



Association of Higher Levels of Ambient Criteria Pollutants with Impaired Cardiac Autonomic Control: A Population-based Study

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An association between air pollution and increased cardiovascular disease (CVD) mortality has been reported, but underlying mechanisms are unknown. The authors examined short-term associations between ambient pollutants (particulate matter less than 10 μm in aerodynamic diameter (PM_{10}), ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide) and cardiac autonomic control using data from the fourth cohort examination (1996–1998) of the population-based Atherosclerosis Risk in Communities Study. For each participant, the authors calculated PM_{10} and gaseous pollutant exposures as 24-hour averages and ozone exposure as an 8-hour average 1 day prior to the randomly allocated examination date. They calculated 5-minute heart rate variability indices and used logarithmically transformed data on high-frequency (0.15–0.40 Hz) and low-frequency (0.04–0.15 Hz) power, standard deviation of normal R-R intervals, and mean heart rate. Linear regression was used to adjust for CVD risk factors and demographic, socioeconomic, and meteorologic variables. Regression coefficients for a one-standard-deviation increase in PM_{10} (11.5 $\mu\text{g}/\text{m}^3$) were -0.06 ms^2 (standard error (SE), 0.018), -1.03 ms (SE, 0.31), and 0.32 beats/minute (SE, 0.158) for log-transformed high-frequency power, standard deviation of normal R-R intervals, and heart rate, respectively. Similar results were found for gaseous pollutants. These cross-sectional findings suggest that higher ambient pollutant concentrations are associated with lower cardiac autonomic control, especially among persons with existing CVD, and highlight a putative mechanism through which air pollution is associated with CVD.

air pollution; cardiovascular diseases; heart rate

Abbreviations: AIRS, Aerometric Information Retrieval System; ARIC, Atherosclerosis Risk in Communities; HRV, heart rate variability; PM_{10} , particulate matter less than 10 μm in aerodynamic diameter; ppm, parts per million; SD, standard deviation.

A number of epidemiologic studies have linked short-term changes in fine particulate air pollution with changes in daily morbidity and mortality from cardiopulmonary diseases (1–5). Effects of gaseous criteria pollutants (including ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide) on cardiovascular disease risk have also been reported in some studies (6–8). The underlying biologic mechanisms linking particulate air pollution with cardiopulmonary disease continue to be a subject of research. Several studies in selected human samples or animal models have suggested that higher levels of ambient particles are associated with

reduced heart rate variability (HRV) (9–13), a noninvasive measure of cardiac autonomic control that is predictive of coronary heart disease incidence and mortality in population-based studies (14, 15). The mechanisms linking ambient particulate pollution and reduced HRV are not fully understood. Several hypotheses have been proposed (11, 16–18), including direct disruption of cardiac autonomic control by inhaled particulates via sympathetic stress response and imbalance of cardiac autonomic control caused indirectly through fine particles' stimulating the release of inflammatory cytokines in the lungs and into the circulation. Because

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few studies have reported on the association between air pollutants and cardiac autonomic control in population-based samples, we investigated the short-term (1- to 3-day) effects of ambient criteria pollutants (particulate matter less than 10 μm in aerodynamic diameter (PM_{10}), ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide) on cardiac autonomic control in a population-based sample. Our operational hypothesis was that higher levels of such pollutants are associated with lower levels of various indices of HRV and with higher heart rate.

MATERIALS AND METHODS

Source population

Study subjects were participants in the Atherosclerosis Risk in Communities (ARIC) Study. The design and objectives of the ARIC Study have been reported in detail elsewhere (19). Briefly, the ARIC Study is a population-based longitudinal study of atherosclerosis and its sequelae sponsored by the National Heart, Lung, and Blood Institute. The ARIC cohort was selected as a probability sample of 15,792 men and women aged 45–64 years at entry from four US study centers, three of which enumerated and enrolled populations reflective of their respective ethnic compositions (Washington County, Maryland; Forsyth County, North Carolina; and selected suburbs of Minneapolis, Minnesota). The fourth quarter of the ARIC cohort was sampled exclusively from Black residents of Jackson, Mississippi. Eligible participants were interviewed at home and then invited to undergo a baseline clinical examination (conducted in 1987–1989). The date for the baseline clinical examination was assigned at random. The cohort has undergone three follow-up clinical examinations every 3 years since the baseline clinical examination, and cohort reexaminations are scheduled as close to the baseline examination anniversary as possible. Of the 15,792 cohort members inducted during the baseline survey, 11,656 participated in the fourth cohort examination (1996–1998).

The HRV data collected during the fourth cohort examination were used in combination with the air pollution data gathered during the same period for this study (9 years after study entry). Since there was no air quality monitor in Washington County, Maryland, participants from that center ($n = 3,126$) were excluded from this study. Additionally, because of small numbers, persons of ethnicities other than European or African American ($n = 31$) were excluded. Because ambient pollutant levels were not measured daily in all field centers, nitrogen dioxide data for Jackson, Mississippi, were not available for the entire study period, and a small number of persons had no HRV data ($n = 58$), the effective sample sizes for this report were 4,899, 5,431, 6,232, 4,390, and 6,784 for analyses involving PM_{10} , ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide, respectively.

