American Journal of Epidemiology

Vol. 176, No. 2
DOI: 10.1093/aje/kwr511
Advance Access publication:
July 4, 2012

Original Contribution

Air Pollution and Autonomic and Vascular Dysfunction in Patients With Cardiovascular Disease: Interactions of Systemic Inflammation, Overweight, and Gender

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Initially submitted June 20, 2011; accepted for publication December 20, 2011.

The authors conducted a 2-year follow-up of 40 cardiovascular disease patients (mean age = 65.6 years (standard deviation, 5.8)) who underwent repeated measurements of cardiovascular response before and during the 2008 Beijing Olympics (Beijing, China), when air pollution was strictly controlled. Ambient levels of particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), black carbon, nitrogen dioxide, sulfur dioxide, ozone, and carbon monoxide were measured continuously, with validation of concurrent real-time measurements of personal exposure to $PM_{2.5}$ and carbon monoxide. Linear mixed-effects models were used with adjustment for individual risk factors, time-varying factors, and meteorologic effects. Significant heart rate variability reduction and blood pressure elevation were observed in association with exposure to air pollution. Specifically, interquartile-range increases of 51.8 μg/m^3, 2.02 μg/m^3, and 13.7 ppb in prior 4-hour exposure to $PM_{2.5}$, black carbon, and nitrogen dioxide were associated with significant reductions in the standard deviation of the normal-to-normal intervals of 4.2% (95% confidence interval (CI): 1.9, 6.4), 4.2% (95% CI: 1.8, 6.6), and 3.9% (95% CI: 2.2, 5.7), respectively. Greater heart rate variability declines were observed among subjects with C-reactive protein values above the 90th percentile, subjects with a body mass index greater than 25, and females. The authors conclude that autonomic and vascular dysfunction may be one of the mechanisms through which air pollution exposure can increase cardiovascular disease risk, especially among persons with systemic inflammation and overweight.

air pollution; carbon; heart rate; inflammation; obesity; particulate matter; soot

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; ECG, electrocardiographic; HRV, heart rate variability; IQR, interquartile range; PKUHSC, Peking University Health Science Center; PM, particulate matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals; SDNN, standard deviation of the normal-to-normal intervals.

Epidemiologic evidence suggests that acute and chronic cardiovascular disease (CVD) mortality and morbidity are related to exposure to ambient pollutants (especially particulate matter (PM)) that may trigger cardiovascular events within hours or days of exposure (1). Increased incidences of specific acute CVDs, including myocardial infarction, ischemic stroke, heart failure, cardiac arrhythmia, atrial fibrillation, and peripheral arterial and venous diseases, have been found to be associated with exposure to increased ambient PM (2–8). Among the hypothesized mechanisms for ambient pollution-associated cardiovascular effects, PM and its heterogeneous constituent exposures are thought to induce systemic inflammation, oxidative stress, increased blood coagulability, and autonomic and vascular imbalance (9–11). Studies have suggested that pollution from traffic-related sources, estimated by PM, black carbon, and gaseous pollutants, might be responsible for the cardiovascular endpoints (12–16).

Extensive studies have examined associations between decreased heart rate variability (HRV) and elevated blood pressure and exposure to fine particulates (particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$)) (17–20). Recent studies have focused on examining potential roles of CVD risk factors, such as inflammation, overweight, and metabolic syndrome, in modifying particulate-associated autonomic and vascular dysfunction (21–28). These studies have suggested that the air pollution-related cardiovascular responses may be enhanced in subjects with the noted risk factors for adverse cardiac outcomes. Thus, better understanding of the pathophysiologic mechanisms of ambient PM-mediated cardiovascular risk has important public health implications for the larger population with and without health condition impairments.

In 2008, unprecedented air pollution control actions focusing on control of traffic pollution throughout the Beijing Summer Olympic (August 8–24) and Paralympic (September 6–17) games temporarily resulted in dramatic improvements in Beijing's air quality (29–31). Since some sources of air pollution were controlled more intensively than others, the PM chemical composition and concentrations of PM and gaseous copollutants may have differed dramatically before and during the Olympics, thus providing a unique opportunity to address several prominently hypothesized pathophysiologic mechanisms of air pollution cardiovascular health effects that have not been clearly answered by previous studies. In this 2-year longitudinal follow-up of CVD patients before and during the 2008 Beijing Olympics, we hypothesized that increased exposure to air pollution would trigger cardiovascular dysfunction in vulnerable subjects with high baseline exposure to air pollution. We further assessed whether systemic inflammation, diabetes, overweight, and/or gender might modify cardiovascular responses in association with exposure to air pollution.

MATERIALS AND METHODS

Study subjects and design

Our study population consisted of 40 nonsmoking CVD patients (mean age = 65.6 years (standard deviation, 5.8) recruited through the on-campus clinic of Peking University Health Science Center (PKUHSC), Beijing, China (32). All subjects were retired employees of PKUHSC and lived on campus. Of these subjects, 40 patients participated in 24-hour ambulatory electrocardiographic (ECG) monitoring repeatedly, during summer 2007 and summer 2008. A subset of 23 patients participated in 24-hour ambulatory blood pressure monitoring conducted in summer 2008. The institutional review board of PKUHSC approved the study protocol. Informed consent was obtained from each subject prior to study participation.

