

Association of Heart Rate Variability With Occupational and Environmental Exposure to Particulate Air Pollution

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Background—Airborne particulate matter has been linked to excess morbidity and mortality. Recent attention has focused on the effects of particulate exposure on cardiac autonomic control. Inhaled particulates may affect the autonomic nervous system either directly, by eliciting a sympathetic stress response, or indirectly, through inflammatory cytokines produced in the lungs and released into the circulation.

Methods and Results—This longitudinal study examined the association of particulates ≤ 2.5 μm in diameter ($\text{PM}_{2.5}$) with heart rate variability (HRV) in an occupational cohort ($N=40$). Continuous monitoring of exposure and HR was performed during and away from work. $\text{PM}_{2.5}$ levels were higher than ambient levels typically reported in Boston, 0.167 ± 3.205 mg/m^3 (geometric mean \pm geometric SD). We found a 2.66% decrease (95% CI, -3.75% to -1.58%) in the 5-minute SD of normal RR intervals (SDNN) for every 1 mg/m^3 increase in the 4-hour moving $\text{PM}_{2.5}$ average and a 1.02% increase (95% CI, 0.59% to 1.46%) in HR after adjusting for potential confounding factors. The decrease in SDNN became larger as the averaging interval increased.

Conclusions—Workers experienced altered cardiac autonomic control after exposure to occupational and environmental $\text{PM}_{2.5}$. There appears to be either a long-acting (several hours) and a short-acting (several minutes) component to the mechanism of action that may be related to the production of cytokines and the sympathetic stress response, respectively, or a cumulative effect that begins shortly after exposure begins. The clinical significance of these effects in a healthy working population is unclear. (*Circulation*. 2001;104:986-991.)

Key Words: air pollution ■ heart rate ■ nervous system, autonomic ■ epidemiology

The link between particulate air pollution and morbidity and mortality associated with cardiopulmonary disease has been reported in the literature.¹ Recent attention has focused on the cardiac effects of particulate exposure by examining cardiac autonomic function.^{2,3} The main aims of this study were to examine the magnitude and time course of effect of particulates with a mean aerodynamic diameter ≤ 2.5 μm ($\text{PM}_{2.5}$) on cardiac autonomic function by using time-domain heart rate variability (HRV) parameters in conjunction with several exposure measures.

The mechanisms responsible for this association remain unclear. Several hypotheses have been proposed, including disruption of the autonomic nervous system. Inhaled particulates may affect the autonomic nervous system directly, by eliciting a sympathetic stress response,⁴ or indirectly, through inflammatory cytokines produced in the lungs and released into the circulation.⁵ Controlled exposures of animals to particulates from ambient air and residual oil fly ash (ROFA), the ash that remains after the high-temperature combustion of fuel oil in a boiler, have demonstrated altered autonomic function.⁴

Several HRV indexes have been developed to characterize cardiac autonomic function. These measurements are collected noninvasively and allow the researcher to characterize the sympathetic and parasympathetic components of the autonomic nervous system.⁶ This study used the 5-minute standard deviation of the normal-to-normal intervals (SDNN) as a measure of HRV. This measure explains all cyclic components responsible for variability within the length of the recording and is a general measure of cardiac autonomic function.⁶ Reductions in HRV have been associated with increased mortality among survivors of myocardial infarction⁷ and with increased mortality among general population cohorts.⁸

In this study, we used air quality measurements obtained with a small, personal device worn by the study subject to investigate the association of $\text{PM}_{2.5}$ with cardiac autonomic function. The study population consisted of a relatively young cohort of boilermaker construction workers occupationally exposed to ROFA and metal fumes. Continuous and simultaneous monitoring of $\text{PM}_{2.5}$ concentrations and heart rhythms

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TABLE 1. Summary Statistics for All Study Subjects and for Those Subjects With 4-Hour and 9-Hour Moving-Average Data

	Total Population	4-Hour Population	9-Hour Population
Subjects, n	40	33	24
Race, % white	93	94	96
% Smokers	50	55	50
Age, y			
Mean	38.2±12.6	38.1±12.9	40.8±14.1
Range	19–59	19–59	19–59
Years as boilermaker			
Mean	13.0±13.2	12.5±13.6	17.1±14.7
Range	0–40	0–40	0–40
HR, 5-min mean, bpm	83.3±9.4	92.9±12.9	81.0±10.5
SDNN, 5-min mean, ms	58.9±19.8	55.1±19.8	60.4±20.6
SDNN, 5-min mean, log ₁₀ , ms	1.70±0.17	1.68±0.18	1.72±0.17

Data are presented as mean±SD unless otherwise indicated.

in 5-minute intervals during and away from work was performed.