Air pollution data

We obtained data on levels of criteria pollutants at the ARIC Study field centers for 1996–1998 from the Environmental Protection Agency's Aerometric Information

Retrieval System (AIRS) database. AIRS is a computer-based repository of information on airborne pollution in the United States. The AIRS system is administered by the Environmental Protection Agency's Office of Air Quality Planning and Standards. The AIRS database contains measurements of ambient concentrations of air pollutants from thousands of monitoring stations operated by the Environmental Protection Agency or by state or local agencies. These monitoring sites conform to uniform criteria of site selection, instrumentation, and quality assurance. The directly measured daily ambient air pollution data are sent to the AIRS system for storage and analysis. The AIRS database also contains descriptive information about each monitoring station, including its location and operator (20–22).

The PM_{10} data obtained from the AIRS database were monitor-specific daily 24-hour averages. From these monitor-specific 24-hour averages, we calculated a county-specific daily average PM_{10} value by averaging all available PM_{10} measures from all operating monitors within a county on any calendar date. The gaseous pollutant data obtained from the AIRS database were hourly monitor-specific measures. From these hourly monitor-specific measures, we calculated monitor-specific daily concentrations as either the 8-hour average (10 a.m.–6 p.m.) for ozone or 24-hour averages for carbon monoxide, sulfur dioxide, and nitrogen dioxide. Then, from these monitor-specific daily concentrations, we calculated county-specific daily average concentrations of each gaseous pollutant by averaging all available monitor-specific daily concentrations from all operating monitors within a county on any calendar date.

From the National Weather Center, we obtained data on relative humidity (percentage), temperature (degrees Kelvin), and sky cloud cover (fraction of the celestial dome covered by clouds on a scale of 0 to 10, where 0 indicates a very clear sky and 10 indicates a totally obscured sky), with the calendar date and county/state identifiable. In this report, "daily meteorologic variables" were defined as the relative humidity, temperature, and sky cloud cover in the county at 2:00 p.m.

We linked the individual-level cardiovascular disease risk factor data and HRV data with the county-specific daily average air pollution data and daily meteorologic data, according to the clinical examination date and the state and county of each participant's residence. Thus, the individual-residence-level air pollution and meteorologic parameters 1, 2, and 3 days prior to clinical examination (HRV measurement date) were combined with individual-level information on cardiovascular disease risk factors and HRV data to form the analytical database.

HRV data

Study participants were asked to fast for 12 hours and abstain from smoking prior to examination. Following venipuncture, a light snack (with caffeine-free beverages) was provided, followed within 1 hour by the HRV data collection. Participants had three electrocardiographic electrodes placed on the epigastrium. Resting, supine, 5-minute beat-to-beat R-R interval data were collected between 8:30 a.m. and 12:30 p.m. after the participant had rested comfortably for 15