Outcome measurements

Demographic information on each subject's age, gender, body mass index (weight (kg)/height $(m)^2$), smoking status, and medical history was obtained through a baseline questionnaire interview administered during the participant recruitment process. During each visit, subjects were given a diary to record any symptoms such as shortness of breath during physical activity, at the time of the visit and 24 hours before. Fasting venous blood samples were obtained from each participant at the end of each visit. Blood samples were analyzed by the clinical laboratory of PKUHSC Third Affiliated Hospital for high-sensitivity C-reactive protein, von Willebrand factor, fibrinogen, and viscosity.

Each subject was fitted with an ambulatory ECG monitor that recorded heart rate data between 8:00 AM and 10:00 AM the next day, when it was removed. The hookup of a V7 bipolar lead placement of the ECG monitor and skin preparation was conducted by trained personnel at each subject's home, following a standard protocol. ECG data were recorded digitally on removable flash cards using a standard 3-channel Holter Monitor (model MGY H7; DM Software Inc., Stateline, Nevada). The ECG digital recordings were reviewed and processed by trained cardiologists. Consecutive 5-minute measurements of heart rate and various measures of HRV were calculated for each monitoring session of each subject using personal computer-based software (Holter System, version 12.Net for Windows; DM Software Inc.). Each 5-minute segment was processed to measure the normal-to-normal intervals of the heartbeat, which were used to calculate the time-domain HRV index: the standard deviation of all normal-to-normal intervals (SDNN) and the root mean square of successive differences between adjacent normal cycles (rMSSD), as well as the frequency-domain HRV metrics of low frequency (0.04–0.15 Hz) and high frequency (0.15–0.4 Hz). On average, approximately 240–280 successful segments of 5-minute HRV measurements were obtained for data analysis from each subject during each visit.

Concurrent with ECG monitoring, ambulatory blood pressure measurements were taken every 30 minutes throughout the 24-hour monitoring period (MGY-ABP1; DM Software Inc.). The blood pressure recordings were reviewed and processed to obtain 30-minute systolic blood pressure and diastolic blood pressure readings, using personal computer-based software (Ambulatory Blood Pressure Monitor Analysis Software 1.0 for Windows; DM Software Inc.).

Air pollution measurements

Concurrent with ambulatory ECG monitoring, ambient pollution concentrations and meteorologic conditions were monitored continuously at a long-term air monitoring station located on the main campus of Peking University, which is approximately 3 km west of the PKUHSC campus. Both the Peking University air monitoring station and the PKUHSC campus study site are within 500 m of the fourth traffic ring road, which is one of the major traffic roads surrounding the urban area of Beijing.

The Peking University air monitoring station is located on the roof of a 4-story teaching building on campus. Routinely monitored pollutants include $PM_{2.5}$, black carbon, sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone. Minute-to-minute average $PM_{2.5}$ mass concentrations were determined with Tapered Element Oscillating Microbalance monitors (Thermo Fisher Scientific Inc., Franklin, Massachusetts). Five-minute black carbon concentrations were measured using the Multi-Angle Absorption Photometer (model 5012; Thermo Fisher Scientific Inc.). Minute-to-minute average sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone concentrations were monitored by means of EC9800 series ambient gas analyzers (EcoTech Pty. Ltd., Knoxfield, Victoria, Australia), where the instruments were maintained by a contract instrument maintenance company and autocalibrated between midnight and 1:00 AM on a daily basis. Temperature (°C) and relative humidity (%) were measured using a Met One unit (Met One Instruments Inc., Grants Pass, Oregon) at the same location. All minute-to-minute environmental observations were processed into 5-minute and 30-minute averages corresponding to concurrent 5-minute HRV and 30-minute blood pressure measurements for further analysis.

Concurrent with fixed-location air monitoring, we conducted personal exposure assessment for each subject, using portable samplers measuring real-time $PM_{2.5}$ concentrations with a DustTrak instrument (model 8520; TSI Inc., Shoreview, Minnesota) and real-time concentrations of carbon monoxide, carbon dioxide, temperature, and relative humidity with a QTrak instrument (model 7565; TSI Inc.). Integrated personal samples of $PM_{2.5}$ mass were concurrently collected using an impactor (PEM200; MSP Corporation, Shoreview, Minnesota) for daily calibration of the average DustTrak response and for $PM_{2.5}$ mass composition analyses. High correlations between ambient and personal measurements of $PM_{2.5}$, using DustTrak monitors, were observed ($r \approx 0.95$; data not shown).

Statistical analysis

The initial descriptive statistical analysis was conducted for all 5-minute HRV and 30-minute blood pressure variables and environmental measurements. Data for all HRV variables were logarithmically transformed because of right-skewed distributions. Collinearity of pollutants was examined using Spearman correlation analyses. Linear mixed-model analysis was used to estimate the association between ambient pollution and repeatedly measured outcomes.