Methods

Study Subjects

The study was approved by the Institutional Review Board of the Harvard School of Public Health, and written, informed consent was obtained from each subject. All testing was done in accordance with institutional guidelines. The study population consisted of 39 male boilermakers and 1 male pipe fitter. A self-administered questionnaire was used to collect information on medical history, including respiratory and cardiac systems, and the use of prescription and nonprescription medications.

Subjects were studied in 2 different work settings. Apprentice boilermakers were studied at their local welding school, whereas journeymen subjects were studied during overhaul of an oil-fired boiler. All subjects were exposed to environmental PM_{2.5} and welding fumes, whereas journeymen were additionally exposed to ROFA.

Exposure Assessment

Continuous, personal PM_{2.5} monitoring was conducted during each workday and most non-workdays with a TSI Inc DustTrak device. PM_{2.5} was measured because it has been strongly associated with cardiopulmonary morbidity and mortality. These fine particles are thought to be particularly toxic because of their penetration and retention in the alveolar region. The PM_{2.5} monitor was placed in a padded pouch, with the inlet tubing secured in the participant's breathing zone, and attached to each worker before work began. The monitor was worn throughout the day. It took measurements every 10 seconds and reported 5-minute averages.

In addition to workday monitoring, most participants also consented to non-workday cardiac and PM_{2.5} monitoring. These subjects were instructed to keep the DustTrak with them at all times, ensuring that the tubing inlet remained in their breathing zone. Non-workday monitoring, from several hours to 24 hours, was performed on 36 subjects.

Urinary Nicotine, Cotinine, and Creatinine Measurement

Subjects were asked to collect urine samples in sterile cups at the beginning and end of each shift. These samples were divide into aliquots and frozen at −20°C until analysis (ESA Laboratories, Chelmsford, Mass). Nicotine and cotinine were analyzed by reverse-phase high-performance liquid chromatography with UV spectro-

photometry detection⁹ and normalized for creatinine, which was measured by the Jaffe reaction.

Continuous Holter Monitoring and Tape Processing

Continuous HR monitoring was performed by using a 5-lead Holter monitor from Cardio Data Systems, a Dynacord 3-channel device (model 423). Each participant's skin was prepared and electrodes were placed in a modified V₁ and V₅ position. They were checked periodically throughout the workday. Each subject was given a diary to record activities and any symptoms.

Each 24-hour tape was sent to Raytel Cardiac Services and analyzed by using a Delmar Avionics model Strata Scan 563. Only beats with an RR interval between 0.6 and 1.5 seconds and an RR ratio of 0.8 to 1.2 were included in the analysis. Trained personnel performed all analyses, and all normal and abnormal findings were either accepted or rejected on the basis of standard criteria to ensure quality control. Tapes were analyzed in the time domain, and reports summarizing heart rhythm, rate analysis, and ST segment changes were generated. The mean HR and the SDNN were calculated in standard 5-minute segments throughout the entire recording.

Statistical Analysis

Mixed-effects regression models constructed by using SAS, version 8¹⁰, were used to investigate the association of moving PM_{2.5} averages from 15 minutes to 9 hours, generated from the continuous 5-minute data, with HRV parameters. The log₁₀-transformed response variables, 5-minute HR and 5-minute SDNN, were regressed on the various moving averages. The response variables were log₁₀-transformed to improve normality and stabilize the variance. A random effect for each subject and fixed covariates such as time of day, smoking, age, urinary nicotine, and HR were included in the models.

Results

Descriptive statistics are summarized in Table 1. The study population consisted of 40 men, mostly white (93%), half of whom were current smokers. Their average age was 38.2 years (SD 12.6), and they had spent an average of 13 years (SD 13.2) as boilermakers. The mean HR was 83.3 bpm (SD 9.4).