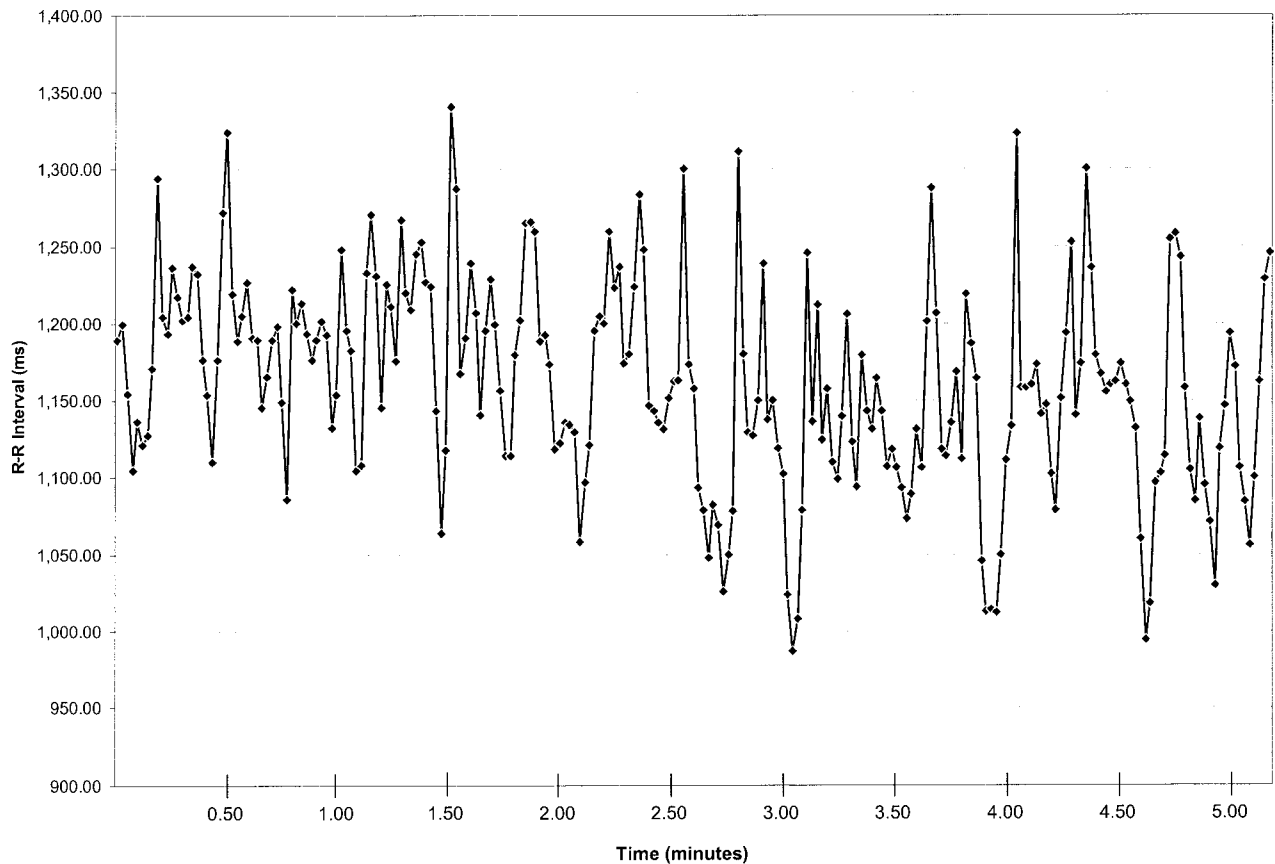


FIGURE 1. An example of 5-minute time domain heart rate data.

minutes in the supine position in a quiet, semidark room with a constant temperature of 24°C. A dedicated computer and specialized software (PREDICT II HRVECG; Arrhythmia Research Technology, Inc., Austin, Texas) were used for continuous detection and recording of the electrocardiographic R waves and R-R intervals, at a sampling frequency of 1,000 Hz (9).

Measurement of beat-to-beat HRV for assessment of cardiac autonomic control was performed on all study participants in the ARIC HRV reading center by trained and certified technicians. Overall, 95 percent of the records were "artifact-free," defined as having fewer than 1 percent artifactual QRS complexes in the entire record. Details on the data processing and analysis have been published previously (9, 23). Briefly, 5-minute raw heart rate data were first subjected to a filter program for identification and removal of any artifacts under visual control by a single, trained operator. A plot of the smoothed version of the heart rate data over time was then superimposed on the plot of the raw data, to confirm a good fit of any segment of smoothed data. The procedure could be repeated until a satisfactory plot was obtained. After the above smoothing, each R wave in a record was labeled as either a normal R wave or an artifactual R wave. These labeled R-R interval data were then

analyzed by means of PREDICT II HRVECG for further processing and power spectral analysis and time domain analysis. During the data processing phase, a data-editing program was used to remove any R-R intervals labeled as artifactual from the HRV analysis. Segments with such artifacts were imputed, and R-R intervals in these segments were recalculated using an algorithm developed by Arrhythmia Research Technology, Inc. Fast Fourier transformation was performed for estimation of the power spectral density. An example of 5-minute time domain heart rate data is shown in figure 1, and an example of a power spectral density curve following fast Fourier transformation of the time domain heart rate data for one participant is shown in figure 2. From the power spectral density curve, the high-frequency spectral power (0.15–0.40 Hz) and low-frequency spectral power (0.04–0.15 Hz) were calculated. Following the recommendation of the Task Force on HRV Research (24), high-frequency power and low-frequency power were defined as the power (area) between the 0.15- and 0.40-Hz bands and the 0.04- and 0.15-Hz bands under the power spectral density curve, respectively. The standard deviation (SD) of all normal R-R intervals and heart rate were calculated from the time domain data after replacement of artifacts.