We first built basic models without including pollutants. Subjects' age, gender, and body mass index were included in the basic models. Temperature and relative humidity were modeled with linear, squared, and cubic terms controlling for meteorologic effects on autonomic and vascular function. Day of the week and visit were included as categorical variables controlling for environmental changes over time. Because our elderly subjects may have engaged in more quiet and sedentary activities during the morning and night and may have become more active during the late morning to early afternoon, we chose to include centered time and time-squared terms controlling for the quadratic activity pattern of our subjects. The first-order autoregressive model was chosen to account for temporal autocorrelation of outcome variables on the basis of minimizing Akaike's Information Criterion.

Single-pollutant models were then developed by including pollutant variables to examine the association between various autonomic and vascular outcomes and exposure to air pollution during prior hours. We used residual diagnostics to investigate deviations from standard linear mixed-model assumptions, the presence of influential observations, and subject clusters. We further explored whether the association could be partially explained by certain blood markers by including high-sensitivity C-reactive protein, fibrinogen, and von Willebrand factor in the models. Results were insensitive to inclusion of any of the blood markers, so they were not considered further.

To evaluate potential interaction by systemic inflammation, overweight, diabetes, and gender, we conducted stratified analysis for SDNN to obtain the effect estimates for each air pollutant and compared effect differences between strata for statistical significance ($P < 0.05$). The stratification cutpoint for systemic inflammation status was determined by the C-reactive protein value at the 90th percentile, 1.76 mg/L. Stratification by overweight status was conducted for subjects with a body mass index less than 25 (normal weight; $n = 24$) and subjects with a body mass index greater than or equal to 25 ($n = 16$; only 1 of these subjects had a body mass index greater than or equal to 30). The interactions were examined with a Z test.

To assess whether the associations observed in single-pollutant models were attributable to other pollutants from the same source or different sources, we then examined the effects of 2-pollutant mixtures with the joint exposure contrasts. Further, we derived exposure-response curves of HRV reduction versus lagged air pollution exposures to examine the linear association assumption of mixed models.

All estimates are presented as percent changes (with 95% confidence intervals) associated with interquartile-range (IQR) increases in pollutant concentrations. All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Eligible study subjects included 40 CVD patients, who had repeated measurements taken on multiple outcomes of interest (Table 1). Subjects were on average 65.6 years of age (standard deviation, 5.8); 60% were female, 40% were overweight, and 22.5% had diagnosed diabetes. The correlations among log-transformed HRV indices were modest (coefficients ranged from 0.54 to 0.82; data not shown).

Ambient air quality changes before and during the Olympics

We observed significant reductions in mean air pollutant concentrations during the 2008 Olympic period (visit 4), when air pollution control measures were in place (Table 2), as compared with the pre-Olympic period (visit 3): $PM_{2.5}$ levels decreased by 28%, black carbon levels decreased by 27.6%, and reductions of 12%–47% were observed for levels of gaseous pollutants. Compared with visit 2, conducted in 2007, the pollution level reductions from visit 2 to visit 4 were also significant but mostly of smaller magnitude. Among the pollutants, correlations were highest between $PM_{2.5}$ and the traffic markers black carbon and carbon monoxide (coefficients were 0.57 and 0.60, respectively) and between black carbon, nitrogen dioxide,

Table 1. Demographic Characteristics and Cardiac Outcomes for 40 Cardiovascular Disease Subjects Followed Before and During the Summer Olympics in Beijing, China, 2007–2008

Characteristic	No.	%	Mean (SD)
Age, years			65.6 (5.8)
Body mass index[a]			24 (4.0)
Cardiac outcome measure[b]			
High-sensitivity C-reactive protein, mg/L			1.05 (1.83)
Fibrinogen, g/L			3.10 (1.07)
von Willebrand factor, μmol/L			154.0 (45.0)
Heart rate, beats/minute			64.2 (16.8)
SDNN, msec			44.5 (27.0)
r-MSSD, msec			26.5 (20.1)
Low frequency, ms^2			338.3 (602.1)
High frequency, ms^2			162.2 (296.9)
Gender			
Male	16	40	
Female	24	60	
Primary cardiovascular diagnosis			
Coronary artery disease	6	15	
Angina pectoris	18	45	
Arrhythmia	16	40	
High-sensitivity C-reactive protein, mg/L			
>1.76	6	15	
≤1.76	34	85	
Diabetic status			
Diabetes	9	22.5	
No diabetes	31	77.5	
Overweight status (body mass index ≥25)			
≥25 (overweight)			16 (40)
<25 (normal weight)			24 (60)

Abbreviations: r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals; SD, standard deviation; SDNN, standard deviation of the normal-to-normal intervals.

[a] Weight (kg)/height $(m)^2$.

[b] Mean values for outcome measures were calculated on the basis of the total number of measurements, ignoring the intrasubject correlation from repeated measures.

and carbon monoxide (coefficients ranged from 0.53 to 0.73), whereas sulfur dioxide and ozone were not correlated with other pollutants or were negatively correlated with other pollutants (Table 3).

