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Long-Term Air Pollution Exposure and Blood Pressure in the Sister Study

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Abstract

Background: Exposure to air pollution has been consistently associated with cardiovascular morbidity and mortality but mechanisms remain uncertain. Associations with blood pressure (BP) may help to explain the cardiovascular effects of air pollution.

Objective: We examined the cross-sectional relationship between long-term (annual average) residential air pollution exposure and BP in the National Institute of Environmental Health Sciences' Sister Study, a large U.S. cohort study investigating risk factors for breast cancer and other outcomes.

Methods: This analysis included 43,629 women aged 35-76, enrolled 2003 to 2009, who had a sister with breast cancer. Geographic information systems contributed to satellite-based nitrogen dioxide (NO_2) and fine particulate matter ($PM_{2.5}$) predictions at participant residences at study entry. Generalized additive models were used to examine the relationship between pollutants and measured BP at study entry, adjusting for cardiovascular disease risk factors, and including thin plate splines for potential spatial confounding.

Results: A 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with 1.4 mmHg higher systolic BP (95% CI: 0.6, 2.3; $p<0.001$), 1.0 mmHg higher pulse pressure (95% CI: 0.4, 1.7; $p=0.001$), 0.8 mmHg higher mean arterial pressure (95% CI: 0.2, 1.4; $p=0.01$), and no significant association with diastolic BP. A 10 ppb increase in NO_2 was associated with a 0.4 mmHg (95% CI: 0.2, 0.6; $p<0.001$) higher pulse pressure.

Conclusions: Long-term $PM_{2.5}$ and NO_2 exposures were associated with higher blood pressure. On a population scale, such air pollution-related increases in blood pressure could, in part, account for the increases in cardiovascular disease morbidity and mortality seen in prior studies.

Introduction

There is a well-established relationship between combustion-related air pollution exposure, especially particulate matter ≤2.5 microns in diameter ($PM_{2.5}$), and cardiovascular disease (CVD) morbidity and mortality (Brook et al. 2010). Although there have been numerous studies that demonstrate this relationship, the mechanisms are poorly understood.

One potential mechanism is an effect of inhaled air pollution on blood pressure (BP), mediated through autonomic nervous system dysfunction and/or changes in inflammation and oxidative stress. Increased BP is a strong risk factor for CVD including increases in left ventricular mass, which have been associated with long-term air pollution exposures (Van Hee et al. 2009).

Recent work has suggested that short-term (over hours to days) particulate matter and traffic-related pollutant exposures may lead to transient increases in BP (Baccarelli et al. 2011; Baumgartner et al. 2011; Brook et al. 2011; Cosselman et al. 2012; Hoffmann et al. 2012; Langrish et al. 2012; Wu et al. 2013). In contrast, a study of 9,238 nonsmoking adults in Taiwan found reductions in systolic BP (SBP) and pulse pressure (PP) following short-term exposure to air pollution (Chen et al. 2012).

The relationship between chronic, long-term (e.g., yearly average) air pollution exposure and BP is less well understood, with some studies demonstrating an increase in BP associated with $PM_{2.5}$ (Chuang et al. 2011; Fuks et al. 2011) and black carbon (Schwartz et al. 2012) exposure. Additional studies have investigated associations of BP with oxides of nitrogen (NO_x,a marker of traffic-related pollution) (Dong et al. 2013; Sørensen et al. 2012) or have investigated the associations between BP and long-term exposures to both $PM_{2.5}$ and gaseous traffic-related pollution exposure (Chuang et al. 2011; Coogan et al. 2012).

Developments in fine-scale spatial modeling of air pollution—using advanced statistical methods, geographic information systems, and both ground-based and satellite-based monitoring information—are now available. Together with large national cohorts, these exposure advances provide the opportunity for an improved analysis of this important research question.

We conducted a cross-sectional study to evaluate the relationship between BP (systolic, diastolic, pulse pressure, and mean arterial pressure) and long-term (annual average) exposure to $PM_{2.5}$ and nitrogen dioxide (NO_2) in a large U.S. cohort of women.

Methods

Study population

Study participants were selected from the Sister Study, a large nationwide, prospective women's cohort study investigating environmental and genetic risk factors for breast cancer and other diseases. 50,884 sisters of women with breast cancer, aged 35-76, were enrolled into the cohort between 2003 and 2009, as described elsewhere (Weinberg et al. 2007). The Sister Study was approved by the Institutional Review Board (IRB) of the National Institute of Environmental Health Sciences, National Institutes of Health, and the Copernicus Group IRB; all participants provided their informed consent. In this analysis, participants were excluded due to residence outside of the continental U.S. (2% of participants), invalid address information (6%), missing BP measurement (0.3%), missing modeled NO_2 estimates (0.06%), or other missing key covariate data (6%). Therefore, this analysis includes 43,629 (86%) of the recruited participants residing in the conterminous United States at enrollment.

Computer-assisted telephone interviews were administered by extensively trained staff and collected information on participant demographics, socioeconomic (SES) factors, residential

history, occupational history, personal medical history (including self-reported diabetes, hypercholesterolemia, and hypertension), medication use, perceived stress (4-item perceived stress scale) (Cohen et al. 1983), and behavioral factors such as alcohol use and smoking. Participants were asked whether they had ever been diagnosed by a medical professional with diabetes, hypercholesterolemia, and hypertension. Responses were self-reported as no, yes, or "borderline," with the last category added to accommodate participants who have been told that they had or nearly had the condition but did not require medications. Medication lists were coded using the Slone Drug Dictionary (Kelley et al. 2003), and anti-hypertensive medication use was defined as self-reporting one or more drugs in anti-hypertensive drug classes.

Women were enrolled throughout the U.S. and completed telephone interviews as close to the time they volunteered as possible; participation was not geographically or seasonally clustered. Home visits were conducted by examiners from a national company that performs insurance physicals, and were not scheduled in a manner to maximize geographic efficiency. The home visits provided measurements of anthropometry, fasting phlebotomy, and BP.

Approximately 10% of participants were sisters with one or more study participant, and the analyses do not account for familial clustering in the population because the most common cluster size was very small.

