NIH Public Access
Author Manuscript
Epidemiology. Author manuscript; available in PMC 2009 April 21.

Published in final edited form as:
Epidemiology. 2008 January ; 19(1): 111–120. doi:10.1097/EDE.0b013e31815c408a.

Air Pollution and Heart Rate Variability:

Effect Modification by Chronic Lead Exposure

Sung Kyun Park[*], **Marie S. O'Neill**[*,†], **Pantel S. Vokonas**[‡], **David Sparrow**[‡,§,‖], **Robert O. Wright**[¶,‖], **Brent Coull**[**], **Huiling Nie**[¶,‖], **Howard Hu**[*,¶,‖], and **Joel Schwartz**[¶,‖]

*From the Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan

†Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan

‡Department of VA Normative Aging Study, Veterans Affairs Boston Healthcare System, West Roxbury, Massachusetts

§Department of Medicine, Boston University School of Medicine, Boston, Massachusetts

¶Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

‖Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts

**Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts

Abstract

Background—Outdoor air pollution and lead exposure can disturb cardiac autonomic function, but the effects of both these exposures together have not been studied.

Methods—We examined whether higher cumulative lead exposures, as measured by bone lead, modified cross-sectional associations between air pollution and heart rate variability among 384 elderly men from the Normative Aging Study. We used linear regression, controlling for clinical, demographic, and environmental covariates.

Results—We found graded, significant reductions in both high-frequency and low-frequency powers of heart rate variability in relation to ozone and sulfate across the quartiles of tibia lead. Interquartile range increases in ozone and sulfate were associated respectively, with 38% decrease (95% confidence interval = -54.6% to -14.9%) and 22% decrease (-40.4% to 1.6%) in high frequency, and 38% decrease (-51.9% to -20.4%) and 12% decrease (-28.6% to 9.3%) in low frequency, in the highest quartile of tibia lead after controlling for potential confounders. We observed similar but weaker effect modification by tibia lead adjusted for education and cumulative traffic (residuals of the regression of tibia lead on education and cumulative traffic). Patella lead modified only the ozone effect on heart rate variability.

Conclusions—People with long-term exposure to higher levels of lead may be more sensitive to cardiac autonomic dysfunction on high air pollution days. Efforts to understand how environmental exposures affect the health of an aging population should consider both current levels of pollution and history of lead exposure as susceptibility factors.

Correspondence: Sung Kyun Park, SPH II-M6240, Department of Environmental Health Sciences, University of Michigan School of Public Health, 109 S. Observatory Street, Ann Arbor, MI 48109. E-mail: E-mail: sungkyun@umich.edu..

Supplemental material for this article is available with the online version of the journal at www.epidem.com; click on "Article Plus."

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

As people age, their ability to respond to the stress of current and accumulated environmental exposures may diminish due to physiologic and metabolic changes, resulting in increased susceptibility to health problems related to environmental contamination and other challenges.[1] Preventing, postponing, or slowing down common diseases of aging are important goals,[2] and reducing environmental exposures may help meet these goals.[3]

Cardiovascular disease (CVD) is an important cause of both morbidity and mortality in the United States, especially among the elderly, accounting for 38% of total mortality in 2002.[4] Weight management, healthy diet, appropriate exercise, and avoidance of tobacco smoke exposure are recommended to reduce the risk.[5] Environmental factors, such as air pollution[6-8] and lead exposures,[9-12] also contribute to the burden of CVD, but underlying biologic mechanisms are poorly understood.

Air pollution and lead exposures may affect cardiovascular health through the autonomic nervous system. Heart rate variability provides a noninvasive and quantitative measure of cardiac autonomic function.[13] Decreased variability independently predicts mortality in middle-age and elderly subjects, in patients with diabetes, and in survivors of myocardial infarction and other coronary heart diseases.[14-17] Decreased heart rate variability has also been associated with short-term exposures to air pollution[18-23] and lead.[24-27]

Oxidative stress occurs when the production of reactive oxygen species exceeds the antioxidant capability of the cell,[28] resulting in several adverse physiological consequences.[29-31] Both air pollution and lead exposures can increase generation of reactive oxygen species and induce oxidative stress.[32-35] Associations between air pollution, lead exposures, and heart rate variability were modified by underlying CVD and genotype,[18,19,21,22,36] and so oxidative stress-related conditions may affect susceptibility to air pollution and lead. If oxidative stress is a common mechanism linking both air pollution and lead exposures with cardiac autonomic dysfunction, then individuals with high lead body burden may experience an even greater cardiac response to air pollution exposure. We tested this hypothesis by examining whether bone lead levels, which represent cumulative lead exposure, modify the short-term effects of air pollution on heart rate variability.

METHODS

Study Population

Participants were drawn from the Normative Aging Study, a longitudinal study of aging established by the US Veterans Administration (VA) in 1963.[37] The methods are described in detail elsewhere.[18,36] Briefly, 2280 community-dwelling men aged 21 to 80 years from the Greater Boston area were enrolled between 1963 and 1968 if they had no history of known chronic diseases. At each subsequent visit, extensive physical examination, laboratory, anthropometric, and questionnaire data were collected.

Beginning in 2000, during each participant's regularly scheduled evaluation in the VA system, we measured heart rate variability. Participants visited the study center in the morning after an overnight fast and abstinence from smoking. We collected data related to cardiovascular risk including body mass index, heart rate, systolic and diastolic blood pressure, and fasting blood glucose. Blood pressure was measured with the subject seated. Cigarette smoking, alcohol consumption, medical history (including respiratory and cardiovascular conditions), and subjects' use of medications were ascertained by questionnaire. We recorded the temperature of the room where the heart rate variability was measured.

Beginning in 1991, participants who gave their informed consent were invited to undergo bone lead measurements. Bone lead levels were measured between 1991 and 2002. For the 75% of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

subjects with more than 1 bone lead measurement during this period, the measurement taken closest to the date of the heart-rate-variability measurement was used for this analysis. Characteristics of participants with and without bone lead measurements were similar.[10]

From November 14, 2000, to December 22, 2004, 671 active cohort members were examined. Of these, we excluded the following: 110 subjects with problematic heart rate measurements (atrial fibrillation, atrial bigeminy and trigeminy, pacemakers, irregular rhythm, irregular sinus rhythm, frequent ventricular ectopic activity, ventricular bigeminy, multifocal atrial tachycardia, or measurement time less than 3.5 minutes); subjects without tibia and paella lead measurements (n = 131 and n = 142, respectively); 10 subjects with high uncertainties (greater than 10 and 15 μg/g for tibia and patella, respectively); subjects with extreme tibia and patella lead levels, (n = 5 and n = 9, respectively); and 29 subjects with missing values of potential confounding factors. Hence, 384 (tibia) and 369 (patella) subjects were available for analyses. All participants had given written informed consent. This study was reviewed and approved by the Institutional Review Boards of Harvard School of Public Health and the VA Boston Healthcare System.