Association between air pollution and autonomic and vascular dysfunction

Significant inverse associations between air pollution and the HRV index were observed in cumulative exposure assessment (Table 4). In association with an IQR increase of 48.4 μg/m^3 in preceding 12-hour average exposure to $PM_{2.5}$, we observed the greatest reductions for SDNN (4.7%, 95% confidence interval (CI): 1.7, 7.6) and low frequency (14.2%, 95% CI: 6.8, 21.0). For $PM_{2.5}$ exposure, the reductions in the frequency-domain variables low frequency and high frequency were 2- to 3-fold greater than those in time-domain variables across all of the time periods examined. Per an IQR increase of 2.02 μg/m^3 in preceding 4-hour exposure to black carbon, the decreases in SDNN (4.2%, 95% CI: 1.8, 6.6) and low frequency (10.5%, 95% CI: 4.4, 16.3) were of similar magnitude and in the same direction as $PM_{2.5}$ exposure associated with SDNN and low frequency reductions. We observed some negative effects of nitrogen dioxide and carbon monoxide on HRV reductions associated within hours of exposure, but not for sulfur dioxide and ozone overall.

Both systolic blood pressure and diastolic blood pressure were found to be significantly increased within minutes to hours of exposure to $PM_{2.5}$ (Table 5). We observed 2.2- to 8.5-mm Hg increases in blood pressure with an IQR increase of 56.9 μg/m^3 in prior 30-minute exposure to $PM_{2.5}$. There was a significant increase of 3.1 mm Hg (95% CI: 0.4, 5.7) in diastolic blood pressure associated with prior 12-hour exposure to black carbon. We also observed significant blood pressure increases of up to 6.7 mm Hg with prior 12-hour exposure to carbon monoxide.

To assess whether the observed effects of $PM_{2.5}$ on HRV decline were attributable to other pollutants, we compared the effects estimated in single-pollutant models of $PM_{2.5}$ exposure alone with those estimated in 2-pollutant models including black carbon, nitrogen dioxide, sulfur dioxide, carbon monoxide, and ozone, respectively, as the second variable (Figure 1). After adjustment for the other pollutants, the overall $PM_{2.5}$ effects remained significant, with some apparent confounding effects from black carbon, nitrogen dioxide, and carbon monoxide on the $PM_{2.5}$-HRV association.

Mixed-model analyses with restricted spline functions confirmed the linear relation between HRV reduction and increased exposures to $PM_{2.5}$, black carbon, nitrogen dioxide, and carbon monoxide (data not shown). We observed similar exposure-response patterns for SDNN, rMSSD, low frequency, and high frequency, with prior 1-, 4-, and 12-hour averaged exposure to air pollution.

Interactions of systemic inflammation, overweight, and gender

We examined possible interaction of systemic inflammation, overweight, diabetes, and gender for the stratified subgroups (Table 6). Within the subgroups, greater HRV reductions were observed with exposure to $PM_{2.5}$, black carbon, and nitrogen dioxide among obese subjects and females. In association with IQR increases of 51.8 μg/m^3 and 2.02 μg/m^3 in preceding 4-hour average exposures to $PM_{2.5}$ and black carbon, the decreases in SDNN were significant (9.3% (95% CI: 5.4, 13.0) and 8.8% (95% CI: 4.9, 12.6), respectively) for overweight subjects (body mass index ≥25) but not significant in subjects with normal body weight. For females, significant decreases in SDNN

Table 2. Summary Statistics (Mean Values) for Hourly Ambient Air Pollution Concentrations and Meteorologic Parameters Measured Before and During the Summer Olympics in Beijing, China, 2007–2008

	Summer 2007		Summer 2008		Change in Pollution Level, %	
	Visit 1 (July 1–9)	Visit 2 (August 15–25)	Visit 3 (July 4–11)	Visit 4 (August 23–29)	Visit 4 vs. Visit 3	Visit 4 vs. Visit 2
$PM_{2.5}$, μg/m^3	112.5 (61.3)[a]	78.3 (50.6)	89.2 (53.9)	64.2 (39.9)	−28.0	−18.0
Black carbon, μg/m^3		4.0 (2.0)	2.9 (1.5)	2.1 (1.1)	−27.6	−47.5
Sulfur dioxide, ppb	2.4 (2.8)	8.2 (4.7)	11.2 (9.1)	5.9 (4.0)	−47.3	−28.0
Nitrogen dioxide, ppb	33.8 (14.3)	26.3 (11.2)	29.2 (9.0)	22.9 (11.6)	−21.6	−12.9
Ozone[b], ppb	51.8 (27.7)	57.8 (23.4)	60.5 (39.1)	53.4 (17.9)	−11.7	−7.6
Carbon monoxide, ppm	2.6 (1.6)	1.3 (0.6)	1.1 (0.4)	0.9 (0.3)	−18.2	−30.1
Temperature, °C	29.7 (3.8)	30.2 (2.9)	30.3 (4.4)	27.7 (5.3)		
Relative humidity, %	60.7 (15.1)	54.2 (15.6)	63.0 (19.6)	65.4 (22.5)		

Abbreviation: $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm.
[a] Numbers in parentheses, standard deviation.
[b] 10-hour maximum values for hourly ozone were used.