Blood pressure ascertainment

During baseline home visits, following consent and review of self-completed forms, participants were instructed to sit and rest for a few minutes prior to BP ascertainment. Trained examiners made three consecutive measurements of BP using an aneroid sphygmomanometer (Model 760 & 775X, American Diagnostic Corporation). Measurements were taken from alternating arms,

starting with the left arm using a left-right-left protocol, approximately two minutes apart. Exams were scheduled, whenever possible, in the morning, and participants were encouraged to fast prior to the visit (excluding medications) and record whether anything had been taken by mouth

For SBP and diastolic blood pressure (DBP) separately, the second and third measurements were averaged when three measurements were available. In some cases, examiners were unable to obtain three BP measurements. When only two BP measurements were available (n=1,677), the two were averaged and when only one BP measurement was recorded, the single value was used (n=684).

Because the mechanism through which air pollution exposure may affect BP is not well understood, we also examined PP and mean arterial pressure (MAP), as other studies have also done (Auchincloss et al. 2008; Chen et al. 2012). PP, representing stroke volume and vascular compliance (Dart and Kingwell 2001), was determined by subtracting DBP from SBP, and MAP, a function of ventricular contractility, resistance, elasticity, and heart rate (Sesso et al. 2000), was calculated by PP/3 + DBP.

Exposure assessment

Participant home latitude and longitude at study entry was geocoded using ArcGIS 9.3.1 or 10.1 (ESRI, Redlands, CA) in conjunction with TeleAtlas Dynamap 2000 v16.1 road network (TeleAtlas, Boston, MA). Based on the residential geocodes, we assigned the census block..

For $PM_{2.5}$, we developed a national prediction model for the year 2006, using partial least squares to select relevant components for the mean regression and universal kriging for spatial smoothing (Sampson et al. 2013). Briefly, the $PM_{2.5}$ prediction model included satellite-based

land-use/land cover, road network characteristics, population density, vegetative index, distance to selected geographic features, and annual average U.S. EPA Air Quality System monitor concentrations. The model was fit using maximum likelihood, with each region having its own parameters (cross-validated R^2=0.88). Individual $PM_{2.5}$ concentrations were predicted for each residential geocode.

National NO_2 predictions were developed using a previously described satellite-based land-use regression model for the year 2006 (Novotny et al. 2011). In short, atmospheric NO_2 surface concentrations were predicted using multivariable linear regression based on land-use characteristics (impervious surfaces, tree canopy, sum of road lengths, elevation, and distance to coast) and tropospheric NO_2 column abundance measurements from the Ozone Monitoring Instrument sensor (cross-validated R^2=0.78). Individual NO_2 concentrations were assigned based on the census block of the subject's residential address.

Predicted annual average $PM_{2.5}$ and NO_2 concentrations were used to approximate long-term residential exposure at the time of baseline examination (2003-2009). The correlation between $PM_{2.5}$ and NO_2 for this population was 0.37, and while both exposure models contain similar terms, the modeling approaches are quite different.

Other geographic covariate measurement

To describe the overall urbanicity of the county in which participants reside, we used the Rural-Urban Continuum Codes of the U.S. Department of Agriculture (USDA 2013). The socioeconomic environment of the participants' neighborhoods was defined by using neighborhood-level SES Z-score based on U.S. Census block groups, which has been used in

other studies (Diez Roux et al. 2001). A higher SES Z-score signifies higher socioeconomic advantage.

Statistical analysis

For descriptive analyses, annual average air pollution exposure predictions ($PM_{2.5}$ and NO_2) and BP parameters (SBP, DBP, MAP, and PP) were divided into quartiles. Global F tests (ANOVA) were used to examine the differences in mean values of continuous variables (age, BP parameters, pollution measures) across quartiles of pollutants and BP parameters. The chi-squared test was used to compare the frequencies of categorical variables across quartiles of exposure and outcomes. Categorical covariates were included in the main models and interactions as defined in Table 1 and Table 2. To examine the overall spatial distribution of the exposures and outcomes, we plotted the mean BP parameters and air pollution exposure metrics for the participants by state, county, and census tract on U.S. maps.

We then fit multivariable linear models to investigate the relationship between individual BP parameters and each of the two pollutants of interest, adjusted for potential confounders including space (using unpenalized thin-plate regression splines (TPRS) in the MGCV package). TPRS are a flexible way of adjusting for spatial confounding. Using singular value decomposition, they decompose the distance matrix of all participant locations into a set of basis functions, the first *k* of which are included as adjustment covariates in the health models (Wood 2003).

Our final model included all covariates considered *a priori* as potential confounders. The *a priori* selection was based on a review of the literature prior to the analysis to avoid model selection bias. To evaluate the effect of groups of covariates, we added variables to successive models in

series, with Model 1 including age and race/ethnicity, Model 2 also including SES variables (household income, education, marital status, working ≥20 hours per week outside the home, perceived stress score, and SES Z-score), Model 3 additionally including spatial features that are likely to vary both with pollution and BP (Rural-Urban continuum code and TPRS for latitude and longitude), Model 4 additionally including CVD risk factors (body mass index (BMI), waist-to-hip ratio, smoking status, alcohol use, history of diabetes, and history of hypercholesterolemia), and the full Model 5 additionally including BP medication use. For the categorical SES variables in Model 2, we assume that collinearity does not exist because within the levels of each categorical variable there is some heterogeneity of the other categorical variables. Unpenalized TPRS for latitude and longitude were fit in two dimensions using 10 degrees of freedom (d.f.). Statistical analyses were carried out using R 2.15.0 (R Development Core Team, Vienna, Austria) and Stata/IC 12.1 (StataCorp LP, College Station, Texas, USA). In all instances, a p-value of <0.05 was considered significant.

When we observed significant associations with exposure in the full model, we additionally explored interactions with race/ethnicity, age, BMI, smoking, diabetes, and anti-hypertensive medication use by adding product terms of these variables with the exposure variable, and we examined interactive effect sizes and 95% confidence intervals (CI) within-strata using linear combinations of terms from the regression models (using wald.test and svycontrast in R).