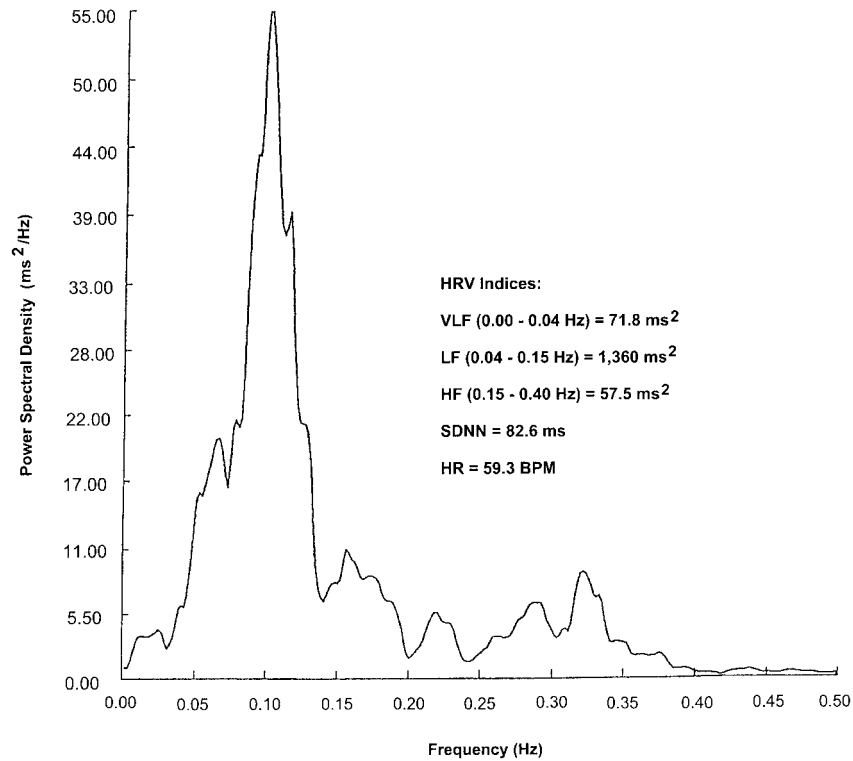


FIGURE 2. An example of a power spectral density curve following fast Fourier transformation of time domain heart rate data. HRV, heart rate variability; VLF, very low frequency; LF, low frequency; HF, high frequency; SDNN, standard deviation of normal R-R intervals; HR, heart rate; BPM, beats per minute.

Other measurements

Data on demographic characteristics and cardiovascular disease risk factors were ascertained according to standardized protocols common to all ARIC study sites and were subject to regular quality-control checks (25, 26). Briefly, prevalent coronary heart disease was defined by a history of hospitalized myocardial infarction, a history of cardiac revascularization procedures, or prevalent myocardial infarction documented by electrocardiograph (significant Q wave or borderline Q wave with significant S-T segment or T-wave abnormalities in the absence of ventricular conduction defects that interfere with Q-wave coding). Smoking status was dichotomized into current smoking versus no current smoking. For each participant, ARIC investigators identified and coded all medications, vitamins, and supplements used in the 2 weeks prior to the clinical examination. Current use of medications known to affect the cardiac autonomic nervous system, including beta blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, antianginal agents, antihypertensive agents (excluding diuretics), vasodilators, and digitalis, were grouped into a dichotomized variable, "cardiac medication usage." Diabetes was defined as a fasting serum glucose level of ≥ 126 mg/dl, a nonfasting glucose level of ≥ 200 mg/dl, or self-reported current use of diabetes medication. Sitting blood pressure was measured three times using a random-

zero sphygmomanometer after a 5-minute rest. The average of the last two measurements was used in this study. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or reported use of hypertension medication. Body mass index was calculated as the ratio of weight (kg) to standing height (m) squared.

Statistical analysis

Data on population characteristics were obtained as means and SDs or proportions. Multivariable linear regression models were used to assess the associations between each individual pollutant measured 1–3 days prior to the HRV measurement and each HRV index and to adjust for relevant confounding factors. Following convention (24), logarithmically transformed high-frequency power and low-frequency power were used in the analysis. Statistical interactions between each pollutant and major covariates were evaluated via the inclusion of an interaction term in the regression models, and $p \leq 0.10$ was used to identify statistically significant interaction terms. In the presence of a statistical interaction, stratum-specific regression coefficients were calculated. To elucidate the time course of PM_{10} and HRV, we fitted lagged regression models by including in the models the primary measure of PM_{10} (PM_{10} 1 day prior to HRV measurement) and 1- and 2-day lags (PM_{10} measured 2

TABLE 1. Characteristics of the study population (mean and standard deviation or proportion), overall and by quartile of high-frequency power (0.15–0.40 Hz) heart rate variability, Atherosclerosis Risk in Communities Study, 1996–1998

Variable	Total (n = 6,784)	Quartile of high-frequency power	
		Quartile 1	Quartiles 2–4
		(n = 1,696)	(n = 5,088)
Age (years)	62.4 (5.7)*	63.9 (5.7)	61.9 (5.6)
Sex (% male)	43	48	41
Ethnicity (% Black)	31	27	32
Current smoking (%)	15	15	15
Body mass index†	28.8 (5.6)	28.5 (5.4)	28.9 (5.7)
Diabetes mellitus (%)	14.0	20.4	11.9
Hypertension (%)	47	53	45
Prevalent coronary heart disease (%)	7.0	9.2	6.3
Log-transformed high-frequency power (ms ²)	4.538 (1.198)	3.051 (0.623)	5.033 (0.895)
Log-transformed low-frequency power (ms ²)	5.004 (1.186)	3.962 (1.005)	5.351 (1.028)
Standard deviation of normal R-R intervals (ms)	37.5 (20.5)	23.1 (10.0)	42.4 (20.8)
Heart rate (beats/minute)	64 (9.8)	68 (10.4)	62 (9.2)
PM ₁₀ ‡ (µg/m ³)	24.3 (11.5)	24.4 (11.7)	24.2 (11.4)
Ozone (ppm‡)	0.041 (0.016)	0.042 (0.016)	0.041 (0.016)
Carbon monoxide (ppm)	0.65 (0.44)	0.66 (0.43)	0.64 (0.44)
Sulfur dioxide (ppm)	0.004 (0.004)	0.004 (0.004)	0.004 (0.003)
Nitrogen dioxide (ppm)	0.021 (0.008)	0.020 (0.008)	0.021 (0.008)
Humidity (%)	77.3 (14.0)	76.7 (14.0)	77.4 (13.9)
Temperature (°K)	285.6 (11.8)	285.9 (11.5)	285.4 (11.9)
Cloud cover score§	4.7 (3.4)	4.8 (3.4)	4.7 (3.4)

* Numbers in parentheses, standard deviation.

