on heart rate variability even within strata of the baseline measures of vascular function and C-reactive protein. Another potential confounder is respiratory ventilation, as this affects heart rate variability and may be correlated with PM_{2.5} exposure. We did not measure this, and thus some of the observed effects may be due to changes in ventilation, particularly during working hours when physical activity and minute ventilation would be expected to be greater; however, controlling for welding likely accounted for some of the potentially confounding effects of ventilation.

Confounding by gaseous co-pollutants, such as ozone and nitrogen dioxide, is of concern in particulate air pollution studies. In general, concentrations of these gaseous pollutants are low in manual metal arc welding under a variety of operating conditions (54). Because our previous field measurements of gaseous pollutants during welding by boilermakers were low and uncorrelated with PM₁₀, confounding by these gaseous pollutants was unlikely during the work day (55). Although confounding by gaseous co-pollutants during monitoring times away from the welding school remains a legitimate concern, exposure scientists have also reported low correlations between personal measurements of ozone, nitrogen dioxide, and sulfur dioxide and personal indoor exposure to PM_{2.5} (56).

Different exposure patterns and PM_{2.5} characteristics found in the ambient environment and other work settings may limit the generalizability of our findings to the general population and other workers with occupational PM_{2.5} exposures. Although we attempted to disentangle potential differences between work and environmental exposures, our data were limited during non-work hours, and our study was not designed to assess the effects of ambient exposures. However, given that the main effect finding from our primary analysis was consistent with the air pollution literature, it is likely that the modifying factors identified in this study are germane to other populations. Larger studies of effect modification in general populations, as well as other occupational cohorts, are needed to determine this.

In summary, systemic inflammation as measured by C-reactive protein and vascular function as measured by the AIx and pulse pressure appeared to modify the association between PM_{2.5} exposure and heart rate variability in

this group of workers. The long-term consequences of short-term changes in heart rate variability are unclear in healthy young workers; however, individuals who have an increased inflammatory state and poorer vascular health may be at increased risk over time of developing cardiovascular disease and experiencing particulate matter-elicited acute cardiovascular events. Future research is needed to confirm our findings and to further identify vulnerable subpopulations of workers with regular exposure to PM_{2.5}.

ACKNOWLEDGMENTS

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This research was supported by grants ES009860 and ES00002 from the National Institute of Environmental Health Sciences and by a pilot project research training grant from the Education and Research Center of the Harvard-National Institute for Occupational Safety and Health (grant T42 OH008416). Shona Fang and Jennifer Cavallari were supported by training grants T42 OH008416 and T32 ES 07069.

The authors thank Christine Dobson, Dr. Ema Rodrigues, Dr. Mike Wang, Li Su, Dr. Amy Nuernberg, Marcia Chertok, Merideth Jones, and the International Brotherhood of Boilermakers, Local 29, in Quincy, Massachusetts.

Conflict of interest: none declared.

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