Measurement of Heart Rate Variability

Heart rate variability was measured between 6:00 AM and 1:00 PM with a 2-channel (5-lead) electrocardiogram (ECG) monitor (Model: Trillium 3000; Forest Medical, East Syracuse, NY). After the participant had rested for 5 minutes, the ECG was recorded (sampling rate of 256 Hz per channel) for approximately 7 minutes with the subject seated. The ECG digital recordings were processed, and heart rate and variability measures were calculated with PC-based software (Trillium 3000 PC Companion Software for MS Windows; Forest Medical), which conforms to established guidelines.[13] Beats were automatically detected and assigned tentative annotations, and then an experienced scanner reviewed the results to correct for any mislabeled beats or artifacts. We used only normal-to-normal beat intervals in the analysis. We used the best 4-consecutive-minute intervals for the variability calculations and computed high frequency (0.15–0.4 Hz) and low frequency (0.04–0.15 Hz) using a fast Fourier transform.

Bone Lead Measurements

Bone lead levels were measured with a K-shell x-ray fluorescence instrument at the midtibial shaft and the patella. The physical principles, technical specifications, and validation of this instrument are described in detail elsewhere.[38] The tibia consists mainly of pure cortical bone, and the patella of pure trabecular bone, thus representing the 2 main bone compartments. Lead in trabecular bone (patella) has a faster turnover rate and therefore reflects more recent exposure than the lead in the cortical bone (tibia). The x-ray fluorescence instrument provides an unbiased estimate of bone lead levels (normalized for bone mineral content as micrograms of lead per gram of bone mineral) and an estimate of the uncertainty associated with each measurement.

Bone lead and heart rate variability were not measured simultaneously, with most of the bone lead measurements taken well before the heart rate variability measurements (median 3.2 years). Previously, we used estimated patella lead levels to account for the decay trend of patella lead levels over time.[36] Lead levels in patella bone decreased 23% in the 3-year follow-up (7.7%/yr); no change in tibia lead levels occurred.[39] Following other studies which predicted "peak tibial lead," assuming first-order exponential kinetics,[40,41] we accounted for the declining trend in patella lead levels by estimating patella lead as follows.

Estimated patella lead = measured patella lead × $(1–0.0767)^d$, where d denotes the difference in years between dates of bone lead and heart rate variability measurement.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Air Pollution and Weather Data

Particulate matter <2.5 μm in aerodynamic diameter ($PM_{2.5}$), black carbon, and sulfate were measured at the Harvard School of Public Health monitoring site, which is 1 km from the examination site. Ozone, temperature and dew-point temperature were obtained from Massachusetts Department of Environmental Protection local monitoring sites. To control for weather in the analyses of heart rate variability, we used apparent temperature, defined as a person's perceived air temperature.[42,43] Apparent temperature combines the effects of heat and humidity in 1 variable and has been associated with both pollution and heart rate variability. We used 48-hour moving averages of $PM_{2.5}$ and black carbon, and 4-hour averages of ozone matched on the time of measuring heart rate variability for each subject as our exposure indices, because a previous study showed the strongest association in these exposure periods (lags).[18] Sulfate was measured as daily integrated mean concentrations, and so we used averages of the same and the previous days' levels of sulfate as the exposure variable.

Other Long-Term Exposures: Traffic and Educational Attainment

Subjects' residential addresses since enrollment were assigned latitude and longitude using standard methods.[44,45] Cumulative traffic exposure was calculated by summing the product of average daily traffic and road length in meters for roads within 100 m of addresses using the MassHighway 2002 Road Inventory and ArcGIS software (version 9; ESRI, Redlands, WA). We calculated a weighted average of cumulative traffic exposure for each subject by duration of each residence.

Individual educational attainment was reported by participants as the highest level of education achieved. We used 3 categories: did not graduate from high school; graduated from high school; and graduated from a 4-year college or higher.[45]

Statistical Methods

Linear regression analyses were conducted to assess the association between heart rate variability and air pollutants. To improve normality and stabilize the variance, we used $\log_{10}$-transformed measures of heart rate variability as the response variables. Previously, we identified, a priori, the biologically important covariates for inclusion: age, body mass index, fasting blood glucose, antihypertensive medications (beta-blockers, calcium channel blockers, and ACE inhibitors), cigarette smoking, alcohol consumption, season (spring/summer/fall/winter) and apparent temperature.[18,36] These variables were kept in the regression models regardless of significance. We also included 2 additional potential con-founders: mean arterial pressure, which changed the effect estimates by more than 10%, and the temperature of the room where the heart rate variability measurement was taken. Room temperature did not change the associations between air pollution and heart rate variability but may account for some variance in the cardiac measurements. Finally, individual education attainment and cumulative traffic were included in the models as potential confounders. To account for the nonlinear association of apparent temperature with heart rate variability, a cubic spline with 3 degrees of freedom was used (model 1). We used log-transformed cumulative traffic because the distribution was skewed. To evaluate whether cumulative bone lead levels modify the effects of air pollutants on heart rate variability, we introduced interaction terms between quartiles of tibia or patella lead and each air pollutant in the models. Tests for linear trend of air pollution effects across quartiles of bone lead were computed. We calculated adjusted percent changes for an increase equal to the inter-quartile range (IQR) for each air pollutant, with 95% confidence intervals. We included the covariances as well as the variances in computing the standard errors of the effect estimates for the interaction terms.

We also calculated the residuals of the regression of bone lead on individual education attainment and cumulative traffic, our other 2 long-term exposures. These residuals represent

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

the information in bone lead levels that cannot be explained by education and cumulative traffic, allowing us to evaluate whether long-term lead exposure is modifying the effect of air pollution on heart rate variability, independent of these other life-course experiences. Then we categorized these residuals into quartiles and ran the regression models above without education and traffic as covariates (model 2).

RESULTS

The mean ± SD age of study participants was 73 ± 6.5 years, and the median concentrations of lead were 19 μg/g in tibia and 23 μg/g in patella. The correlation between tibia and patella lead levels was 0.66. Table 1 shows demographic and clinical characteristics of subjects stratified by quartile of tibia lead levels. Older age and history of diabetes, ischemic heart disease, and hypertension were related to higher concentrations of tibia lead. Cumulative cigarette smoking (pack-years) was marginally associated with tibia lead levels. Individual education attainment was significantly inversely associated with tibia lead levels, but cumulative traffic was not. The low frequency component of heart rate variability decreased slightly with increasing tibia lead levels (*p* for trend = 0.14). When stratified by quartile of patella lead levels, smoking status and pack-years of cigarettes were associated with quartiles of patella lead, but no association with history of diabetes, ischemic heart disease and hypertension was found (eTable, available with the online version of this article). The other trends were not much different from those stratified by quartile of tibia lead levels.

Table 2 shows distributions of air pollution and apparent temperature and their correlations. The correlations between ambient particle pollutants were relatively high. Ozone was significantly correlated with $PM_{2.5}$ (r = 0.51) and sulfate (r = 0.58), but not with black carbon (r = -0.01). The correlation coefficients with apparent temperature ranged from 0.33 for black carbon to 0.58 for ozone.