Because there may be spatially varying characteristics that we were unable to account for, sensitivity analyses included varying the number of degrees of freedom for spatial adjustment and investigating the impact on main effect sizes and standard errors of alternate forms of the other independent and dependent variables (including non-linear associations for the exposure

metrics using penalized TPRS). To provide a complementary view, logistic regression was used to examine the hypertension as an outcome, defined as using anti-hypertensive medication or having a SBP ≥140mmHg and DBP ≥90mmHg. We also examined the effect of several subgroup analyses, restricting the full model analysis to individuals with stable residence (defined as the current address at the time of the examination representing their longest lived address) to account for potential exposure misclassification from characterizing current residence as a location of long-term exposure, and, separately, restricting the analysis to those with three valid, left-right-left arm, BP measurements to examine precision based on potential BP measurement error. Finally, we examined models including both air pollution exposure variables in a co-pollutant model.

Results

Participant characteristics

Table 1 presents baseline demographic characteristics and Table 2 shows baseline health characteristics of participants, overall and by quartile of pollutant exposure. Among the 43,629 women, the mean±standard deviation age was 55±8.9 years; range 35-76 years. 31% had self-reported hypertension or "borderline" hypertension, and 30% were on anti-hypertensive medications. Participants lived at their current address for a median of 11 years (interquartile range of 16 years), ranging from less than one year to 75 years.

Bivariate associations

Compared to the remainder of the sample, the highest quartile of both NO_2 and $PM_{2.5}$ exposure was significantly associated with younger participants, fewer non-Hispanic Whites and more Blacks, higher household income, fewer married women, more working >20 hours per week,

higher stress scores, greater residential stability, and with living in large metropolitan areas. Higher NO_2 (but not $PM_{2.5}$) quartile was associated with higher neighborhood SES, less overweightness, more former smokers, and more current alcohol users, whereas higher $PM_{2.5}$ (but not NO_2) was associated with significantly lower SES Z-scores, more obesity, more current smokers, and fewer current alcohol users. NO_2 was not associated with diabetes or anti-hypertensive medication use but was associated with self-reported hypertension and hypercholesterolemia, whereas higher $PM_{2.5}$ was associated with more diabetes, higher anti-hypertensive use, and more self-reported hypertension but not hypercholesterolemia in these unadjusted univariate comparisons. All risk factors and other SES and geographic covariates were highly statistically significantly associated with quartiles of SBP, DBP, MAP, and PP (data not shown).

Residential pollutant exposures

Figure 1 shows the distribution of participants' geocoded residential locations, with numbers representing the number of participants per state. The distribution of participants generally corresponds to the distribution of population across the U.S. Figure 2 presents boxplots of the distribution of exposure predictions for $PM_{2.5}$ and NO_2, by U.S. census division. See Supplemental Material, Figures S1 and S2, for maps of mean pollutant levels of participants by U.S. census tract. $PM_{2.5}$ shows large-scale spatial structure across the U.S. NO_2 exhibits a different spatial pattern, with high levels in highly urbanized areas, reflecting the traffic-related nature of NO_2. Thus, $PM_{2.5}$ exhibits greater between-city variability while NO_2 exhibits more within-city variability

Adjusted relationship between pollutants and BP

Figure 3 shows the results of adjusted linear models by pollutant. In the fully adjusted models (Model 5) shown in Table 3, a 10μg/m^3 increment in $PM_{2.5}$ was associated with a 1.4mmHg higher SBP (95%CI: 0.6, 2.3; p<0.001), a 1.0mmHg higher PP (95%CI: 0.4, 1.7; p=0.001), a 0.8mmHg higher mean arterial pressure (95%CI: 0.2, 1.4; p=0.01), and a 0.4mmHg higher DBP (95%CI: -0.2, 1.0; p=0.15). A 10ppb increase in NO_2 was associated with a 0.4mmHg (95%CI: 0.2, 0.6; p<0.001) higher PP, a 0.2mmHg higher SBP (95%CI: 0.0, 0.5; p=0.10), a 0.2mmHg lower DBP (95%CI: -0.4, 0.0; p=0.05), and no difference in MAP (95%CI: -0.2, 0.1; p=0.63).

For $PM_{2.5}$, adjustment for spatial features (Model 3 versus Model 2) had the largest impact on effect estimates reflecting the large-scale spatial structure in $PM_{2.5}$, with an increase in the positive association with SBP, a slight decrease in the positive association with DBP, and a concomitant increase in the PP association after adjustment (Table 3). For NO_2, adjustment for variables representing individual and neighborhood SES (Model 2 versus Model 1) had the largest impact on effect estimates particularly for SBP, with the association changing from negative and statistically significant to positive and approaching statistical significance. The importance of adjusting for these variables reflects the within-city nature of NO_2 variability. After full adjustment, associations with NO_2 and SBP are positive and DBP are negative, leading to a significant positive association with total PP. In general, all other added potentially confounding variables showed little impact on effect estimates.

Interactions

For our finding of an association between $PM_{2.5}$ and SBP, there was no significant evidence of interaction with BMI, race/ethnicity, age, smoking, diabetes, or anti-hypertensive medication use (see Supplemental Material, Figure S3).

Sensitivity analyses

The results of varying the number of d.f. used for spatial adjustment are shown in Supplemental Material, Figures S4 and S5. For $PM_{2.5}$ the estimated associations with BP were fairly stable with ≥8 d.f. Varying the d.f. had little impact on the associations of BP with NO_2. Using natural logarithmic transformations of the exposure and outcome variables produced no appreciable changes in the overall findings of the analysis (data not shown). When the analysis was restricted to (n=26,217) participants with residential stability, $PM_{2.5}$ effect estimates for SBP and PP were somewhat stronger; a 10μg/m^3 increase in $PM_{2.5}$ was associated with a 2.1mmHg higher SBP (95%CI: 1.0, 3.2; p<0.001) and a 1.6mmHg higher PP (95%CI: 0.7, 2.4; p<0.001), and no substantive changes in other effect estimates (data not shown). Restricting the analysis to participants with three valid BP measurements at the exam (n=41,263) also produced no change in estimates (data not shown).