† Weight (kg)/height (m)².

‡ PM₁₀, particulate matter less than 10 µm in diameter; ppm, parts per million.

§ Fraction of the celestial dome covered by clouds on a scale of 0 to 10, where 0 indicates a very clear sky and 10 indicates a totally obscured sky.

and 3 days prior to HRV measurement, respectively). In the regression models, we adjusted for individual cardiovascular disease risk factors known to be significantly associated with HRV in this population (22) and the meteorologic factors (humidity, temperature, and season) that were significantly associated with pollution levels in our preliminary analysis. All statistical computations were performed using SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Descriptive statistics for the largest effective sample size (from the analysis of sulfur dioxide and HRV) are summarized in table 1 to represent the characteristics of the study population at the time these data were collected. The average age of participants was 62 years. Fifty-seven percent were female, and 67 percent were White. Fifteen percent were current smokers. The mean body mass index was 29.0, and the prevalences of hypertension, diabetes, and coronary heart disease were 47 percent, 14 percent, and 7 percent, respectively. Comparisons of these characteristics between persons included in the analysis of each pollutant and those

excluded from the analysis (data not shown) did not reveal important differences between included and excluded persons, except for the ethnic composition of the study population (because of the exclusion of persons from Washington County, Maryland (all Whites), for all analyses and the exclusion of persons from Jackson, Mississippi (all Blacks), for the analysis of nitrogen dioxide and HRV).

The mean values for log-transformed high-frequency power, log-transformed low-frequency power, SD of normal R-R intervals, and heart rate were 4.538 ms² (SD, 1.198), 5.004 ms² (SD, 1.186), 37.5 ms (SD, 20.45), and 64 beats/minute (SD, 9.8), respectively. The mean values for PM₁₀, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide measured 1 day prior to HRV measurement were 24.3 µg/m³ (SD, 11.5), 0.041 parts per million (ppm) (SD, 0.016), 0.65 ppm (SD, 0.44), 0.004 ppm (SD, 0.004), and 0.021 ppm (SD, 0.008), respectively. Similarly defined relative humidity, temperature, and cloud cover score were 77.3 percent (SD, 14.0), 285.6°K (SD, 11.8), and 4.7 (SD, 3.4), respectively.

To highlight potentially confounding factors, we have also presented in table 1 the mean values or proportions of major

TABLE 2. Multivariable-adjusted† regression coefficients for indices of heart rate variability per one-standard-deviation (11.5 µg/m³) increment of PM₁₀‡ concentration measured 1 day prior to heart rate variability measurement, Atherosclerosis Risk in Communities Study, 1996–1998

Heart rate variability index	All participants		Hypertensive participants		Normotensive participants	
	β	SE‡	β	SE	β	SE
Log-transformed high-frequency power (ms ²)	-0.06*	0.018	-0.08*	0.024	-0.02	0.026
Log-transformed low-frequency power (ms ²)	-0.02	0.018	-0.03	0.024	-0.004	0.026
Standard deviation of normal R-R intervals (ms)	-1.03*	0.31	-1.29*	0.41	-0.65	0.43
Heart rate (beats/minute)	0.32*	0.158	0.69*	0.208	-0.024	0.22

* $p < 0.01$.

† Adjusted for age, ethnicity-center, sex, education, smoking, body mass index, use of cardiovascular medication, prevalent coronary heart disease, diabetes, hypertension (where appropriate), heart rate (where appropriate), season, temperature, humidity, and total sky cover.

‡ PM₁₀, particulate matter less than 10 µm in diameter; SE, standard error.

covariates by quartile of HRV high-frequency power (representing the outcome variable). On the basis of these data and our previous experience, we adjusted all of our statistical models for age, ethnicity-center, sex, current smoking, body mass index, heart rate, use of cardiovascular medication, hypertension, prevalent coronary heart disease, and diabetes. When analyzing the PM₁₀-HRV association, we also adjusted for season, temperature, humidity, and total sky cover, because our exploratory data analysis identified these meteorologic variables as important confounders for the PM₁₀-HRV association but not for the associations between gaseous pollutants and HRV.

Multivariable-adjusted regression coefficients, standard errors, and p values for the association of PM₁₀ with HRV indices are presented in table 2. As is indicated in the column for all participants, ambient PM₁₀ concentrations measured 1 day prior to the HRV measurement were inversely associated with both frequency and time domain HRV indices and were positively associated with heart rate. Since the interactions between PM₁₀ and hypertension were statistically significant ($p < 0.05$) for all HRV indices analyzed, we have

also presented in table 2 the regression coefficients, standard errors, and p values stratified by hypertension status. These stratified results suggest consistently more pronounced associations between PM₁₀ and HRV among persons with a history of hypertension.