In a model including all 384 subjects, an IQR increase in $PM_{2.5}$ (7 $\mu g/m^3$) was associated with a 15% decrease (95% confidence interval = -27.9% to 1.2%) in high-frequency heart rate variability after adjustment for potential confounders. Ozone (16 ppb) was associated with a 21% reduction (-32.7% to -7.8%) in low-frequency heart rate variability. Black carbon and sulfate, and tibia lead and patella lead were more weakly associated with decreased high-frequency and low-frequency heart rate variability (data not shown).

The effects of air pollution across quartiles of bone lead are presented in Table 3. In the fully adjusted model (model 1), high frequency decreased by 22% (-37.4% to -1.7%) in association with 1 IQR increase in $PM_{2.5}$ in subjects with high tibia lead levels (quartile 4), whereas little effect was observed in persons with relatively low tibia lead levels (quartiles 1–3). No important differences were observed across quartiles of tibia lead in the association between $PM_{2.5}$ and low frequency. $PM_{2.5}$ was associated with high frequency in the third and fourth quartiles of patella lead, and the effect of $PM_{2.5}$ on high frequency was slightly stronger in persons with high patella lead levels (*p* for trend = 0.08). The association between ozone and reduced high frequency became stronger at higher levels of tibia lead, reaching 38% (-54.6% to -14.9%) in the fourth quartile of tibia lead (*p* for trend <0.01). Similarly, reductions in low frequency with ozone became stronger across the quartiles of tibia lead (*p* for trend <0.01), reaching 38% (-51.9% to -20.4%) with the highest tibia lead levels. Ozone associations across strata of patella lead were similar to those with tibia lead. Sulfate produced graded reductions in high frequency (*p* for trend <0.01) and low frequency heart rate variability (*p* for trend = 0.04) across the quartiles of tibia lead. One IQR increase in sulfate (2.5 $\mu g/m^3$) was associated with a 22% decrease (-40.4% to 1.6%) in high frequency in the fourth quartile of tibia lead levels, whereas a 51% increase (5.4%–115.5%) in the first quartile of lead. Weaker less significant decreasing trends for sulfate were found across the quartiles of patella lead. Black carbon associations

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

with heart rate variability did not differ across quartiles of tibia and patella lead. For quartiles of education and cumulative traffic-adjusted bone lead levels (model 2), the overall trends were slightly weaker.

DISCUSSION

In this large study of community-dwelling older men, we found evidence of effect modification by cumulative lead exposure in associations of sulfate and ozone with heart rate variability. This modification seems to be largely independent of individual education attainment or earlier traffic particle exposure. People who have been exposed to higher concentrations of lead may be more susceptible to impairments in cardiac autonomic function on days with higher levels of ozone and ambient fine particles. We do not know of previous studies that have assessed the interaction between air pollution and lead exposure in association with a health outcome.

Older adults and persons with diabetes are consistently reported as being more sensitive to fine particles, suggesting that impairment of antioxidant defense due to aging or preexisting oxidative stress-related conditions might play a role in the impact of particles on a susceptible population.[18,46-48] Therefore, we hypothesized that chronic lead exposure, also known to increase oxidative stress, would modify the effect of ambient air pollutants.

In the present study, ozone associations with heart rate variability became stronger across quartiles of both tibia and patella lead levels, and the dose-response relations seemed either linear or to have thresholds. We previously reported that ozone exposure is independently associated with low frequency heart rate variability, which reflects largely sympathetic activity.[18] Other studies have also found a relation between ozone and alterations in heart rate variability.[22,23] In addition, numerous epidemiologic studies have demonstrated that ozone exposure is associated with increased total and cardiovascular mortality,[49–52] acute myocardial infarction,[53,54] and ventricular arrhythmias.[55] Ozone is a secondary air pollutant, formed by the reaction of nitrogen dioxide with hydrocarbons in the presence of sunlight. Ozone can irritate lung epithelium,[56] but because ozone is not thought to penetrate the lung, it may affect the autonomic nervous system through indirect inflammatory response due to generation of reactive oxygen species. Thus, we expected that persons with low lead levels would have less oxidative stress and would be less responsive to ozone exposure, whereas people exposed to lead chronically would retain high bone lead levels and have greater autonomic responses to the additional oxidative stress caused by ozone in both parasympathetic and sympathetic branches of the nervous system. Blood lead, a marker of recent lead exposure, may better indicate oxidative stress than bone lead, but blood lead measurements among the participants ceased just as heart rate variability measurements began. Future studies should consider evaluating interactions between blood lead and air pollution.

Though time-activity pattern data were not available for participants, they are elderly and likely to spend most of their time indoors. Ozone concentrations are low indoors, and so ozone may be acting a proxy for other, secondary, particle pollutants, such as sulfate. This hypothesis is supported by research showing that ambient ozone is a good predictor of personal exposure to sulfate[57] and that both ozone and sulfate had similar associations with inflammation, oxidative stress, blood coagulation and autonomic dysfunction.[58]

We also found interactions between sulfate and tibia lead. Sulfates represent mainly regionally transported particles from coal-burning power plants and constitute the majority of $PM_{2.5}$.[59] In this study, sulfate and $PM_{2.5}$ were relatively highly correlated ($r = 0.91$, Table 2). Sulfates have been associated with mortality and respiratory morbidity,[60] but few studies have shown associations between sulfate particles and cardiovascular endpoints. Sulfate was positively associated with CVD mortality among elderly people[61] and with CVD hospital admissions in

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

the warm season.[62] Sulfate exposure independently predicted reduced vascular reactivity, which is related to increased cardiovascular risk, especially in people with type-2 diabetes.[47] In addition, secondary particles (primarily sulfates) were weakly associated with decreased heart rate variability.[19] In our study, sulfate, but not other air pollutants, was positively related with heart rate variability measures in subjects with the lowest bone lead levels. People in this quartile were younger and less likely to have diabetes, ischemic heart disease, and hypertension (Table 1). However, this association controlled for fasting blood glucose (diabetes) and mean arterial pressure (an index related to hypertension). Additional adjustment for use of statins, which have antioxidant and antiinflammatory activity and may block the effect of ambient particles,[47] and ischemic heart disease did not change this association. Elevated heart rate variability may be induced by stimulation of irritant receptors in the lung parenchyma and respiratory airways, which may increase bronchoconstriction and vagal responses of the heart associated with bradyarrhythmia.[63] If what we saw is a valid association, stratifying by individual lead levels when examining the effect of sulfate on heart rate variability is important, lest the positive association in people with low lead levels dilute the negative association in those with high lead levels. This is a possible reason why we did not see a main effect of sulfate on heart rate variability in the whole population. Further epidemiologic and animal studies are needed to confirm this finding.

Bone lead weakly modified the association between $PM_{2.5}$ and heart rate variability, although a significant reduction in high frequency was found among subjects with the highest tibia lead levels. Furthermore, associations with black carbon, which is mainly emitted by motor vehicles, were similar across quartiles of tibia and patella lead levels. This result, along with the consistent findings for the secondary pollutants, sulfate, and ozone, suggests that particle components have differential effects on the cardiovascular system. Sulfate exists as metal oxides, such as vanadium sulfate in fine particles, and therefore higher concentrations of sulfate may be paralleled by higher concentrations of toxic metals.[64] These divalent metals may share the same mechanical pathway as lead for influence on the cardiac function, whereas ultrafine particles consisting of black carbon may have a different pathway. The weak association with $PM_{2.5}$ may reflect the combined effects of sulfate and black carbon, the main constituents of $PM_{2.5}$.