(4.8% (95% CI: 2.4, 7.2) and 9.3% (95% CI: 6.8, 11.7)) were observed as compared with nonsignificant declines in males.

In the 6 subjects with C-reactive protein values in the upper 10th percentile range, we also observed significant reductions in HRV with increased exposure to nitrogen dioxide and carbon monoxide and greater reduction in exposure to $PM_{2.5}$ and black carbon. However, the diabetic subjects were found to be less susceptible to air pollution exposure.

DISCUSSION

CVD is now the leading cause of death among Chinese adults aged 40 years or older, accounting for approximately 40% of total mortality in China (33). Although the increased cardiovascular mortality risks associated with air pollution observed in the Chinese population might be similar in magnitude, per the amount of pollution, to the risks found in other parts of the world (34, 35), few studies have assessed cardiovascular morbidity or subclinical variables in relation to ambient pollution exposure among vulnerable urban residents in China.

In this 2-year longitudinal follow-up of a group of CVD patients, we observed significant declines in levels of most pollutants (except ozone) during the 2008 Summer Olympic period, when air pollution reductions efforts were in place. Over the exposure range measured during the study period, we observed significant HRV reduction in CVD patients associated with short-term exposure to air pollution, and the largest effects were found for the particulate measures $PM_{2.5}$ and black carbon. The associations were found to be stronger for females, overweight persons, and those with increased systemic inflammation. We also observed some significant increases in blood pressure with acute exposure to $PM_{2.5}$, black carbon, and carbon monoxide. Our results are largely consistent with existing literature on the short-term effects of PM on autonomic and vascular function (1, 17, 26, 36). Our study also adds to the cumulative evidence that exposure to traffic-related pollutants such as black carbon, nitrogen dioxide, and carbon monoxide may alter cardiovascular function (23, 37, 38).

Table 3. Spearman Correlation Coefficients for Correlations Between Daily Air Pollutant Concentrations and Meteorologic Parameters Measured Before and During the Summer Olympics in Beijing, China, 2007–2008

	$PM_{2.5}$	Black Carbon	Nitrogen Dioxide	Sulfur Dioxide	Carbon Monoxide	Ozone	Temperature	Relative Humidity
$PM_{2.5}$	1.00	0.57	0.34	−0.01	0.60	−0.06	−0.02	0.32
Black carbon		1.00	0.61	0.09	0.73	−0.46	−0.24	0.36
Nitrogen dioxide			1.00	−0.03	0.53	−0.43	−0.20	0.28
Sulfur dioxide				1.00	−0.04	−0.07	−0.03	−0.06
Carbon monoxide					1.00	−0.19	−0.03	0.27
Ozone						1.00	0.65	−0.55
Temperature							1.00	−0.86
Relative humidity								1.00

Abbreviation: $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm.

Table 4. Adjusted Percent Change in Heart Rate Variability Indices Per Interquartile-Range Increase in Prior 1-Hour, 4-Hour, and 12-Hour Moving Average Exposure to Ambient Pollutants in Single-Pollutant, Mixed-Effects Models[a], Beijing, China, 2007–2008

Heart Rate Variability Index	$PM_{2.5}$		Black Carbon		Nitrogen Dioxide		Sulfur Dioxide		Carbon Monoxide		Ozone	
	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI
SDNN												
1-hour	−3.5	−5.6, −1.4	−3.3	−5.7, −0.8	−1.9	−3.4, −0.3	0.5	−0.6, 1.6	−0.3	−2.5, 2.0	−1.1	−3.1, 0.8
4-hour	−4.2	−6.4, −1.9	−4.2	−6.6, −1.8	−3.9	−5.7, −2.2	0.6	−0.4, 1.5	−2.7	−5.3, 0.4	−0.5	−2.5, 1.5
12-hour	−4.7	−7.6, −1.7	−4.2	−7.5, −0.8	−3.6	−5.5, −1.6	−0.8	−2.5, 0.9	−2.2	−6.2, 2.1	0.8	−1.8, 3.5
r-MSSD												
1-hour	−4.2	−7.5, −0.8	−4.2	−8.4, 0.1	1.4	−1.1, 3.9	1.4	0.0, 2.8	−2.5	−5.6, 0.5	−2.6	−5.6, 0.5
4-hour	−5.5	−9.4, −1.5	−4.1	−8.4, 0.4	−2.2	−5.7, 1.5	1.0	−0.5, 2.5	−4.0	−7.5, −0.4	−4.0	−7.5, −0.4
12-hour	−10.7	−15.5, −5.7	−5.5	−11.8, 1.3	−2.2	−6.1, 2.0	2.6	−1.1, 6.5	−3.0	−7.6, 1.9	−3.0	−7.6, 1.9
Low frequency												
1-hour	−8.8	−14.0, −3.4	−9.1	−15.0, −2.7	−5.4	−9.3, −1.4	1.1	−1.7, 4.0	0.2	−4.8, 5.5	0.2	−4.8, 5.5
4-hour	−9.9	−15.4, −4.1	−10.5	−16.3, −4.4	−8.9	−13.2, −4.3	0.7	−1.8, 3.2	−2.4	−7.4, 2.9	−2.4	−7.4, 2.9
12-hour	−14.2	−21.0, −6.8	−9.3	−17.6, −0.2	−7.9	−12.8, −2.8	−4.8	−9.1, −0.3	−6.6	−12.8, 0.0	−6.6	−12.8, 0.0
High frequency												
1-hour	−9.3	−15.2, −2.9	−12.1	−19.1, −4.6	−3.5	−8.2, 1.4	2.5	−0.5, 5.7	−2.3	−8.1, 3.9	−2.3	−8.1, 3.9
4-hour	−8.4	−15.2, −1.0	−9.8	−17.0, −2.1	−5.1	−11.0, 1.3	3.4	0.3, 6.5	−6.0	−12.1, 0.5	−6.0	−12.1, 0.5
12-hour	−16.3	−24.3, −7.5	−4.0	−15.1, 8.6	−3.7	−10.4, 3.5	4.1	−2.2, 10.9	−8.7	−16.4, -0.2	−8.7	−16.4, −0.2