The results of sensitivity analyses using penalized TPRS to assess nonlinearity of associations between BP and the exposures of interest were generally consistent with linearity, with some evidence of nonlinearity at the extremes of the exposure distributions (data not shown). Neither a 10μg/m^3 increase in $PM_{2.5}$ nor a 10ppb increase in NO_2 exposure was associated with increased odds of hypertension in Model 5 (OR: 0.95, 95%CI: 0.38, 2.36, p=0.92; OR: 1.02, 95%CI: 0.75, 1.38, p=0.91, respectively).

Though not observed for SBP, PP, or MAP, we saw a quadratic association association between DBP and age. Using a quadratic rather than linear adjustment for age in the DBP models yielded null results between DBP and both exposures (data not shown). Age range did not vary across quartiles of exposure (data not shown).

Co-pollutant analysis

Results from the co-pollutant analysis are shown in Supplement Material, Table S1. In the models that included both NO_2 and $PM_{2.5}$, the positive association between $PM_{2.5}$ and DBP became stronger and statistically significant while the association with PP became essentially null and insignificant. Specifically in fully adjusted models (Model 5), a 10μg/m^3 increase in $PM_{2.5}$ was associated with a 1.2mmHg higher DBP (95%CI: 0.5, 1.9; p=0.001) and a 0.4mmHg higher PP (95%CI: -0.4, 1.2; p=0.3). The negative association between NO_2 and DBP became stronger and remained statistically significant in the co-pollutant analysis, whereas the association between NO_2 and MAP became stronger and statistically significant. For NO_2, a 10ppb increase in NO_2 was associated with a 0.4mmHg lower DBP (95%CI: -0.6, -0.2; p<0.001) and a 0.3mmHg lower MAP (95%CI: -0.5, -0.1; p=0.02). No other associations were meaningfully changed from the primary single-pollutant models.

Discussion

This is the first large national cohort studied with individual BP measurements and the use of advanced modeling methods to assess fine-scale intra-urban gradients in major criteria air pollutants, $PM_{2.5}$ and NO_2. Prior studies have either used coarser scale exposure assessment (e.g., nearest regulatory monitor) or administrative records (e.g., records of hypertension diagnoses)

for outcome assessment. With exposures in the range currently experienced in the United States, these findings are interesting and important.

Our study demonstrates an association between increases in long-term residential exposure to $PM_{2.5}$ and NO_2 and higher measures of blood pressure (SBP, PP, and MAP for $PM_{2.5}$ and PP for NO_2). These relationships were robust to adjustment for multiple potential confounders, including SES and spatial characteristics, and apparently without threshold. The study also found an inverse relationship between NO_2 and DBP in the fully adjusted model (Model 5). We saw little evidence of effect modification by age, race/ethnicity, smoking, diabetes, anti-hypertensive medication use, or BMI (see Supplemental Material, Figure S3). Evidence of a long-term impact of air pollution on BP in our study population provides support to the hypothesis that air pollution induces autonomic dysfunction that may ultimately lead to vascular remodeling, increased BP and atherosclerosis (Brook et al. 2010).

Although these associations are modest at the individual-level, the potential public health consequences of population-level changes in BP of this magnitude are substantial (Whelton et al. 2002). The effect sizes estimated in this study are the same order of magnitude as other traditionally recommended behavioral health interventions (He and MacGregor 2004). As air pollution exposure is experienced at a population-level, even a small pro-hypertensive response to long-term air pollution exposures could contribute significantly to CVD.

In this analysis, neither $PM_{2.5}$ nor NO_2 exposure was associated with increased odds of hypertension, consistent with findings elsewhere (Chen et al. 2014; Foraster et al. 2014; Fuks et al. 2011); this null finding may be due to misclassification of hypertension cases (many cases are unrecognized) or regional differences in diagnosis and treatment.

Few studies have examined the relationship between long-term average exposure to both $PM_{2.5}$ and NO_2 and BP, and none have done so over a large, spatially dispersed population such as this one. Furthermore, the few studies who have examined PP and/or MAP as outcomes focused on short-term air pollution exposure (Auchincloss et al. 2008; Chen et al. 2012; Dvonch et al. 2009; Zanobetti et al. 2004). Long-term average $PM_{2.5}$ was shown to be associated with increased arterial BP in population-based cohort study (n=4,291) in a single metropolitan area in Western Germany (Fuks et al. 2011). In Taiwan, a study with large air pollution exposure contrasts (n=1,023) and no ability to account for neighborhood-level confounding showed strong positive associations between BP and both annual average $PM_{2.5}$ and NO_2 (Chuang et al. 2011). A study in an Ontario cohort found an association between $PM_{2.5}$ estimated using satellite-based methods and the incidence of a hypertension diagnosis in electronic medical records (Chen et al. 2014).

In contrast, a Danish population-based cohort study (n=57,053) found a small reduction in SBP with long-term average NO_x exposure (Sørensen et al. 2012). A study of Chinese adults (n=24,845) found no relationship between nearest monitor NO_2 and BP, but did find small increases in SBP and DBP in men associated with changes in PM_{10}, SO_2, and O_3 (Dong et al. 2013). The inverse relationship between NO_2 and DBP found in this study has not been reported by others (Chuang et al. 2011; Dong et al. 2013; Foraster et al. 2014), but it is possible that the inverse results may have been related to residual confounding.

Alternatively, differences in exposure metrics (NO_x versus NO_2) or other modeling methods may have contributed to differences in findings among studies. In a study of 853 elderly men in the Veterans Administration Normative Aging Study (Schwartz et al. 2012), positive associations between traffic particles and BP were observed.

Primary strengths of this study include its large size, high quality measurements of BP, detailed characterization of potential confounders including individual and neighborhood-level SES and spatial features, its large geographic extent, and the use of estimates of exposure to both $PM_{2.5}$ and NO_2.

The cross-sectional nature of this study is its primary limitation. The cohort consists only of women and, thus, results might not be generalizable to men. Given that the cohort is composed entirely of sisters of women with breast cancer, it might also not be representative of the general U.S. female population. The prevalence of hypertension in the study population (31%) is similar to that of U.S. women (31.7%, 95%CI: 29.9% - 33.5%) according to the 2005-2008 National Health and Nutrition Examination Survey (Gillespie et al. 2011). Mean SBP was slightly lower and DBP was slightly higher in the study population (115mmHg and 72mmHg, respectively) compared to women in the general U.S. population (121mmHg and 70mmHg, respectively) (Wright et al. 2011).