The observed effect modification by bone lead may be attributable to factors in the life experience of participants that correlate with cumulative lead exposure, other than individual education attainment and cumulative traffic, which we considered. Low socioeconomic status (eg, educational attainment, income, assets) is a well-known determinant of bone lead levels.[45,65] Further, most adults have accumulated a substantial body burden of lead through past exposures to traffic particles from combustion of leaded gasoline.[66] Bone lead modified air pollution and its associations with heart rate variability in the models adjusted for individual education attainment and cumulative traffic. In addition, utilization of education and cumulative traffic-adjusted bone lead levels (regression residuals) slightly reduced the strength but not the pattern of the trends seen using the bone lead quartiles. Thus, these other life-course experiences do not fully explain current susceptibility to air pollution among participants with higher cumulative lead exposure.

The trends in association between air pollution and heart rate variability across quartiles of tibia and patella lead levels were inconsistent, especially for sulfate. Tibia and patella lead have shown inconsistent associations with health outcomes in other epidemiologic studies: patella lead but not tibia lead has been associated with declines in hematocrit and hemoglobin,[67] an increased risk of hypertension,[68] and a steeper decline in cognitive function.[69] However, tibia lead but not patella lead has been associated with an increased risk of hypertension,[9] lower birth weight,[70] and increased risk of age-related cataracts.[71] These observed inconsistencies

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

might be due to different lead kinetics and toxicity, with different clearance half-times in these cumulative lead exposure markers.

Previous evaluations of study participants did not show substantial main effects of lead on heart rate variability.[36] Although low-level lead exposure is only weakly associated with cardiac autonomic function, it may play a role in enhancing the effects of ozone and sulfate. Lead exposure increases the generation of reactive oxygen species by depletion of glutathione and protein-bound sulfhydryl groups, leading to oxidative stress.[72] Lead induces iron-dependent lipid peroxidation in liposomal membranes.[73] Lead exposure also down-regulates nitric oxide generation.[74] Further, lead inhibits the intracellular calcium messenger system and alters calcium homeostasis because of its mimicry of the calcium ion.[75,76] These effects are associated with sympathetic excitation and vagal withdrawal.[75,77,78]

We have reported[36] that associations between patella bone lead levels on heart rate variability are stronger among study participants with metabolic syndrome (a set of cardiovascular risks that increases the odds of developing type-2 diabetes, hypertension and coronary heart disease) and with individual components of metabolic syndrome.[36] Thus, the increased sensitivity with higher cumulative lead exposure to air pollution could be attributed to higher prevalence of metabolic syndrome and its component conditions among participants in higher-lead quartiles. However, when we restricted to the subpopulation without metabolic syndrome (n = 275), the overall trends by lead quartile were similar (data not shown), suggesting that the observed interactions with lead may be independent of metabolic syndrome.

We have remarked previously on limitations of this study.[18,36] The subjects are predominantly white men, and so results may not be generalizable to women or to other racial/ethnic groups. Use of a single ambient monitoring site instead of personal exposure monitoring may misclassify exposure. However, $PM_{2.5}$ is spatially homogeneous in the Boston metropolitan area[79] and outdoor particle measures are uniformly distributed across urban areas, suggesting that ambient particle concentrations are a good surrogate for personal exposure in greater Boston.[57] Although bone lead data were not available for all subjects with heart rate variability measurements, characteristics of subjects who did and did not have bone lead levels measures were similar, and so the current study population is representative of the whole study sample.

In summary, long-term exposure to low-level lead, as measured in bone, modified the associations between cardiac autonomic function and short-term exposure to air pollution, especially secondary pollutants such as sulfate and ozone. This study provides evidence that people with higher past exposures to lead are at increased risk of adverse health outcomes from air pollution. Although in the United States leaded gasoline is no longer sold to the general public, and airborne concentrations have dropped dramatically,[80] this study points to the enduring legacy of the accumulated exposure to this contaminant. Airborne exposure, diet, genetics, occupation, place of residence, age, and secular trends all influence accumulation of lead in bones where it is released over a lifetime.[81] Additionally, although air quality has improved significantly, health-based standards are still violated in many communities.[82]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank Elaine R. Dibbs and Jordan D. Awerbach for their contributions to the VA Normative Aging Study. We are also grateful to the reviewers for suggestions that greatly improved the paper.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Supported by US Environmental Protection Agency grants EPA R827353 and R832416 and National Institute of Environment Health Sciences (NIEHS) grants ES00002, P01-ES009825, ES05257, P42-ES05947, and ES10798. The VA Normative Aging Study is supported by the Cooperative Studies Program/Epidemiology Research and Information Center of the US Department of Veterans Affairs and is a component of the Massachusetts Veterans Epidemiology Research and Information Center, Boston, Massachusetts.

REFERENCES

1. Geller AM, Zenick H. Aging and the environment: a research framework. Environ Health Perspect 2005;113:1257–1262. [PubMed: 16140638]
2. Kaplan GA, Haan MN, Wallace RB. Understanding changing risk factor associations with increasing age in adults. Annu Rev Public Health 1999;20:89–108. [PubMed: 10352851]
3. U.S. Environmental Protection AgencyAging Initiative2004 Available at: http://www.epa.gov/aging/index.htm Accessed September 19, 2005
4. American Heart Association. Heart Disease and Stroke Statistics—2005 Update. American Heart Association; Dallas, TX: 2005.
5. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388–391. [PubMed: 12119259]
6. Schwartz J. Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 1999;10:17–22. [PubMed: 9888275]
7. Pope CA III, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 2002;287:1132–1141. [PubMed: 11879110]
8. Samet JM, Dominici F, Curriero FC, et al. Fine particulate air pollution and mortality in 20 U.S. cities, 1987-1994. N Engl J Med 2000;343:1742–1749. [PubMed: 11114312]
9. Hu H, Aro A, Payton M, et al. The relationship of bone and blood lead to hypertension. The Normative Aging Study. JAMA 1996;275:1171–1176. [PubMed: 8609684]
10. Cheng Y, Schwartz J, Vokonas PS, et al. Electrocardiographic conduction disturbances in association with low-level lead exposure (the Normative Aging Study). Am J Cardiol 1998;82:594–599. [PubMed: 9732886]
11. Lustberg M, Silbergeld E. Blood lead levels and mortality. Arch Intern Med 2002;162:2443–2449. [PubMed: 12437403]
12. Schwartz J. Lead, blood pressure, and cardiovascular disease in men and women. Environ Health Perspect 1991;91:71–75. [PubMed: 1828226]
13. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043–1065. [PubMed: 8598068]
14. Dekker JM, Schouten EG, Klootwijk P, et al. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men: The Zutphen Study. Am J Epidemiol 1997;145:899–908. [PubMed: 9149661]
15. Gerritsen J, Dekker JM, TenVoorde BJ, et al. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. Diabetes Care 2001;24:1793–1798. [PubMed: 11574444]
16. Tapanainen JM, Thomsen PE, Kober L, et al. Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. Am J Cardiol 2002;90:347–352. [PubMed: 12161220]
17. Tsuji H, Larson MG, Venditti FJ, et al. Impact of reduced heart rate variability on risk for cardiac events: the Framingham Heart Study. Circulation 1996;94:2850–2855. [PubMed: 8941112]
18. Park SK, O'Neill MS, Vokonas PS, et al. Effects of air pollution on heart rate variability: the VA Normative Aging Study. Environ Health Perspect 2005;113:304–309. [PubMed: 15743719]
19. Schwartz J, Litonjua A, Suh H, et al. Traffic related pollution and heart rate variability in a panel of elderly subjects. Thorax 2005;60:455–461. [PubMed: 15923244]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