Abbreviations: CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals; SDNN, standard deviation of the normal-to-normal intervals.
[a] Results were adjusted for age, body mass index, gender, time of day, day of the week, visit, temperature, and relative humidity.

Constituents of ambient particulates from traffic emissions were found to be more toxic than those from other sources (14, 39). Recent analyses have provided evidence that exposure to the ambient particulates $PM_{2.5}$ and black carbon can mediate autonomic dysfunction (19, 38). In the current study, the observed time course, direction, and magnitude of HRV and blood pressure changes in association with exposure to $PM_{2.5}$, black carbon, and other pollutants support the biologic plausibility of a causal relation between particulate air pollution and autonomic and vascular dysfunction: Following inhalation of ambient particulates, the toxic constituents in ambient particulates may have direct and immediate effects on blood and cardiovascular systems through pulmonary receptors (40). Toxic

Table 5. Adjusted Change in Blood Pressure Indices per Interquartile-Range Increase in Prior 30-Minute, 2-Hour, 12-Hour, and 24-Hour Moving Average Exposure to Ambient Pollutants in Single-Pollutant, Mixed-Effects Models[a], Beijing, China, 2008

	$PM_{2.5}$		Black Carbon		Nitrogen Dioxide		Sulfur Dioxide`		Carbon Monoxide		Ozone	
	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI
Systolic blood pressure												
30-minute	5.7	2.9, 8.5	0.4	−1.8, 2.5	1.8	−0.5, 4.0	−0.9	−2.0, 0.2	−0.2	−2.0, 1.7	−0.3	−1.3, 0.8
2-hour	3.9	0.0, 7.7	−1.1	−3.1, 1.1	0.0	−2.6, 2.6	−0.4	−1.7, 0.8	0.5	−2.1, 3.2	−1.6	−3.4, 0.2
12-hour	5.3	−1.3, 11.8	2.2	−1.0, 5.5	0.7	−3.2, 4.6	−0.4	−2.5, 1.7	3.3	0.0, 6.7	−0.2	−2.5, 2.1
24-hour	−1.2	−3.6, 1.2	−0.5	−5.4, 4.4	−0.8	−6.6, 5.0	−0.6	−2.2, 0.9	-0.4	−2.9, 2.1	1.5	−0.2, 3.2
Diastolic blood pressure												
30-minute	4.6	2.2, 7.0	−0.2	−2.0, 1.6	1.1	-0.9, 3.0	−0.3	−1.2, 0.6	0.3	−1.2, 1.8	−0.3	−1.2, 0.6
2-hour	1.9	−1.3, 5.0	−1.4	−3.2, 0.3	-0.1	−2.3, 2.1	0.0	−1.1, 1.1	0.4	−1.8, 2.5	−1.1	−2.7, 0.4
12-hour	5.2	−0.1, 10.5	3.1	0.4, 5.7	1.2	−2.1, 4.5	0.3	−1.3, 2.0	3.5	0.9, 6.1	−0.5	−2.5, 1.4
24-hour	−0.7	−2.8, 1.3	1.8	−2.2, 5.8	1.5	−3.4, 6.4	0.1	−1.2, 1.3	0.6	−1.4, 2.6	1.0	−0.5, 2.4

Abbreviations: CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm.
[a] Results were adjusted for age, body mass index, gender, time of day, day of the week, visit, temperature, and relative humidity.