$PM_{2.5}$ and NO_2 exposures were modeled for the year 2006, whereas BP was measured between 2003 and 2009. The air pollution measures linked to residence at time of study enrollment were chosen as generally representative of long-term air pollution exposure. When our analysis was restricted to participants with residential stability, effect estimates appeared somewhat larger, suggesting that bias in these reported associations resulting from this exposure measurement error may underestimate the true associations.

The results may have also been affected by exposure misclassification. This study evaluated long-term residential air pollution exposure, and did not account for occupational, personal, or indoor air pollution exposure. There may be residual confounding by short-term exposure to air

pollution that this study was unable to account for, which was associated with higher SBP and DBP in a study of young adults in Taiwan (Lin et al. 2009). Additionally, the analysis assessed the effects of a 10μg/m^3 change in $PM_{2.5}$ (interquartile range: 3.58μg/m^3; 10^{th}–90^{th} percentile: 7.38–13.38μg/m^3) and a 10ppb change in NO_2 (interquartile range: 6.21ppb; 10^{th}–90^{th} percentile, 4.11–16.41ppb) which may be extrapolating beyond the data in some regions or comparing extremes of the exposure distributions. A moderate amount of correlation between $PM_{2.5}$ and NO_2 was observed (R=0.37), suggesting that one exposure is not acting as a surrogate for the other, which is consistent with other studies that have reported differences in associations with BP based on multi-pollutant models compared with single pollutant models (Chuang et al. 2011; Coogan et al. 2012).

Despite the detailed characterization of potential confounders, most were self-reported, including medication lists used to determine anti-hypertensive medication use. Similarly, physical activity and diet were not included which could affect validity of the results via residual confounding; it is possible that the spatial adjustments may capture some of the anticipated variation in physical activity and diet. While anti-hypertensive treatment lowers blood pressure, there was not an ideal way to account for medication use in our analysis; it does not appear to behave as a confounder in this analysis (Foraster et al. 2014).

It should also be noted that BP ascertainment on a single-day does not allow a precise measurement of the individual's true BP levels. Whenever possible, BP was measured in the morning but hour of measurement was not included in the analysis. Although seasonal trends in BP could contribute to non-differential misclassification, no discernable patterns were observed when reviewing exam month by geographic region.

Potential residual confounding by traffic noise is a possibility (Dratva et al. 2012; Sørensen et al. 2011). However, confounding by noise in this study might be limited given the wide area studied and the large sample size, as demonstrated elsewhere (Tétreault et al. 2013).

Conclusions

Our findings suggest that chronic $PM_{2.5}$ exposure may lead to increases in both SBP and PP, and that chronic NO_2 exposure may increase PP. These findings are consistent with our hypothesis that air pollution leads to CVD through mechanisms involving increased BP, potentially via the long-term vascular remodeling that accompanies chronic autonomic dysfunction or inflammation and oxidative stress.

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Table 1. Baseline demographic characteristics of participants, *n*, mean ± standard deviation, or %.

Characteristics	Quartile of Exposure to $PM_{2.5}$ in $\mu g/m^3$				Quartile of Exposure to NO_2 in ppb				All
	2.2-8.8	8.8-10.8	10.8-12.4	12.4-17.4	1.0-6.4	6.4-9.2	9.2-12.6	12.6-34.2	Participants
Number of Participants (*n*)	10929	10924	10915	10861	10927	10917	10884	10901	43629
Age (years)	55.5±8.9	55.1±9.1	54.8±8.9	54.5±8.9	55.3±8.8	55.1±8.9	54.8±9.0	54.7±9.0	55.0±8.9
Race or Ethnic Group									
Non-Hispanic White	92	89	86	75	91	88	84	78	85
Black	2	5	9	20	5	7	10	14	9
Hispanic	3	3	3	3	1	2	4	5	3
Other	3	3	2	2	3	3	2	3	3
Household Income									
<$20,000	26	25	23	25	28	25	23	23	25
$20,000-<$50,000	45	45	44	43	46	45	44	41	44
$50,000-<$100,000	26	26	28	27	23	25	28	30	27
≥$100,000	4	4	5	5	3	4	4	6	4
Education									
≤High school	14	16	15	14	17	16	14	12	15
Some college	35	35	32	32	37	35	33	31	34
Bachelor's or above	51	49	52	53	46	50	53	57	52
Married	76	72	72	63	80	74	68	60	71
Working >20 hrs/week	58	60	61	64	59	60	61	64	61
Perceived Stress Score									
Low (0-2)	60	57	57	55	59	58	57	55	57
Medium (3-6)	34	35	36	36	34	35	35	37	35
High (>6)	7	8	8	8	7	7	8	8	8
Stable Residence	57	59	62	62	59	57	59	65	60
Neighborhood SES Z-score Tertile									
Low	31	34	31	37	45	32	27	30	33
Medium	37	34	32	30	35	36	33	29	33
High	31	32	37	33	20	33	39	41	33
Rural-Urban Continuum Code									
Metro area ≥1 million	39	58	58	72	25	44	67	90	57
Metro area <1 million	39	29	31	23	42	41	30	10	31
Non-Metro county	22	12	12	5	33	14	3	0	13

Shown as annual Neighborhood SES (Socioeconomic Status) Z-Score Tertile: The socioeconomic environment of the participants' neighborhoods was defined by U.S. Census block group characteristics. A higher SES Z-score signifies higher socioeconomic advantage. Metro: Metropolitan.

Table 2. Baseline health characteristics of participants, mean ± standard deviation or %.