20. Pope CA III, Hansen ML, Long RW, et al. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. Environ Health Perspect 2004;112:339–345. [PubMed: 14998750]
21. Liao D, Duan Y, Whitsel EA, et al. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. Am J Epidemiol 2004;159:768–777. [PubMed: 15051586]
22. Holguin F, Tellez-Rojo MM, Hernandez M, et al. Air pollution and heart rate variability among the elderly in Mexico City. Epidemiology 2003;14:521–527. [PubMed: 14501266]
23. Gold DR, Litonjua A, Schwartz J, et al. Ambient pollution and heart rate variability. Circulation 2000;101:1267–1273. [PubMed: 10725286]
24. Bockelmann I, Pfister EA, McGauran N, et al. Assessing the suitability of cross-sectional and longitudinal cardiac rhythm tests with regard to identifying effects of occupational chronic lead exposure. J Occup Environ Med 2002;44:59–65. [PubMed: 11802467]
25. Murata K, Araki S. Autonomic nervous system dysfunction in workers exposed to lead, zinc, and copper in relation to peripheral nerve conduction: a study of R-R interval variability. Am J Ind Med 1991;20:663–671. [PubMed: 1665313]
26. Murata K, Araki S, Yokoyama K, et al. Autonomic and central nervous system effects of lead in female glass workers in China. Am J Ind Med 1995;28:233–244. [PubMed: 8585520]
27. Teruya K, Sakurai H, Omae K, et al. Effect of lead on cardiac parasym-pathetic function. Int Arch Occup Environ Health 1991;62:549–53. [PubMed: 1856009]
28. Klaunig JE, Xu Y, Isenberg JS, et al. The role of oxidative stress in chemical carcinogenesis. Environ Health Perspect 1998;106(suppl 1):289–295. [PubMed: 9539021]
29. Lefer DJ, Granger DN. Oxidative stress and cardiac disease. Am J Med 2000;109:315–323. [PubMed: 10996583]
30. Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: part I: basic mechanisms and in vivo monitoring of ROS. Circulation 2003;108:1912–1916. [PubMed: 14568884]
31. Giordano FJ. Oxygen, oxidative stress, hypoxia, and heart failure. J Clin Invest 2005;115:500–508. [PubMed: 15765131]
32. Donaldson K, Stone V, Seaton A, et al. Ambient particle inhalation and the cardiovascular system: potential mechanisms. Environ Health Perspect 2001;109(suppl 4):523–527. [PubMed: 11544157]
33. Brook RD, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 2004;109:2655–2671. [PubMed: 15173049]
34. Stohs SJ, Bagchi D. Oxidative mechanisms in the toxicity of metal ions. Free Radic Biol Med 1995;18:321–336. [PubMed: 7744317]
35. Ercal N, Gurer-Orhan H, Aykin-Burns N. Toxic metals and oxidative stress part I: mechanisms involved in metal-induced oxidative damage. Curr Top Med Chem 2001;1:529–539. [PubMed: 11895129]
36. Park SK, Schwartz J, Weisskopf M, et al. Low-level lead exposure, metabolic syndrome, and heart rate variability: the VA Normative Aging Study. Environ Health Perspect 2006;114:1718–1724. [PubMed: 17107858]
37. Bell B, Rose C, Damon A. The Normative Aging Study: an interdisciplinary and longitudinal study of health and aging. Aging Hum Dev 1972;3:4–17.
38. Burger DE, Milder FL, Morsillo PR, et al. Automated bone lead analysis by K-x-ray fluorescence for the clinical environment. Basic Life Sci 1990;55:287–292. [PubMed: 2088281]
39. Kim R, Aro A, Rotnitzky A, et al. K x-ray fluorescence measurements of bone lead concentration: the analysis of low-level data. Phys Med Biol 1995;40:1475–1485. [PubMed: 8532760]
40. Glenn BS, Stewart WF, Links JM, et al. The longitudinal association of lead with blood pressure. Epidemiology 2003;14:30–36. [PubMed: 12500043]
41. Stewart WF, Schwartz BS, Davatzikos C, et al. Past adult lead exposure is linked to neurodegeneration measured by brain MRI. Neurology 2006;66:1476–1484. [PubMed: 16717205]
42. Steadman RG. The assessment of sultriness. Part II: effects of wind, extra radiation, and barometric pressure on apparent temperature. J Appl Meteor 1979;18:874–885.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