Multivariable-adjusted regression coefficients, standard errors, and p values for the association of HRV indices with gaseous pollutants measured 1 day prior to the HRV measurement are presented in table 3. Since interactions between ozone and ethnicity in relation to high-frequency power and between sulfur dioxide and prevalent coronary heart disease in relation to low-frequency power were statistically significant (both p values for interaction were less than 0.05), we present results from models stratified by ethnicity or prevalent coronary heart disease for high-frequency power and low-frequency power in table 4. Ambient ozone concentrations were inversely associated with high-frequency power among Whites. Ambient carbon monoxide concentrations were positively associated with heart rate. Ambient sulfur dioxide concentrations were inversely associated with SD of normal R-R intervals and

TABLE 3. Multivariable-adjusted† regression coefficients for indices of heart rate variability per one-standard-deviation increment of levels of gaseous pollutants, Atherosclerosis Risk in Communities Study, 1996–1998

Heart rate variability index	Pollutant and one-standard-deviation increment							
	Ozone (0.016 ppm‡)		Sulfur dioxide (0.004 ppm)		Carbon monoxide (0.44 ppm)		Nitrogen dioxide (0.008 ppm)	
	β	SE‡	β	SE	β	SE	β	SE
Log-transformed high-frequency power (ms ²)	—§		-0.024	0.016	-0.033	0.020	-0.042*	0.018
Log-transformed low-frequency power (ms ²)	-0.010	0.016	—§		0.006	0.020	-0.035	0.018
Standard deviation of normal R-R intervals (ms)	-0.336	0.290	-0.532*	0.270	-0.274	0.351	-0.739*	0.324
Heart rate (beats/minute)	-0.040	0.130	0.295*	0.130	0.404*	0.160	0.155	0.145

* $p < 0.05$.

† Adjusted for age, sex, ethnicity-center, education, current smoking, body mass index, hypertension, diabetes, prevalent coronary heart disease, heart rate (where appropriate), and use of cardiovascular medication.

‡ ppm, parts per million; SE, standard error.

§ See table 4.

TABLE 4. Multivariable-adjusted† regression coefficients for indices of heart rate variability per one-standard-deviation increment of levels of ozone and sulfur dioxide, Atherosclerosis Risk in Communities Study, 1996–1998

Heart rate variability index and stratification variable	Pollutant and one-standard-deviation increment			
	Ozone (0.016 ppm‡)		Sulfur dioxide (0.004 ppm)	
	β	SE‡	β	SE
Log-transformed high-frequency power (ms ²)				
White race	-0.069**	0.019		
Black race	0.047	0.034		
Log-transformed low-frequency power (ms ²)				
Prevalent CHD‡			-0.122*	0.056
No prevalent CHD			-0.012	0.016

* $p < 0.05$; ** $p < 0.01$.

† Adjusted for age, ethnicity-center (where appropriate), sex, current smoking, education, body mass index, hypertension, diabetes, heart rate, prevalent coronary heart disease (where appropriate), and use of cardiovascular medication.

‡ ppm, parts per million; SE, standard error; CHD, coronary heart disease.

low-frequency power and positively associated with heart rate. The sulfur dioxide association with low-frequency power was much stronger in persons with a history of coronary heart disease than in persons without such a history. Ambient nitrogen dioxide concentrations were inversely associated with high-frequency power and SD of normal R-R intervals. The p values were all less than 0.05 for the above associations.

Note that the regression coefficients presented in tables 2–4 were generally small in magnitude per 1-SD change in pollutant levels, indicating weak associations.

In tables 2–4, the regression models were adjusted for ethnicity and center. To further confirm that the significant associations presented in tables 2–4 were not due to an effect of study center, we performed two additional analyses (data not shown). We first tested center \times pollutant interactions in

relation to each of the HRV indices, and none were found to be statistically significant at $p < 0.10$. We also stratified the main models in tables 2–4 by center, and the patterns of association were similar across the three centers.

To elucidate the time course of PM₁₀ and HRV, we also analyzed 1- and 2-day lags (PM₁₀ measured 2 and 3 days prior to HRV measurement, respectively) between PM₁₀ concentrations and HRV. Several conventional diagnostic tests for collinearity (variance inflation factor, condition index, condition numbers, and variance proportion) were performed, and no significant collinearity was indicated in these lagged models. The findings from these lagged models are presented in table 5. PM₁₀ concentrations measured either 2 or 3 days prior to HRV measurement were not significantly associated with HRV indices. Furthermore, adjustment for 2- and 3-day PM₁₀ simultaneously did not

TABLE 5. Multivariable-adjusted* regression coefficients for indices of heart rate variability per one-standard-deviation increment of PM₁₀† concentration measured 1, 2, or 3 days prior to heart rate variability measurement, Atherosclerosis Risk in Communities Study, 1996–1998

Heart rate variability index	Time of PM ₁₀ measurement (no. of days prior to heart rate variability measurement)								
	1 day prior			2 days prior			3 days prior		
	β	SE†	p value	β	SE	p value	β	SE	p value
Log-transformed high-frequency power (ms ²)	-0.093	0.028	<0.001	0.005	0.033	0.883	-0.004	0.028	0.893
Log-transformed low-frequency power (ms ²)	-0.078	0.028	0.005	0.048	0.033	0.144	-0.021	0.028	0.439
Standard deviation of normal R-R intervals (ms)	-1.746	0.468	<0.001	0.713	0.556	0.199	-0.212	0.469	0.651
Heart rate (beats/minute)	0.474	0.238	0.047	-0.320	0.283	0.258	-0.221	0.239	0.355

* Results from lagged linear regression models that included all three PM₁₀ measures in the model. Data in all models were adjusted for age, ethnicity-center, sex, education, smoking, body mass index, prevalent coronary heart disease, heart rate (where appropriate), use of cardiovascular medication, diabetes, hypertension, season, temperature, humidity, and total sky cover.