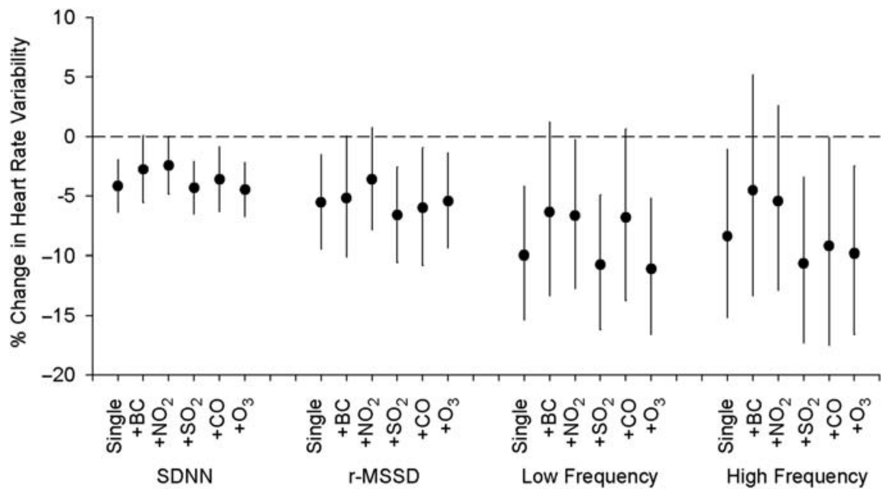

Figure 1. Adjusted percent change in heart rate variability indices per interquartile-range increase in prior 4-hour moving average exposure to $PM_{2.5}$ (particulate matter with an aerodynamic diameter less than 2.5 μm) in single- and 2-pollutant, mixed-effects models, Beijing, China, 2007–2008. Models were adjusted for age, body mass index, gender, time of day, day of the week, visit, temperature, and relative humidity. SDNN, standard deviation of the normal-to-normal intervals; r-MSSD, square root of the mean squared difference between adjacent normal-to-normal intervals; BC, black carbon; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; CO, carbon monoxide; O_3, ozone. Bars, 95% confidence interval.

substances present in $PM_{2.5}$ (i.e., black carbon, primary and secondary aerosols, metals) and gaseous pollutants (e.g., carbon monoxide, nitrogen dioxide) can further cross airway epithelium, reaching the vasculature, and induce the production of proinflammatory cytokines and reactive oxygen species (41, 42). The effects of those agents might subsequently lead to hypertensive responses and changes in autonomic cardiac control (40, 43).

In this study, we observed greater declines in HRV in the subgroups of overweight patients and those with increased systemic inflammation, in association with exposure to ambient particulate pollution. Given that a number of clinical and epidemiologic studies have found that overweight and systemic inflammation are important in modifying air pollution PM-associated CVD risk (21, 36, 44– 46), our findings highlight the importance of examining risk factors that could potentially modify cardiovascular responses to air pollution exposure.

Previous research suggested that gender could modify the associations between air pollution and CVD risk; however, the findings are heterogeneous (47–49). In the Chinese population, women have been found to be more susceptible to the effects of air pollution exposure (50). Although we observed larger HRV declines in association with exposures to black carbon and gaseous pollutants among female CVD patients, the mechanisms for gender-specific interaction are not yet clear and deserve further investigation.

Recent studies have also suggested that the metabolic abnormalities and neuropathophysiologic activities underlying the diabetic state may confer PM-associated autonomic and cardiovascular dysfunction. Some studies found that associations between PM exposure and autonomic dysfunction are stronger among persons with type 2 diabetes (18, 36, 45), whereas others suggested that subjects with individual components of the metabolic syndrome, such as abdominal overweight, type 2 diabetes, hypertension, and dyslipidemia, might be at higher risk of PM-associated cardiovascular dysfunction (26, 27). However, the diagnosed diabetic subjects appeared less susceptible to air pollution exposure in our analyses. Lack of individual data on the metabolic syndrome might have limited our capability for further examining the biologic plausibility of the metabolic syndrome in modifying $PM_{2.5}$-associated cardiovascular dysfunction. Nevertheless, future research is needed to determine how underlying metabolic mechanisms may impart differential autonomic responses between metabolic syndrome groups.

Compared with most of the published studies examining acute effects of ambient particulate pollution on short-term cardiovascular biomarker variations (in each 5-minute ECG and 30-minute blood pressure segment), our study design had the following strengths. First, it took advantage of a once-in-a-lifetime natural experiment in which the Chinese government mandated temporary closures or relocations of industry and reductions in motor vehicle use before and during the 2008 Beijing Summer Olympics. Exposure measurements taken before and during the Olympics clearly showed that there were major reductions in air pollutant concentrations. Second, there was sufficient time to establish a suitable group of CVD subjects who could be followed during this major change in ambient exposures. The collection of data from four 24-hour ECG sessions and two 24-hour blood pressure sessions over an extended 2-year follow-up period allowed us to assess the acute effects of measured air pollution on autonomic and vascular function under contrasting exposure conditions. Lastly, the large variations in levels of the ambient pollutants during the study period provided unique contrasts in ambient pollution exposures with which to examine the exposure-response