43. Kalkstein LS, Valimont KM. An evaluation of summer discomfort in the United States using a relative climatological index. Bull Am Meteorol Soc 1986;67:842–848.
44. Tonne C, Melly S, Mittleman M, et al. A case-control analysis of exposure to traffic and acute myocardial infarction. Environ Health Perspect 2007;115:53–57. [PubMed: 17366819]
45. Elreedy S, Krieger N, Ryan PB, et al. Relations between individual and neighborhood-based measures of socioeconomic position and bone lead concentrations among community-exposed men: the Normative Aging Study. Am J Epidemiol 1999;150:129–141. [PubMed: 10412957]
46. Zanobetti A, Schwartz J. Are diabetics more susceptible to the health effects of airborne particles? Am J Respir Crit Care Med 2001;164:831–833. [PubMed: 11549541]
47. O'Neill MS, Veves A, Zanobetti A, et al. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circulation 2005;111:2913–2920. [PubMed: 15927967]
48. Bateson TF, Schwartz J. Who is sensitive to the effects of particulate air pollution on mortality? A case-crossover analysis of effect modifiers. Epidemiology 2004;15:143–149. [PubMed: 15127905]
49. Levy JI, Chemerynski SM, Sarnat JA. Ozone exposure and mortality: an empiric bayes metaregression analysis. Epidemiology 2005;16:458–468. [PubMed: 15951663]
50. Ito K, De Leon SF, Lippmann M. Associations between ozone and daily mortality: analysis and meta-analysis. Epidemiology 2005;16:446–457. [PubMed: 15951662]
51. Bell ML, Dominici F, Samet JM. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology 2005;16:436–445. [PubMed: 15951661]
52. Gryparis A, Forsberg B, Katsouyanni K, et al. Acute effects of ozone on mortality from the "air pollution and health: a European approach" project. Am J Respir Crit Care Med 2004;170:1080–1087. [PubMed: 15282198]
53. Koken PJ, Piver WT, Ye F, et al. Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. Environ Health Perspect 2003;111:1312–1317. [PubMed: 12896852]
54. Ruidavets JB, Cournot M, Cassadou S, et al. Ozone air pollution is associated with acute myocardial infarction. Circulation 2005;111:563–569. [PubMed: 15699276]
55. Rich DQ, Schwartz J, Mittleman MA, et al. Association of short-term ambient air pollution concentrations and ventricular arrhythmias. Am J Epidemiol 2005;161:1123–1132. [PubMed: 15937021]
56. Bates DV. Ambient ozone and mortality. Epidemiology 2005;16:427–429. [PubMed: 15951659]
57. Sarnat JA, Brown KW, Schwartz J, et al. Ambient gas concentrations and personal particulate matter exposures: implications for studying the health effects of particles. Epidemiology 2005;16:385–395. [PubMed: 15824556]
58. Chuang KJ, Chan CC, Su TC, et al. Urban air pollution on inflammation, oxidative stress, coagulation and autonomic dysfunction. Am J Respir Crit Care Med 2007;176:370–376. [PubMed: 17463411]
59. Suh HH, Nishioka Y, Allen GA, et al. The metropolitan acid aerosol characterization study: results from the summer 1994 Washington, D.C. field study. Environ Health Perspect 1997;105:826–834. [PubMed: 9347898]
60. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental AssessmentAir Quality Criteria for Particulate Matter1996 Available at: http://cfpub.epa.gov/ ncea/cfm/recordisplay.cfm?deid=2832 Accessed September 3, 2005
61. Goldberg MS, Burnett RT, Bailar JC III, et al. The association between daily mortality and ambient air particle pollution in Montreal, Quebec. 2. Cause-specific mortality. Environ Res 2001;86:26–36. [PubMed: 11386738]
62. Anderson HR, Bremner SA, Atkinson RW, et al. Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occup Environ Med 2001;58:504–510. [PubMed: 11452044]
63. Stone PH, Godleski JJ. First steps toward understanding the pathophysiologic link between air pollution and cardiac mortality. Am Heart J 1999;138(5 pt 1):804–807. [PubMed: 10539808]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

64. Park SK, O'Neill MS, Stunder BJ, et al. Source location of air pollution and cardiac autonomic function: trajectory cluster analysis for exposure assessment. J Expo Sci Environ Epidemiol 2007;17:488–497. [PubMed: 17299527]
65. Hu H, Shih R, Rothenberg S, Schwartz BS. The epidemiology of lead toxicity in adults: measuring dose and consideration of other methodologic issues. Environ Health Perspect 2007;115:455–462. [PubMed: 17431499]
66. Vig EK, Hu H. Lead toxicity in older adults. J Am Geriatr Soc 2000;48:1501–1506. [PubMed: 11083332]
67. Hu H, Watanabe H, Payton M, et al. The relationship between bone lead and hemoglobin. JAMA 1994;272:1512–1517. [PubMed: 7966843]
68. Korrick SA, Hunter DJ, Rotnitzky A, et al. Lead and hypertension in a sample of middle-aged women. Am J Public Health 1999;89:330–335. [PubMed: 10076481]
69. Weisskopf MG, Wright RO, Schwartz J, et al. Cumulative lead exposure and prospective change in cognition among elderly men: the VA Normative Aging Study. Am J Epidemiol 2004;160:1184–1193. [PubMed: 15583371]
70. Gonzalez-Cossio T, Peterson KE, Sanin LH, et al. Decrease in birth weight in relation to maternal bone-lead burden. Pediatrics 1997;100:856–862. [PubMed: 9346987]
71. Schaumberg DA, Mendes F, Balaram M, et al. Accumulated lead exposure and risk of age-related cataract in men. JAMA 2004;292:2750–2754. [PubMed: 15585735]
72. Gurer H, Ercal N. Can antioxidants be beneficial in the treatment of lead poisoning? Free Radic Biol Med 2000;29:927–945. [PubMed: 11084283]
73. Adonaylo VN, Oteiza PI. Pb^{2+} promotes lipid oxidation and alterations in membrane physical properties. Toxicology 1999;132:19–32. [PubMed: 10199578]
74. Vaziri ND. Pathogenesis of lead-induced hypertension: role of oxidative stress. J Hypertens 2002;20 (Suppl 3):S15–S20.
75. Kober TE, Cooper GP. Lead competitively inhibits calcium-dependent synaptic transmission in the bullfrog sympathetic ganglion. Nature 1976;262:704–705. [PubMed: 183141]
76. Sandhir R, Gill KD. Alterations in calcium homeostasis on lead exposure in rat synaptosomes. Mol Cell Biochem 1994;131:25–33. [PubMed: 8047062]
77. Dursun N, Arifoglu C, Suer C, et al. Blood pressure relationship to nitric oxide, lipid peroxidation, renal function, and renal blood flow in rats exposed to low lead levels. Biol Trace Elem Res 2005;104:141–149. [PubMed: 15894814]
78. Ding Y, Gonick HC, Vaziri ND. Lead promotes hydroxyl radical generation and lipid peroxidation in cultured aortic endothelial cells. Am J Hypertens 2000;13(5 pt 1):552–555. [PubMed: 10826409]
79. Oh, JA. ScD Thesis. Harvard School of Public Health; Boston, MA: 2000. Characterization and source apportionment of air pollution in Nashville, TN and Boston, MA.
80. U.S. Environmental Protection AgencyAir Trends: Lead2005 Available at: http://www.epa.gov/airtrends/lead.html Accessed September 19, 2005
81. Hu H. Bone lead as a new biologic marker of lead dose: recent findings and implications for public health. Environ Health Perspect 1998;106(suppl 4):961–967. [PubMed: 9703479]
82. U.S. Environmental Protection AgencyEPA Green Book Nonattainment Areas for Criteria Pollutants2005 Available at: http://www. epa.gov/oar/oaqps/greenbk/ Accessed September 19, 2005

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

TABLE 1

Characteristics of the Study Population by Quartile of Tibia Lead Levels, Normative Aging Study, Boston, Massachusetts, 2000–2004