Characteristics	Quartile of Exposure to $PM_{2.5}$ in $\mu g/m^3$				Quartile of Exposure to NO_2 in ppb				All
	2.2-8.8	8.8-10.8	10.8-12.4	12.4-17.4	1.0-6.4	6.4-9.2	9.2-12.6	12.6-34.2	Participants
Systolic BP (mmHg)	114.3±13.7	114.6±13.2	114.8±13.6	115.6±14.1	115.2±13.5	114.6±13.6	114.4±13.6	115.0±13.9	114.8±13.6
Diastolic BP (mmHg)	72.0±8.8	72.2±8.6	72.3±8.7	73.1±9	72.5±8.6	72.3±8.8	72.2±8.9	72.5±8.9	72.4±8.8
Mean Arterial (mmHg)	86.1±9.7	86.3±9.3	86.4±9.5	87.3±9.9	86.8±9.4	86.4±9.6	86.3±9.7	86.7±9.7	86.5±9.6
Pulse Pressure (mmHg)	42.3±9.7	42.4±9.6	42.5±9.9	42.4±10	42.7±9.8	42.3±9.8	42.2±9.7	42.6±9.9	42.4±9.8
Body Mass Index									
Normal (<25)	42	39	38	34	37	38	39	39	38
Overweight (25-<30)	31	31	32	32	33	32	32	31	32
Obese (≥30)	27	30	30	34	30	30	30	30	30
Smoking Status									
Never	53	53	53	55	54	55	54	51	53
Former	40	38	38	36	37	37	38	40	38
Current	7	8	8	9	9	8	8	9	8
Alcohol Use									
Never	3	3	3	4	4	3	3	3	3
Former	14	15	15	16	16	15	14	14	15
Current	84	82	82	80	80	82	83	83	82
Diabetes									
Yes	5	6	6	7	6	5	6	6	6
No	93	92	92	90	91	92	91	91	92
Borderline	3	3	3	3	3	3	3	3	3
Hypercholesterolemia									
Yes	32	34	33	33	34	33	33	32	33
No	56	54	55	55	54	55	56	56	55
Borderline	12	12	12	12	12	12	11	12	12
On BP medication	28	30	30	33	31	30	30	30	30
Hypertension									
Yes	25	27	27	30	27	27	28	27	27
No	71	69	69	65	68	68	69	69	69
Borderline	4	4	4	5	5	4	4	5	4

BP: Blood Pressure. Borderline: Self-reported classification that the participant had or nearly had the condition but did not require medications.

Table 3. Estimated effect of $PM_{2.5}$ and NO_2 exposure on blood pressure (mmHg), estimate (95%CI).

Outcome	Per 10μg/m^3 $PM_{2.5}$ Exposure		Per 10ppb NO_2 Exposure	
Systolic Blood Pressure				
Model 1	0.8 (0.3,1.3)	p=0.002	-0.4 (-0.6,-0.1)	P=0.003
Model 2	0.9 (0.4,1.4)	p<0.001	0.2 (-0.1,0.4)	p=0.17
Model 3	1.9 (1.0,2.8)	p<0.001	0.3 (0.0,0.6)	p=0.07
Model 4	1.5 (0.7,2.4)	p<0.001	0.2 (0.0,0.5)	p=0.09
Model 5	1.4 (0.6,2.3)	p<0.001	0.2 (0.0,0.5)	p=0.10
Diastolic Blood Pressure				
Model 1	0.8 (0.4,1.1)	p<0.001	-0.3 (-0.5,-0.2)	p<0.001
Model 2	0.7 (0.4,1.1)	p<0.001	-0.1 (-0.3,0.0)	p=0.11
Model 3	0.7 (0.1,1.3)	p=0.03	-0.2 (-0.4,0.0)	p=0.10
Model 4	0.5 (-0.1,1.0)	p=0.12	-0.2 (-0.4,0.0)	p=0.06
Model 5	0.4 (-0.2,1.0)	p=0.15	-0.2 (-0.4,0.0)	p=0.05
Mean Arterial Pressure				
Model 1	0.8 (0.4,1.2)	p<0.001	-0.3 (-0.5,-0.2)	p<0.001
Model 2	0.8 (0.4,1.2)	p<0.001	0.0 (-0.2,0.1)	p=0.72
Model 3	1.1 (0.4,1.7)	P=0.001	0.0 (-0.2,0.2)	p=0.84
Model 4	0.8 (0.2,1.4)	P=0.01	0.0 (-0.2,0.2)	p=0.67
Model 5	0.8 (0.2,1.4)	p=0.01	-0.1 (-0.2,0.2)	p=0.63
Pulse Pressure				
Model 1	0.1 (-0.3,0.4)	p=0.73	-0.1 (-0.2,0.1)	p=0.59
Model 2	0.2 (-0.2,0.5)	p=0.42	0.3 (0.1,0.5)	p<0.001
Model 3	1.2 (0.6,1.9)	p<0.001	0.4 (0.2,0.6)	p<0.001
Model 4	1.1 (0.4,1.7)	p<0.001	0.4 (0.2,0.6)	p<0.001
Model 5	1.0 (0.4,1.7)	P=0.001	0.4 (0.2,0.6)	p<0.001

Model 1: Included age and race/ethnicity. Model 2: Model 1 + household income, education, marital status, working ≥20 hours per week outside the home, perceived stress score, and Socioeconomic Status Z-Score. Model 3: Model 2 + Rural-Urban Continuum Codes and unpenalized thin-plate regression splines for latitude and longitude. Model 4: Model 3 + body mass index, wait-to-hip ratio, smoking status, alcohol use, history of diabetes, and history of hypercholesterolemia. Model 5: Model 4 + blood pressure medication use.