† PM₁₀, particulate matter less than 10 μ m in diameter; SE, standard error.

change the pattern of association between PM_{10} 1 day prior to examination and HRV indices. Similar lagged analysis was performed for each gaseous pollutant, and the results (data not shown) were consistent with those for the PM_{10} lagged analysis.

DISCUSSION

Studies using different methods and populations have repeatedly demonstrated significant associations between fine particulate air pollution and increased mortality and morbidity from cardiopulmonary diseases (1–8). However, most previous epidemiologic studies (particularly the time-series studies) lacked individual-level measurements and thus could not address pathogenic processes or subclinical/biologic markers of cardiovascular disease or adjust for individual-level confounders. For such reasons, research on the underlying biologic mechanisms for the air pollution-cardiovascular disease association in humans remains largely unpursued, particularly in population-based samples.

Recently, the relations of several potentially important arrhythmogenic mechanisms to ambient air pollution have been investigated. One of these is the acute adverse effect of air pollution on cardiac autonomic control. It was hypothesized that increased air pollution levels, specifically increased levels of fine particulate matter, stimulate the autonomic nervous system and lead to an imbalance of cardiac autonomic control characterized by sympathetic activation unopposed by parasympathetic control (9–13). Such an imbalance of cardiac autonomic control may predispose people, especially those who are more susceptible to particulate matter exposure, to greater risk of life-threatening arrhythmias and acute cardiac events. These associations may be due to: 1) the direct actions of particles that are hematogenously translocated from the lungs to the heart and vasculature; 2) the reflexive responses of the cardiac autonomic system to direct particulate activation of chemosensitive pulmonary afferents; 3) nonspecific responses of the cardiac autonomic system to noxious pulmonary stress mediated by sympathetic efferents; and/or 4) longer-term, perhaps cumulative responses to stimulus-evoked production and release of inflammatory cytokines (including certain interleukins and tumor necrosis factor) from pulmonary macrophages, epithelial cells, or fibroblasts (11, 16–18). Although the particulate matter-HRV pathway is biologically plausible, no study has yet examined the air pollution-cardiac autonomic control association in a large population-based sample. Few studies have reported associations between gaseous pollutants and cardiac autonomic control.

Results from this large population-based study, which to our knowledge is the first in this field, suggest that higher levels of PM_{10} , ozone, carbon monoxide, nitrogen dioxide, and sulfur dioxide, even at levels far below the current Environmental Protection Agency standards, have adverse effects on cardiac autonomic control. Our findings were cross-sectionally derived from population-based samples and reflect only the short-term effects of air pollution on HRV. To our knowledge, this is the first population-based study to confirm the findings of the previous panel studies

(9–13), and it has better generalizability than the panel studies because of the population-based sample. This study evaluated the association of short-term exposures measured 1 day prior to HRV assessment with cardiac autonomic control, and its findings are suggestive of short-term effects of air pollution on HRV. Thus, if the association is real, the findings suggest that air pollution has an impact on cardiovascular disease by way of an “acute” increase in air pollution levels, even within traditionally low ranges, and such an acute increase in pollution levels may lead to an immediate (short-term) decrease in HRV. Such a decrease in HRV may increase the risk of acute cardiovascular disease events or trigger the onset of a cardiovascular disease event. When the regression coefficients from each individual pollutant model are compared, the effect size for PM_{10} is considerably larger than the effect sizes for gaseous pollutants.

The observed effect modifications by existing cardiovascular conditions (modification by hypertension for PM_{10} and by prevalent coronary heart disease for sulfur dioxide) are suggestive of differential susceptibility to pollutant exposures. This is consistent with findings from studies of the association between ambient fine particle concentrations and cardiac autonomic control (9) and with the observation of a stronger association between air pollutant exposure and cardiopulmonary mortality among elderly persons with a history of cardiopulmonary disease (1, 2). Of the findings in tables 2 and 4, the interactions of hypertension with PM_{10} were the most consistent across all of the HRV indices. The interactions of prevalent coronary heart disease with sulfur dioxide and of ethnicity with ozone were only significant for one of the HRV indices. No other interactions were statistically significant. When making interpretations regarding an interaction or the lack of one, caution should be exercised, since we tested interactions between each of the pollutants and hypertension, history of coronary heart disease, diabetes, chronic pulmonary diseases, age, sex, education, and ethnicity in relation to each of the HRV indices. Testing of multiple interactions was motivated by previous studies that indicated several comorbid conditions as effect modifiers for air pollution and cardiovascular disease risk. The statistically significant interactions we have identified in these data may be chance findings, while the lack of statistical significance for some potential effect modifiers may be due to limited statistical power. Replication of these interactions in other studies is needed before any conclusion of differential susceptibility by comorbid conditions can be made.