	Quartile of Tibia Lead Level				
	1	2	3	4	
	Range ≤11.0 μg/g (n = 101)	12.0–18.0 μg/g (n = 86)	19.0–27.0 μg/g (n = 100)	≥28.0 μg/g (n = 97)	P^*
	Continuous Variables; Mean ± SD				
Tibia lead (μg/g)	6.2 ± 4.4	15.0 ± 1.9	22.2 ± 2.3	37.3 ± 8.9	<0.001
Patella lead (μg/g)†	17.3 ± 10.3	20.7 ± 11.5	25.5 ± 11.2	43.8 ± 23.7	<0.001
Estimated patella lead (μg/g)†	13.2 ± 9.4	14.8 ± 9.8	18.8 ± 8.8	34.6 ± 22.3	<0.001
Age (yrs)	70.2 ± 5.9	72.5 ± 6.8	73.6 ± 6.1	75.9 ± 6.1	<0.001
Body mass index (kg/m^2)	28.4 ± 4.3	27.7 ± 3.5	27.9 ± 4.3	27.8 ± 3.7	0.31
Mean arterial blood pressure (mm Hg)	94.4 ± 9.0	93.7 ± 12.8	93.5 ± 10.9	91.0 ± 11.1	0.04
Heart rate (beats/min)	70.7 ± 8.3	70.3 ± 6.0	71.5 ± 6.6	70.5 ± 6.5	0.86
Fasting blood glucose (mg/dL)	107.7 ± 35.7	107.6 ± 27.3	108.2 ± 25.6	106.2 ± 22.6	0.76
Cholesterol (mg/dL)	194.2 ± 33.5	195.3 ± 38.8	189.8 ± 35.3	188.6 ± 38.8	0.18
HDL (mg/dL)	49.7 ± 14.4	49.4 ± 14.5	49.6 ± 13.8	47.1 ± 10.9	0.22
Triglyceride (mg/dL)	125.5 ± 65.9	129.8 ± 69.0	124.5 ± 70.6	132.4 ± 69.9	0.61
Cumulative traffic (vehicle-km)	1281 ± 2755	948 ± 971	915 ± 974	1206 ± 1622	0.71
Heart rate variability					
Log_{10} HF (msec^2)	1.91 ± 0.70	1.96 ± 0.69	1.84 ± 0.60	1.95 ± 0.68	0.94
Log_{10} LF (msec^2)	2.03 ± 0.52	2.01 ± 0.49	1.99 ± 0.50	1.92 ± 0.57	0.14
	Frequencies; No. (%)				
Smoking status					
Never	41 (40.6)	24 (27.9)	32 (32.0)	26 (26.8)	0.36‡
Former	54 (53.5)	55 (64.0)	64 (64.0)	65 (67.0)	
Current	6 (5.9)	7 (8.1)	4 (4.0)	6 (6.2)	
Pack-years of cigarette smoking					
0	41 (40.6)	24 (27.9)	32 (32.0)	26 (26.8)	0.09‡
>0–29	39 (38.6)	41 (47.7)	38 (38.0)	33 (34.0)	
30–59	16 (15.8)	16 (18.6)	23 (23.0)	24 (24.7)	

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

	Quartile of Tibia Lead Level				
	1	2	3	4	
	Range ≤11.0 μg/g (n = 101)	12.0–18.0 μg/g (n = 86)	19.0–27.0 μg/g (n = 100)	≥28.0 μg/g (n = 97)	*P*[*]
≥60	5 (5.0)	5 (5.8)	7 (7.0)	14 (14.4)	
Education					
Less than high school diploma	6 (5.9)	3 (3.5)	14 (14.0)	15 (15.5)	0.01[‡]
High school diploma and some college	58 (57.4)	53 (61.6)	62 (62.0)	62 (63.9)	
≥4 yrs of college	37 (36.6)	30 (34.9)	24 (24.0)	20 (20.6)	
Alcohol intake (≥2 drinks/d)	17 (16.8)	14 (16.3)	22 (22.0)	21 (21.7)	0.26
Diabetes mellitus	14 (13.9)	15 (17.4)	29 (29.0)	21 (21.7)	0.05
Ischemic heart disease	25 (23.4)	22 (23.9)	37 (35.9)	34 (33.7)	0.03
Hypertension	65 (64.4)	59 (68.6)	74 (74.0)	77 (79.4)	0.01
Use of β-blocker	32 (31.7)	27 (31.4)	36 (36.0)	38 (39.2)	0.21
Use of calcium-channel blocker	13 (12.9)	14 (16.3)	16 (16.0)	13 (13.4)	0.91
Use of ACE inhibitor	18 (17.8)	17 (19.8)	27 (27.0)	22 (22.7)	0.24
Use of statin	44 (43.6)	33 (38.4)	37 (37.0)	32 (33.0)	0.13

HDL indicates high density lipoprotein; HF, high frequency; LF, low frequency; ACE, angiotensin-converting enzyme.

[*] *P* for trend, except where indicated.

[†] Total number for patella lead = 369.

[‡] P value for χ^2 test.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

TABLE 2

Outdoor Air Pollution and Apparent Temperature Levels (24-h Averages) During the Heart Rate Variability Measurement and Their Correlation Coefficients

	Mean ± SD	Range	$PM_{2.5}$	Black carbon	Sulfate*	Ozone	Apparent temperature
$PM_{2.5}$ ($\mu g/m^3$)†	11.8 ± 8.2	0.55–62.8	1				
Black carbon ($\mu g/m^3$)	0.91 ± 0.47	0.19–2.6	0.57‡	1			
Sulfate* ($\mu g/m^3$)	3.4 ± 3.6	0.39–29.0	0.91‡	0.46‡	1		
Ozone (ppb)	23.4 ± 13.0	2.6–84.7	0.51‡	−0.01	0.57‡	1	
Apparent temperature§ (°C)	11.5 ± 10.1	−5.5–35.5	0.36‡	0.33‡	0.37‡	0.57‡	1

*The previous day's level (1-d lag).

†The 24-h National Ambient Air Quality Standard for $PM_{2.5}$ during the study period was 65g/m3 (now 35 $\mu g/m^3$).

‡$P < 0.0001$.

§Apparent temperature = −2.653 ± (0.994 × air temperature) + (0.0153 × dew-point temperature).

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

TABLE 3

Estimated Percent Changes* in Heart Rate Variability Associated With Air Pollution, by Quartile of Bone Lead Levels