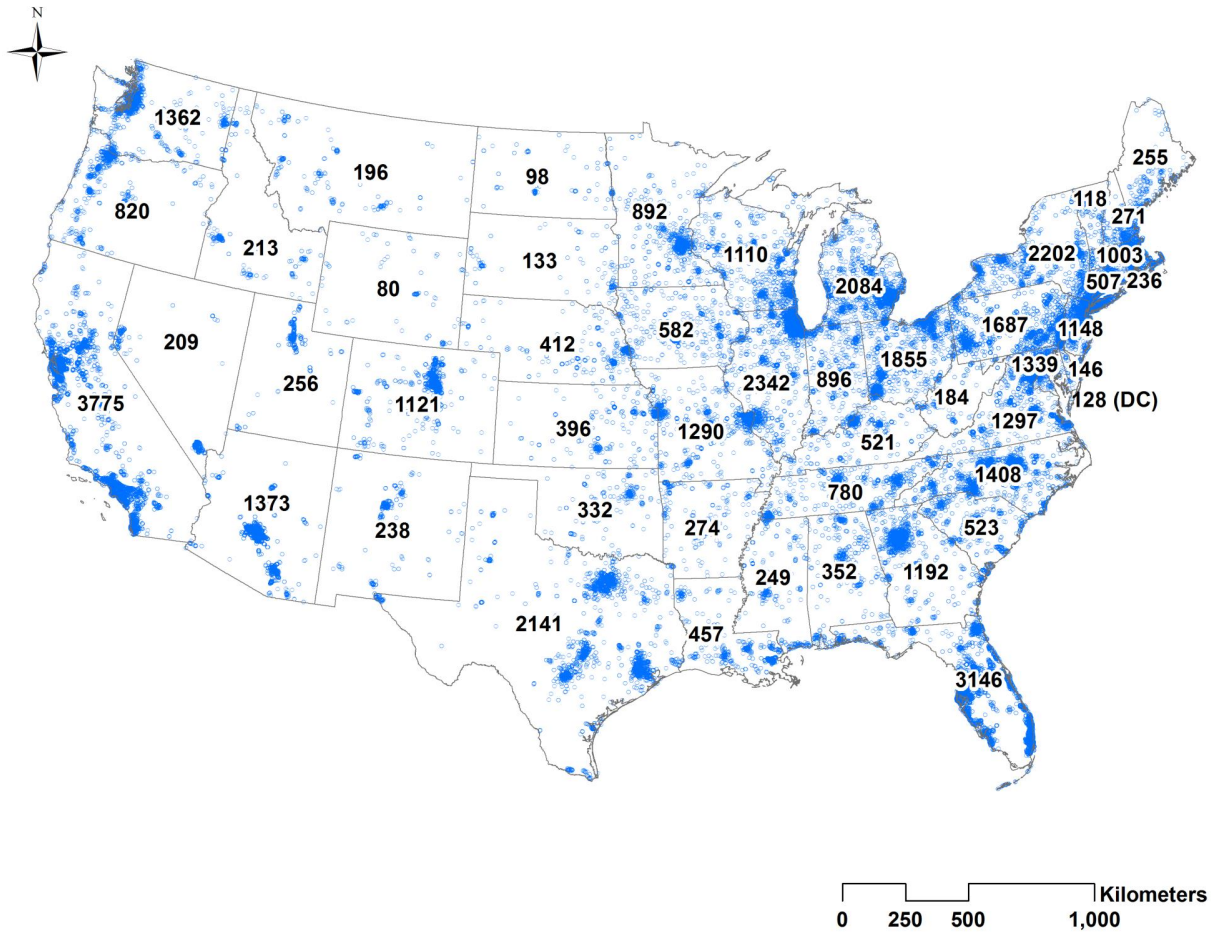
Figure Legends

Figure 1. United States map of participant residential locations, with number of participants per state. Each participant is represented by an open blue circle.

Figure 2. Boxplots of $PM_{2.5}$ and NO_2 participant annual average residential concentrations by U.S. census division. Boxes extend from the 25th to the 75th percentile, horizontal bars represent the median, whiskers extend 1.5 times the length of the interquartile range (IQR) above and below the 75th and 25th percentiles, respectively, and outliers are represented as points.

Figure 3. Relationship between blood pressure and annual average air pollution exposure for $PM_{2.5}$ (left) and NO_2 (right). Model 1: Included age and race/ethnicity. Model 2: Model 1 + household income, education, marital status, working ≥20 hours per week outside the home, perceived stress score, and Socioeconomic Status Z-Score. Model 3: Model 2 + Rural-Urban Continuum Codes and unpenalized thin-plate regression splines for latitude and longitude. Model 4: Model 3 + body mass index, wait-to-hip ratio, smoking status, alcohol use, history of diabetes, and history of hypercholesterolemia. Model 5: Model 4 + blood pressure medication use.

Figure 1.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1290
1297
521
1408
780
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238
332
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Figure 2.