Continuous, uninterrupted PM_{2.5} monitoring in the workplace was difficult to achieve for every subject because of equipment constraints and the difficult working conditions: subjects often worked in confined spaces. For these reasons,

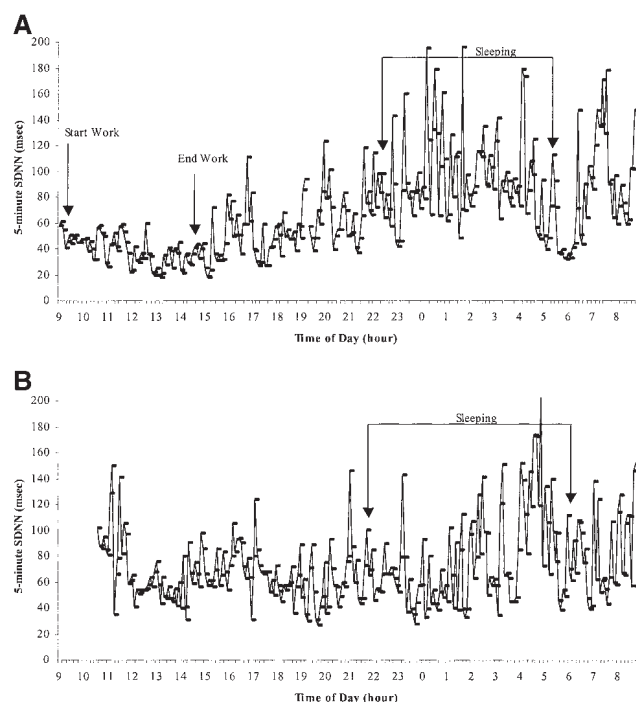


Figure 1. Two graphs of 5-minute SDNN throughout 24-hour monitoring period from typical subject, including work interval (A) and nonwork interval (B). Note depressed 5-minute SDNN throughout work period, followed by increase after end of work shift (A). Note that depression in 5-minute SDNN during work interval does not occur when individual is not working (B).

some subjects were eliminated from a given analysis when they did not have a string of continuous 5-minute $PM_{2.5}$ data points of sufficient length to generate a given moving average. For instance, 7 of the original 40 subjects did not have at least one 4-hour span of time that had complete data for all 5-minute intervals. A 4-hour moving average could not be calculated for them; therefore, the number of subjects with a 4-hour moving average available for analysis dropped to 33. Similarly, the population was further narrowed to 24 subjects when we considered those individuals with complete 9-hour moving-average data. The 4-hour moving average was used as the main exposure measure in the regression analyses because of a drop in the available population with complete data for time periods >4 hours and the similarity of results observed with moving averages >4 hours.

Figures 1A and 1B display examples of 5-minute SDNN plots from a typical study subject throughout the two 24-hour monitoring periods, with the times of interest noted. Figure 1A shows the time that this individual started work (8:30 AM), the time he stopped (2:30 PM), and his sleeping period (from

8:30 PM to 5 AM). The 5-minute SDNN is visibly depressed throughout the workday, reaching a nadir during the work period at 1:10 PM. Also noteworthy is the steady increase in the 5-minute SDNN after he leaves work. The 24-hour period depicted in Figure 1B does not include a work interval. The depression in the 5-minute SDNN during the interval 8:30 PM to 2:30 PM did not occur when the individual was not working.

A summary of exposure history is presented in Table 2. The arithmetic mean exposure for all subjects was 0.697 (SD 0.835) mg/m^3 . The mean 4-hour moving average remained at 0.697 (SD 0.665) mg/m^3 , whereas the arithmetic mean of the 9-hour moving average dropped to 0.159 (SD 0.241) mg/m^3 . This drop was due in part to the fact that the longer moving average was more likely to include lower nonworkplace exposures.

Regression of the 5-minute SDNN on the previous 4-hour moving averages adjusted for potential confounding factors revealed negative, statistically significant associations between the 4-hour $PM_{2.5}$ moving average and the 5-minute SDNN (Table 3). Positive, statistically significant associations were found between the 4-hour $PM_{2.5}$ moving average and HR. Models investigating the interaction between smoking and $PM_{2.5}$ did not detect any difference in the effect of $PM_{2.5}$ on the 5-minute SDNN among smokers versus non-smokers. Individual characteristics such as preexisting respiratory illness (chronic bronchitis), smoking status, hypertension, and worksite (apprentice school vs overhaul site) were examined by using interaction terms with the 4-hour $PM_{2.5}$ moving average in the mixed-effects regression models. These analyses did not reveal any statistically significant interactions between the noted characteristics and the 4-hour $PM_{2.5}$ moving average, indicating that these individual features did not modify the observed associations in this study.