Table 6. Interactions of Systemic Inflammation, Overweight, Diabetes, and Gender With Adjusted Percent Change in SDNN per Interquartile-Range Increase in Prior 4-Hour Moving Average Exposure to Air Pollution in Single-Pollutant, Mixed-Effects Models[a], Beijing, China, 2007–2008

Interaction Variable	$PM_{2.5}$		Black Carbon		Nitrogen Dioxide		Sulfur Dioxide		Carbon Monoxide		Ozone	
	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI	Effect	95% CI
High-sensitivity C-reactive protein, mg/L												
>1.76	−3.2	−7.2, 1.1	−2.5	−6.8, 2.0	−15.5	−19.3, −11.5	19.3	9.6, 29.8	−8.2	−15.3, −0.4	7.3	2.2, 12.7
≤1.76	−1.6	−4.0, 1.0	−0.3	−2.9, 2.4	−1.4	−3.3, 1.0	0.1	−0.8, 1.0	−1.7	−4.9, 1.5	−2.0	−4.0, 0.1
P value[b]	0.51		0.44		<0.001		<0.001		0.13		<0.001	
Overweight status (body mass index[c] ≥25)												
≥25 (overweight)	−9.3	−13.0, −5.4	−8.8	−12.6, −4.9	−4.9	−7.7, −2.0	0.8	−0.4, 2.0	−2.3	−7.2, 2.8	0.7	−2.6, 4.2
<25 (normal weight)	1.4	−1.0, 3.9	0.9	−1.7, 3.7	−3.7	−5.7, −1.5	−2.1	−3.9, −0.2	3.6	−0.1, 7.5	−2.2	−4.3, 0.0
P value	<0.001		<0.001		0.49		0.01		0.07		0.16	
Diabetic status												
Diabetes	1.2	−2.1, 4.6	1.5	−2.0, 5.2	3.0	0.3, 5.7	3.9	2.3, 5.5	2.5	−2.3, 7.4	−7.2	−9.8, −4.5
No diabetes	−5.1	−7.6, −2.5	−5.1	−7.7, −2.3	−6.0	−7.9, −3.9	−0.1	−1.2, 0.9	−1.2	−4.8, 2.6	1.2	−1.1, 3.6
P value	0.003		0.003		<0.001		<0.001		0.24		<0.001	
Gender												
Female	−4.8	−7.2, −2.4	−9.3	−11.7, −6.8	−8.2	−10.1, −6.3	−0.8	−1.8, 0.3	−10.4	−13.6, −7.2	1.6	−0.7, 4.0
Male	−2.7	−6.7, 1.52	1.6	−2.7, 6.0	0.6	−2.4, 3.7	2.6	1.0, 4.4	7.5	1.9, 13.4	−10.3	−18.0, −1.9
P value	0.38		<0.001		<0.001		<0.001		<0.001		0.01	

Abbreviations: CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than 2.5 μm; SDNN, standard deviation of the normal-to-normal intervals.

[a] Results were adjusted for age, body mass index, gender, time of day, day of the week, visit, temperature, and relative humidity.

[b] *P* for difference between subgroups, by *Z* test.

[c] Weight (kg)/height (m)^2.

relations over a wide range of pollution levels. The linear relations observed between HRV reduction and exposure to $PM_{2.5}$ and traffic pollutants extend our knowledge of the CVD risks of ambient pollution exposure at higher levels and a wider range than would normally occur in the developed world.

Despite advantages of this natural experimental study, several limitations should also be noted in interpreting our findings. First, use of nearby fixed-location monitoring data and lack of information on personal exposure to ambient pollution may have resulted in potential exposure misclassification errors and may have biased the effect estimates toward the null. Second, we did not observe a consistently negative association pattern across pollutants, suggesting the possibility of differential measurement errors between pollutants. If the monitoring instrument error were independent of the true ambient pollution level, such differential measurement error would be expected to attenuate the effect estimates and may have biased some results. Lastly, we did not consider exposure from indoor sources, given that our subjects tended to spend a large portion of their time indoors. However, other studies have suggested that daily population average concentrations of pollutants derived from indoor sources are approximately independent of ambient pollution levels (51). When this is true, failure to measure indoor sources will not introduce further bias in the estimated effects of ambient pollutants (52).

In summary, our study documents acute effects of exposure to air pollution on autonomic and vascular dysfunction among CVD subjects, over an extended follow-up period. Our results suggest effects of interactions between overweight, systemic inflammation, and gender on air pollution-attributable cardiovascular dysfunction among populations at risk of CVD.

ACKNOWLEDGMENTS

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This study was supported by the Chinese National Science Foundation (grant 20637020), the China State Ministry of Environmental Protection (grant 201009032), and the Chinese Ministry of Science and Technology (grant 2008AA062503). Dr. Lu was partially supported by grant P30ES005022-21 from the US National Institute of Environmental Health Sciences.

The authors thank Ai Wang, Ya Chen, Dr. Yuping Jia, Dr. Liwen Zhang, Yuming Guo, and Hong Cheng for assisting with data collection. The authors also thank Dr. Thomas J. Smith of the Harvard School of Public Health for his comments.

Conflict of interest: none declared.

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