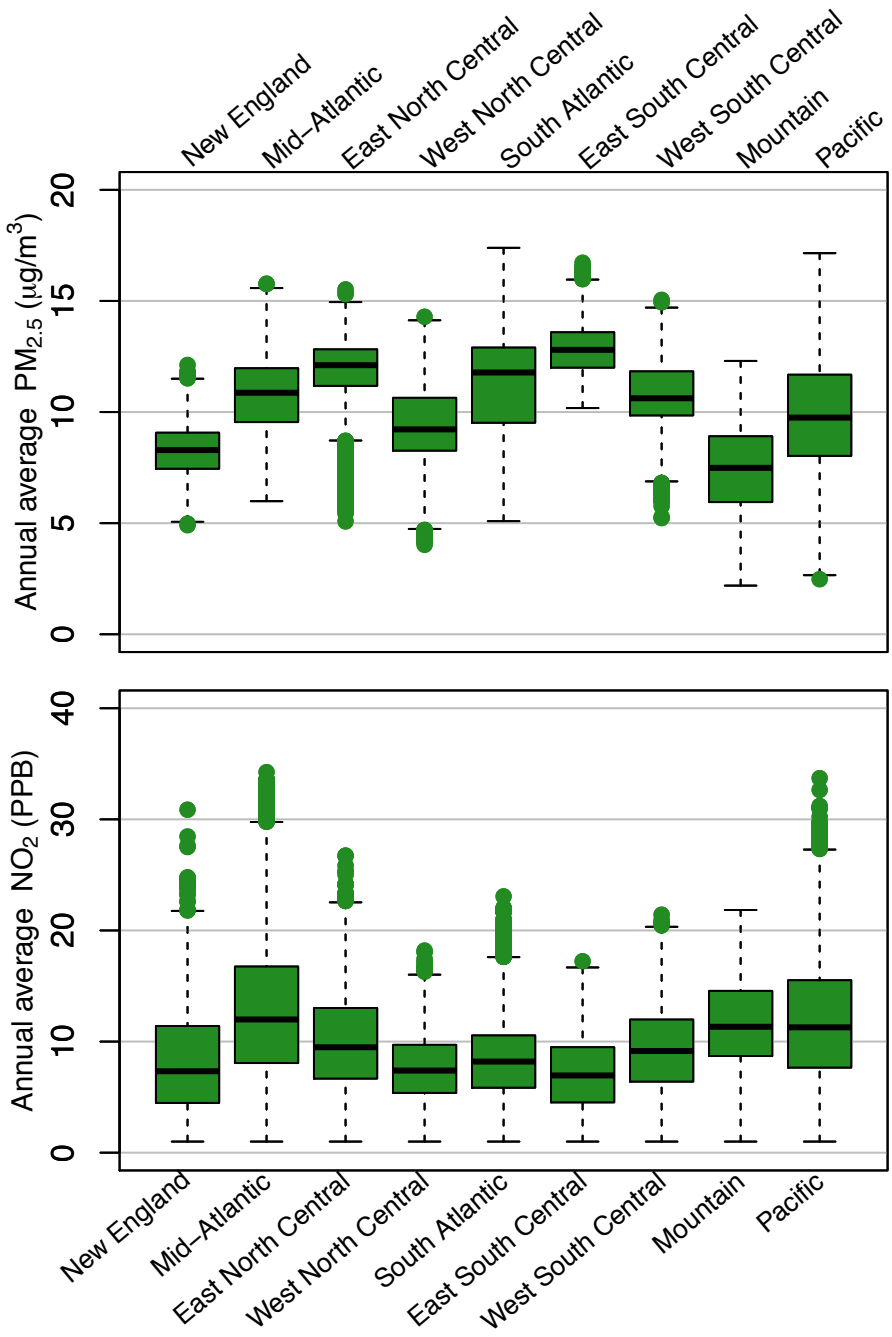
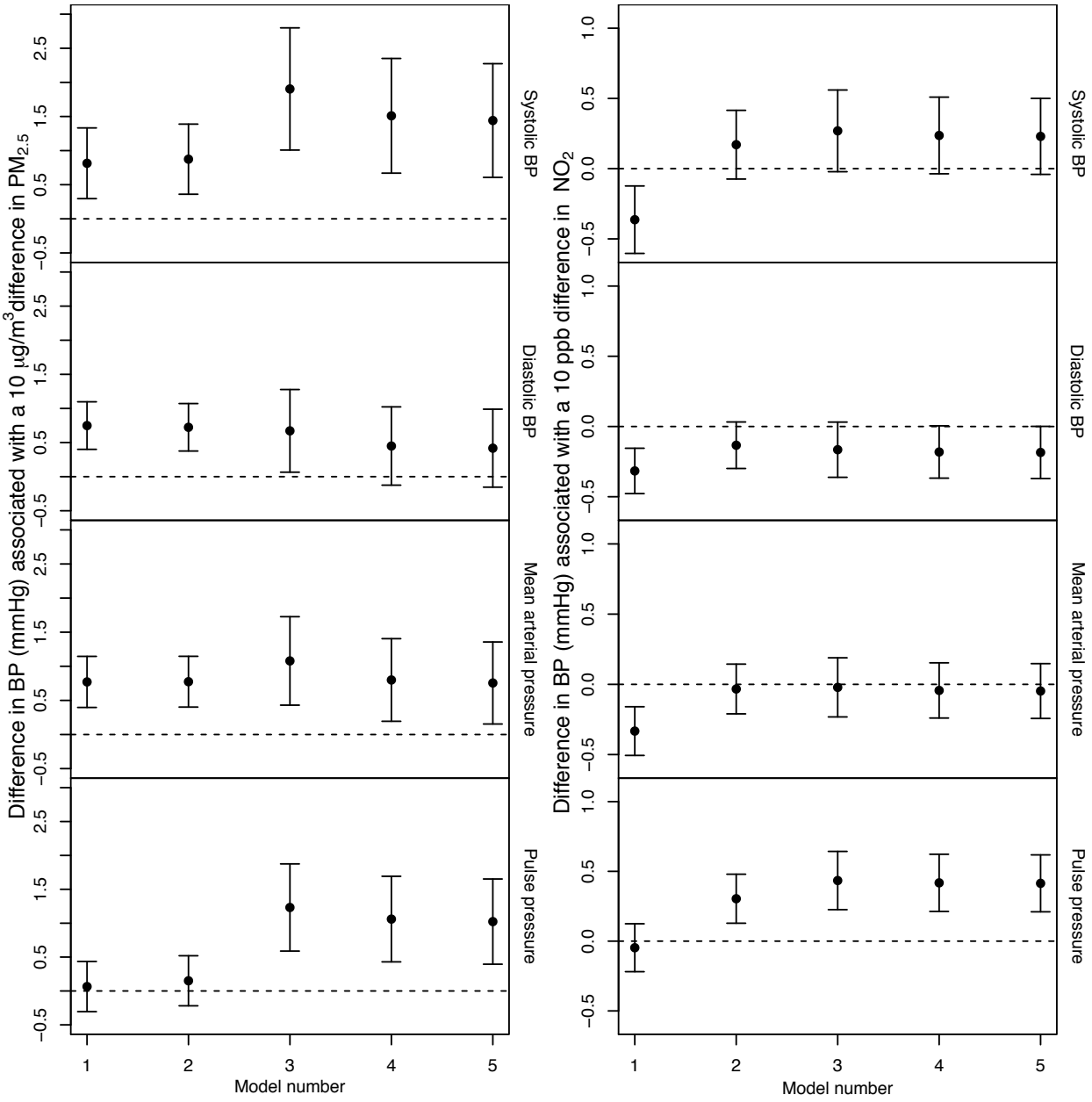

New England
Mid–Atlantic
East North Central
West North Central
South Atlantic
East South Central
West South Central
Mountain
Pacific
Annual average PM2.5 (µg/m3)
0
5
10
15
20
Annual average NO2 (PPB)
0
10
20
30
40

Figure 3.


Difference in BP (mmHg) associated with a 10 μg/m3difference in PM2.5
Difference in BP (mmHg) associated with a 10 ppb difference in NO2
Systolic BP
Diastolic BP
Mean arterial pressure
Pulse pressure
Model number
1
2
3
4
5