Lagged analysis in our data, represented by the results of the lagged PM_{10} analysis presented in table 5, indicated that pollutant concentrations measured 2 or 3 days prior to HRV measurement were not significantly associated with HRV indices. Furthermore, adjusting for 2- and 3-day exposures simultaneously did not change the pattern of association between exposures 1 day prior to HRV measurement and HRV indices. These results are consistent with our previous findings (9) and are indicative of an acute effect of PM_{10} on cardiac autonomic control. Because of the lack of a biologically plausible hypothesis justifying further investigations of lag functions, no additional lags were considered.

In summary, these data are supportive of the hypothesized air pollution-HRV-cardiovascular disease pathway at the

population level. The magnitudes of the estimated effects shown in tables 2–4—that is, the regression coefficients associated with a 1-SD difference in levels of each of the pollutants—are generally small, indicating weak associations. Although results were not adjusted for measurement error, these weak associations suggest that exposures to these pollutants are “minor” risk factors for cardiovascular disease. For example, in this population, a 5-year increment in age, male sex, and a positive history of cardiovascular disease were associated with 0.11-, 0.24-, and 0.15-unit decreases in the log-transformed high-frequency power index, respectively, in comparison with a 0.06-unit decrease associated with a 1-SD increment of PM_{10} . By contrast, from a public health perspective, one could argue that estimates of the magnitude observed in this study would have a significant impact on the health of the population because of its widespread, long-term exposure to low levels of ambient air pollutants. In this regard, the pollutant levels for this study were derived as daily averages from ambient air monitors such as those used in different locations in the United States and are reflective of the low ambient levels to which most of the population is exposed on a daily basis.

This was a cross-sectional study, which precluded consideration of a temporal relation between the air pollutants and cardiac autonomic control, although we were able to assess short-term, prior exposure over the days preceding the HRV measurement. We assessed ambient exposures to five criteria pollutants by calculating the daily averages from measured data available from several monitors within a county. Although this approach provides the technically most feasible measures of exposure for individual residents, we cannot rule out misclassification of the exposures. However, there is no evidence suggesting that such misclassification might be systematic with regard to levels of individual HRV measures and other cardiovascular disease risk factors, because clinical examination (and HRV measurement) dates were assigned at random to all study participants. Following this argument, the associations we observed in this study would have been underestimated because of nondifferential misclassification of exposure. This was a large, population-based study; as such, the skewed distribution of the exposure variables had less of an impact on the overall results than it would have in studies with small sample sizes and panel studies. We performed sensitivity analysis by excluding persons with extremely high levels of pollution exposure prior to their clinical examination, and the results were not meaningfully changed (data not shown).

We emphasize that this study was designed to investigate the short-term association between air pollution and cardiac autonomic control in data obtained 1, 2, and 3 days prior to the HRV measurements and that we are unable to rule out other patterns of exposure-outcome association, such as subacute or long-term cumulative effects. Most of the published literature validating the use of HRV as a measure of cardiac autonomic control and the prediction of incident cardiac events from HRV measures was based on studies of longer duration. It is biologically plausible that chronic air pollution can also impair cardiac autonomic control. In this study, we statistically adjusted for individual-level risk factors for cardiovascular disease, such as age, sex, smoking, body mass index, use of cardiovascular medication, preva-

lent coronary heart disease, diabetes, hypertension, demographic and socioeconomic status, ethnicity-center, educational level, and meteorologic factors such as season, temperature, humidity, and total sky cover. Thus, the results are less likely to reflect bias due to these confounding factors. Although residual confounding by other factors cannot be totally ruled out, we do not believe that minor residual confounding factors could have yielded the consistent findings observed. Finally, we had to exclude a large number of persons from our analysis, mostly because of unavailability of exposure data. This reduces the generalizability of the findings, but it is unlikely to have introduced selection bias, because of the manner in which the four study cohorts were chosen. Our analysis indicated that persons included were similar to those excluded with regard to major cardiovascular disease risk factors.

Particulate matter is a complex mixture of suspended particles that vary in size and composition. In this study, we assessed the acute effects of five criteria pollutants; the ability to generalize these findings to other pollutants, such as particulate matter less than 2.5 μm in diameter, may be limited. Similarly, information on the composition of particles was not available for this analysis; thus, inferences from our data can only be made for the mass concentration of PM_{10} , not its chemical composition or proportions of components in the mixture.

In conclusion, the data from this population-based, cross-sectional study suggest that cardiac autonomic control as measured by HRV and heart rate is adversely associated with higher levels of environmentally relevant ambient pollutants, with the strongest associations being observed for PM_{10} and in persons with positive histories of hypertension and coronary heart disease. Given the established and consistent associations between lower HRV, higher heart rate, and the development of cardiovascular disease, our findings suggest an injury mechanism and a potential underlying pathway by which air pollution could affect the risk of cardiovascular disease morbidity and mortality.

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