In addition, modification of the observed effects by temperature and humidity were considered indirectly. At the welding school, we encountered cool, low humidity environments ($65^{\circ}F$ and $\approx 20\%$, respectively), whereas at the power plant, we encountered high temperatures and high humidity ($90^{\circ}F$ and $>80\%$, respectively). To investigate this difference, interaction terms between collection site and the exposure measure were generated. These analyses revealed no statistically significant differences in the effect of $PM_{2.5}$ on the SDNN and HR between the 2 collection sites and, by induction, the 2 temperature and humidity conditions.

An increase of $1 mg/m^3$ in the 4-hour $PM_{2.5}$ moving average was associated with a 3.68% decrease (95% CI, -4.85% to -2.52%) in the 5-minute SDNN, while controlling for the time of day, age, and urinary nicotine levels

TABLE 2. Particulate Exposure Summary for All Subjects and for Those With 4-Hour and 9-Hour Moving-Average Data

	Total Population (N=40)	4-Hour Population (n=33)	9-Hour Population (n=24)
$PM_{2.5}$ arithmetic mean, mg/m^3	0.697 ± 0.835	0.697 ± 0.665	0.159 ± 0.241
$PM_{2.5}$ geometric mean, mg/m^3	0.167 ± 3.205	0.223 ± 2.203	0.058 ± 2.429
$PM_{2.5}$ range, mg/m^3	$0.068-3.726$	$0.197-2.714$	$0.022-1.177$

Data are presented as mean \pm SD.

TABLE 3. 4-Hour Moving-Average PM_{2.5} Regression Coefficients and 95% CIs

	Model 1	Model 1a	Model 2	Model 2a
5-min SDNN*	-3.09† (-4.20, 1.98)	-2.33† (-3.38, -1.28)	-3.68† (-4.85, -2.52)	-2.66† (-3.75, -1.58)
5-min HR*	0.87† (0.45, 1.28)	N/A‡	1.02† (0.59, 1.46)	NA

N/A indicates not applicable.

*Coefficients are expressed as % change · mg⁻¹ · m⁻³.

†P < 0.0001.

Model 1 was adjusted for time, age, and smoking (yes/no). Model 1a was adjusted for time, age, smoking (yes/no), and log₁₀ heart rate. Model 2 was adjusted for time, age, and log₁₀ urinary nicotine. Model 2a was adjusted for time, age, log₁₀ urinary nicotine, and log₁₀ heart rate.

(postshift creatinine-normalized levels on the day that they wore the monitor). The magnitude of this association decreased when the model was further adjusted for HR. With this adjustment, an increase of 1 mg/m³ in the 4-hour moving average was associated with a 2.66% decrease (95% CI, -3.75% to -1.58%) in the 5-minute SDNN after controlling for time of day, age, urinary nicotine levels, and HR. The effect estimates in those models that included a urinary marker of smoking are slightly larger compared with similar models that controlled for current smoking as a dichotomous (yes/no) variable. These 2 models were rerun after excluding the top and bottom 5% of the 4-hour PM_{2.5} moving-average values from the analyses to investigate the effects of removing extreme values on the regression results. Both estimates became more negative and indicated a 10.27% decrease (95% CI, -12.81% to -7.73%; model 2) and a 6.08% decrease (95% CI, -8.54% to -3.61%; model 2a) in the 5-minute SDNN.

Models regressing the 4-hour PM_{2.5} moving average on HR are summarized in Table 3. There was a 0.87% increase (95% CI, 0.45% to 1.28%) in the HR associated with an increase of 1 mg/m³ in the 4-hour moving average after adjusting for time of day, age, and current smoking status (yes/no). Use of the urinary marker in place of the dichotomous smoking variable

in this same model increased the magnitude of the association to a 1.02% increase (95% CI, 0.59% to 1.46%). These models were rerun with the top and bottom 5% of the 4-hour moving PM_{2.5} averages removed. The magnitude of the association increased, such that a 1 mg/m³ increase in the 4-hour PM_{2.5} moving average was associated with a 5.01% increase (95% CI, 4.07% to 5.96%) (model 1) and a 5.02% increase (95% CI, 4.07% to 5.97%; model 2) in HR.