		Model 1†					Model 2‡				
		Quartiles of Lead					Quartiles of Lead Adjusted for Education and Cumulative Traffic				
Heart Rate Variability	Pollutant	1 % Change (95% CI)	2 % Change (95% CI)	3 % Change (95% CI)	4 % Change (95% CI)	*P* for Trend	1 % Change (95% CI)	2 % Change (95% CI)	3 % Change (95% CI)	4 % Change (95% CI)	*P* for Trend
		Tibia Lead					**Tibia Lead**				
		(n = 101)	**(n = 86)**	**(n = 100)**	**(n = 97)**		**(n = 96)**	**(n = 96)**	**(n = 96)**	**(n = 96)**	
HF	$PM_{2.5}$	2.8 (−33.1 to 57.9)	−16.0 (−43.4 to 24.5)	−4.6 (−32.0 to 33.9)	−21.6 (−37.4 to −1.7)	0.32	0.0 (−35.0 to 53.9)	−19.0 (−45.3 to 19.9)	−17.4 (−46.3 to 27.0)	−17.3 (−33.0 to 2.1)	0.60
	Black carbon	−3.4 (−39.2 to 53.3)	−16.3 (−51.4 to 44.1)	3.0 (−36.5 to 67.2)	−28.1 (−54.0 to 12.4)	0.55	−5.0 (−40.6 to 51.9)	−26.3 (−57.6 to 28.1)	−0.4 (−36.2 to 55.4)	−30.4 (−56.5 to 11.3)	0.58
	Sulfate	50.7 (5.4 to 115.5)	1.4 (−30.1 to 47.1)	−8.4 (−35.9 to 30.9)	−22.2 (−40.4 to 1.6)	<0.01	44.6 (0.0 to 109.3)	−6.2 (−33.7 to 32.7)	−12.2 (−42.7 to 34.5)	−17.0 (−35.6 to 6.9)	0.02
	Ozone	16.1 (−18.9 to 66.2)	−3.2 (−29.7 to 33.2)	−22.4 (−45.4 to 10.3)	−37.9 (−54.6 to −14.9)	<0.01	16.4 (−21.8 to 73.5)	6.4 (−20.7 to 42.8)	−52.5 (−70.7 to −22.8)	−24.9 (−43.0 to −1.1)	0.02
LF	$PM_{2.5}$	2.8 (−27.3 to 45.4)	−18.8 (−40.9 to 11.7)	0.5 (−23.6 to 32.1)	−9.6 (−24.6 to 8.6)	0.77	−4.1 (−32.3 to 35.8)	−12.2 (−36.0 to 20.5)	−5.0 (−32.9 to 34.5)	−8.4 (−22.8 to 8.5)	0.96
	Black carbon	−1.9 (−32.4 to 42.5)	−12.7 (−43.7 to 35.4)	11.8 (−24.4 to 65.2)	−1.7 (−31.4 to 41.0)	0.83	1.4 (−30.5 to 48.1)	−14.3 (−45.1 to 33.9)	9.9 (−23.3 to 57.3)	−14.0 (−41.1 to 25.6)	0.76
	Sulfate	28.3 (−3.6 to 70.6)	−2.6 (−27.6 to 31.1)	−10.6 (−32.8 to 18.8)	−11.7 (−28.6 to 9.3)	0.04	26.2 (−5.9 to 69.2)	−6.9 (−29.3 to 22.6)	−7.7 (−34.2 to 29.5)	−10.7 (−27.0 to 9.2)	0.08
	Ozone	4.2 (−21.8 to 38.8)	−14.5 (−33.8 to 10.4)	−24.3 (−42.9 to 0.2)	−38.1 (−51.9 to −20.4)	<0.01	−3.6 (−30.0 to 32.8)	−7.8 (−27.2 to 16.8)	−43.5 (−61.8 to −16.6)	−26.9 (−41.4 to −8.7)	0.05
		Patella Lead					**Patella Lead**				
		(n = 90)	**(n = 94)**	**(n = 93)**	**(n = 92)**		**(n = 92)**	**(n = 92)**	**(n = 93)**	**(n = 92)**	

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

		Model 1[†]					Model 2[‡]				
		Quartiles of Lead					Quartiles of Lead Adjusted for Education and Cumulative Traffic				
Heart Rate Variability	**Pollutant**	**1 % Change (95% CI)**	**2 % Change (95% CI)**	**3 % Change (95% CI)**	**4 % Change (95% CI)**	***P* for Trend**	**1 % Change (95% CI)**	**2 % Change (95% CI)**	**3 % Change (95% CI)**	**4 % Change (95% CI)**	***P* for Trend**
HF	$PM_{2.5}$	16.0 (−19.1 to 66.5)	−11.0 (−38.2 to 28.3)	−29.2 (−49.5 to −0.8)	−20.5 (−38.4 to 2.5)	0.08	11.3 (−21.5 to 57.8)	−14.1 (−42.0 to 27.2)	−23.4 (−44.7 to 6.1)	−24.7 (−41.5 to −3.1)	0.08
	Black carbon	0.5 (−39.6 to 67.3)	−16.6 (−48.2 to 34.4)	−22.6 (−53.7 to 29.4)	−5.3 (−39.8 to 49.1)	0.84	−6.0 (−43.0 to 55.1)	−9.7 (−42.5 to 42.0)	−33.2 (−61.6 to 16.1)	−10.2 (−42.9 to 41.1)	0.79
	Sulfate	29.8 (−7.3 to 81.6)	−3.4 (−34.8 to 43.0)	−19.9 (−42.4 to 11.2)	−4.1 (−30.4 to 32.2)	0.16	4.1 (−27.3 to 49.0)	22.7 (−15.6 to 78.3)	−13.5 (−37.2 to 19.2)	−15.0 (−38.0 to 16.5)	0.22
	Ozone	6.8 (−21.8 to 45.8)	−14.1 (−39.9 to 22.9)	−19.3 (−44.0 to 16.4)	−41.4 (−59.5 to −15.0)	0.01	15.8 (−16.5 to 60.5)	−17.4 (−42.1 to 17.8)	−12.1 (−36.9 to 22.6)	−45.4 (−61.7 to −22.1)	<0.01
LF	$PM_{2.5}$	16.0 (−13.4 to 55.4)	−12.6 (−35.0 to 17.5)	−18.4 (−37.9 to 7.1)	−9.8 (−26.7 to 10.8)	0.21	15.5 (−12.8 to 52.9)	−12.5 (−36.2 to 20.0)	−20.1 (−38.6 to 3.9)	−9.9 (−26.4 to 10.4)	0.20
	Black carbon	12.1 (−25.7 to 69.1)	−16.0 (−42.9 to 23.4)	8.3 (−28.5 to 64.0)	−0.7 (−31.1 to 43.1)	0.86	21.2 (−18.9 to 81.1)	−6.8 (−35.1 to 34.0)	−21.1 (−49.4 to 22.8)	1.9 (−29.1 to 46.5)	0.51
	Sulfate	4.3 (−20.1 to 36.0)	4.5 (−23.4 to 42.5)	−16.4 (−35.5 to 8.4)	−7.9 (−28.5 to 18.7)	0.34	−0.8 (−25.1 to 31.5)	16.6 (−13.0 to 56.3)	−16.2 (−34.8 to 7.8)	−12.5 (−31.7 to 12.0)	0.25
	Ozone	2.1 (−20.4 to 31.1)	−12.2 (−34.1 to 16.9)	−28.2 (−46.4 to −3.6)	−36.4 (−52.8 to −14.3)	<0.01	2.1 (−21.3 to 32.7)	−13.8 (−35.1 to 14.6)	−18.8 (−37.8 to 6.0)	−40.0 (−54.9 to −20.2)	−0.01

[*] Coefficients were calculated from linear regression models including interaction terms between quartiles of tibia or patella lead and each air pollutant; expressed as percent changes per 1 interquartile range increase (7 μg/m^3 for $PM_{2.5}$; 0.6 μg/m^3 for BC; 2.5 μg/m^3 for sulfate; 16 ppb for ozone).

[†] Model 1 was adjusted for age, body mass index, fasting blood glucose, mean arterial pressure, smoking status (current/former/never), pack years of cigarettes (0/ >0–29/30–59/ ≥60), alcohol consumption, use of beta-blocker, calcium channel blocker, and/or angiotensin converting enzyme inhibitor, season (spring/summer/fall/winter), room temperature, cubic smoothing splines (3 *df*) for apparent temperature, individual education attainment (less than high school/some college/≥4 yr of college) and cumulative traffic.

[‡] Covariates in model 2 were the same as model 1 excluding individual education attainment and cumulative traffic.