To examine the time course of action of the inhaled particulates, models regressing moving PM_{2.5} averages, from 15 minutes to 9 hours, on the 5-minute SDNN were developed. The coefficients for the various moving averages, as a percent decrease, represent the magnitude of the association of PM_{2.5} with the 5-minute SDNN (Figures 2A and 2B). Longer averaging intervals were not investigated because the size of the population with available data dropped substantially when moving averages >9 hours were examined. Figure 2A represents models regressing a given exposure measure on the 5-minute SDNN adjusted for time of day, age, and smoking as a dichotomous variable. Figure 2B represents those coefficients from models further adjusted for HR.

There were measurable, though not statistically significant, decreases in the 5-minute SDNN when a 15-minute averaging

5-minute SDNN Decrease Vs PM_{2.5} Averaging Interval

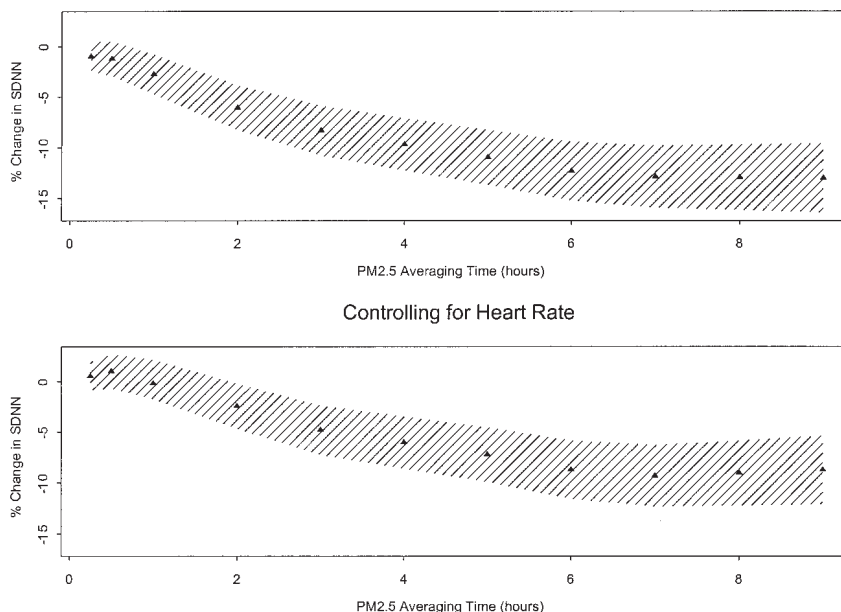


Figure 2. Triangles represent percent decrease in 5-minute SDNN for every 1 mg/m³ increase in PM_{2.5} moving average. 95% CIs are shaded with slanted lines. A, Model 1 is adjusted for time of day, age, and current smoking status. B, Model 2 is additionally adjusted for log₁₀ HR. For both models, PM_{2.5} effect steadily decreased as averaging interval increased.

interval was used. With a 1-hour averaging interval, a statistically significant decrease of 2.76% (95% CI, -4.73% to -0.80%) was observed without adjusting for HR (Figure 2A). After adjusting for HR, a statistically significant decrease of 2.45% (95% CI, -4.68% to -0.23%) was first observed when the 2-hour moving average was used. The magnitude of the negative effect steadily increased for both models, with and without adjustment for HR, until 6 hours, when a plateau appeared. The largest decrease in the 5-minute SDNN, 13.01% (95% CI, -16.44% to -9.58%), was observed with the 9-hour moving $PM_{2.5}$ average shown in Figure 2A, whereas the largest decrease, 9.30% (95% CI, -12.32% to -6.27%), was observed with the 7-hour moving $PM_{2.5}$ average shown in Figure 2B.

Discussion

This study is distinguished from previous work in several ways. It is the first study of which we are aware to examine the effects of $PM_{2.5}$ on a younger population, to incorporate continuous personal monitoring of $PM_{2.5}$, and to examine occupational exposure to $PM_{2.5}$. It is important to note that the particulate exposure investigated during the workday is the dominant air pollutant. Low levels of other air pollutants such as O_3 and CO have been found previously in this occupational setting and are not correlated with particulate concentrations. Without this correlation, other pollutants are unlikely to confound the relationship between $PM_{2.5}$ and cardiovascular effects, another advantage of this study.

The association of environmental levels of $PM_{2.5}$ with various HRV parameters in the elderly has been reported.^{2,3} Given the differences in the composition and range of exposures studied, the effects of $PM_{2.5}$ on both HR and the 5-minute SDNN in this young, working cohort are most comparable to those obtained by Gold et al² in their study of 21 active Boston residents, 53 to 87 years old. These authors reported an 18.8-ms decrease in the 5-minute SDNN for every 1 mg/m^3 increase in the 4-hour $PM_{2.5}$ average for exercising individuals. To facilitate comparison to our study, model 1a was refit by using the linear 5-minute SDNN as the outcome. For the present study, a 1 mg/m^3 increase in the 4-hour average $PM_{2.5}$ was associated with a 4.5-ms decrease in the 5-minute SDNN, compared with the 17.4-ms decrease reported by Gold and colleagues.² This comparison represents an ≈ 4 -fold difference in effect between the elderly and the younger, healthier cohort.

The time course of action for these observed associations was examined in the regression analyses by using $PM_{2.5}$ moving averages of various lengths. Observable decreases in the 5-minute SDNN were noted in regressions with the 15-minute moving $PM_{2.5}$ average, with statistically significant deficits appearing in regressions with the 1-hour $PM_{2.5}$ moving average. This finding suggests a relatively rapid-acting component in the mechanism of action of $PM_{2.5}$ on HRV changes. Additionally, the magnitude of the decrease in the 5-minute SDNN continued to increase as the averaging interval increased. The increase in association observed with a longer averaging exposure interval is consistent with the literature and would suggest either a longer-term component

in the mechanism of action of $PM_{2.5}$ on HRV changes or a cumulative effect that begins shortly after exposure begins.

The clinical effects of reductions in HRV among a young, working cohort have not been explored fully. The HRV decreases reported here may be different in magnitude or direction among those high-risk groups posited to be most susceptible to particulate air pollution (ie, those with preexisting cardiopulmonary conditions). However, Dekker et al⁸ have examined the risk for sudden death, mortality from coronary heart disease, and death from all causes in a general population Dutch cohort of men aged 40 to 85 years and reported a 5-year age-adjusted relative rate of total mortality in men with SDNN measurements <20 ms compared with men with SDNN measurements between 20 and 39 ms of 2.1 (95% CI, 1.4 to 3.0) in middle-aged men and of 1.4 (95% CI, 0.9 to 2.2) in elderly men.

In compromised patients, there are reports regarding the clinical predictability of HRV measures. Lanza et al¹¹ reported a cardiac mortality relative risk of 2.94 ($P=0.03$) among recent myocardial infarction patients who had an SDNN <50 ms. For those patients with heart failure, Nolan et al¹² reported an annual mortality rate in SDNN subgroups of 5.5% for >100 ms, 12.7% for 50 to 100 ms, and 51.4% for <50 ms.

Limitations

We were unable to measure respiratory rate in this occupational setting. Respiration modulates autonomic activity and has been shown to have significant effects on both low- and high-frequency power spectra.¹³ Partial control for respiration was achieved by including the corresponding 5-minute HR in the models.

Although there was little opportunity for confounding of the relationship between $PM_{2.5}$ and HRV during the workday by other environmental copollutants, there is a small possibility that this type of confounding does exist during non-workday monitoring. Our use of personal rather than ambient $PM_{2.5}$ reduced this risk, because the literature suggests that personal indoor $PM_{2.5}$ measurements are not highly correlated with personal measurements of copollutants such as O_3 , NO_2 , and SO_2 .¹⁴ If the concentrations of various other air pollutants do not covary with particle concentrations, then they are unlikely to confound the relationship between $PM_{2.5}$ and the 5-minute SDNN. It should also be noted that statistically significant interactions between individual characteristics, environmental conditions, and $PM_{2.5}$ were not found. The sample size may not have been sufficient in this study to fully examine these interactions, and they should be given consideration in future studies.

Last, although a range of $PM_{2.5}$ exposure intensities was examined in this study, they were, on average, higher than those to which the general public is exposed daily. In addition, $PM_{2.5}$ exposures experienced during work may not be representative of the composition of ambient $PM_{2.5}$ to which the general public is exposed. Ambient $PM_{2.5}$ is derived primarily from the combustion of fossil fuels and will contain ROFA, albeit a small fraction. Welding fumes and ROFA do, however, contain sulfates and other metals commonly found in ambient $PM_{2.5}$.

The finding of detectable disturbances in autonomic function in this young, otherwise healthy cohort is concerning. Further research is needed to elucidate the clinical significance of HRV changes in young, healthy individuals who are exposed to particulate air pollution.

Acknowledgments

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