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# Short-term Air Pollution Levels and Blood Pressure in Older Women

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**Background:** Evidence of associations between daily variation in air pollution and blood pressure (BP) is varied and few prior longitudinal studies adjusted for calendar time.

**Methods:** We studied 143,658 postmenopausal women 50 to 79 years of age from the Women's Health Initiative (1993–2005). We estimated daily atmospheric particulate matter (PM) (in three size fractions: $PM_{2.5}$, $PM_{2.5\text{-}10}$, and $PM_{10}$) and nitrogen dioxide ($NO_2$) concentrations at participants' residential addresses using validated lognormal kriging models. We used linear mixed-effects models to estimate the association between air pollution concentrations and repeated measures of systolic and diastolic BP (SBP, DBP) adjusting for confounders and calendar time.

**Results:** Short-term $PM_{2.5}$ and $NO_2$ were each positively associated with DBP {0.10 mmHg [95% confidence interval (CI): 0.04, 0.15]; 0.13 mmHg (95% CI: 0.09, 0.18), respectively} for interquartile range changes in lag 3-5 day $PM_{2.5}$ and $NO_2$. Short-term $NO_2$ was negatively associated with SBP [−0.21 mmHg (95%CI: −0.30, −0.13)]. In two-pollutant models, the $NO_2$–DBP association was slightly stronger, but for $PM_{2.5}$ was attenuated to null, compared with single-pollutant models. Associations between short-term $NO_2$ and DBP were more pronounced among those with higher body mass index, lower neighborhood socioeconomic position, and diabetes. When long-term (annual) and lag 3-5 day $PM_{2.5}$ were in the same model, associations with long-term $PM_{2.5}$ were stronger than for lag 3-5 day.

**Conclusions:** We observed that short-term $PM_{2.5}$ and $NO_2$ levels were associated with increased DBP, although two-pollutant model results suggest $NO_2$ was more likely responsible for observed associations. Long-term $PM_{2.5}$ effects were larger than short-term.

**Keywords:** Air pollution; Blood pressure; Nitrogen dioxide; Particulate matter; Women's health

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Because the WHI data are confidential, data are not available. Code for analyzing data can be requested by contacting the corresponding author.

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Both short-term (from hours to days) and long-term (from months to years) variations in particulate matter (PM) and traffic-related air pollutants such as nitrogen dioxide ($NO_2$) have been associated with cardiovascular health outcomes in previous studies.[1–3] PM-mediated arterial blood pressure (BP) elevation may potentially be an important part of the causal mechanism leading to increased risk of acute cardiovascular outcomes.[4,5] Examining long-term levels, one recent study using the Women's Health Initiative (WHI) cohort suggested exposure to PM < 2.5 μm ($PM_{2.5}$) and PM < 10 μm ($PM_{10}$) may be modifiable risk factors of hypertension in postmenopausal women.[6]

Exposure to air pollution has been shown to cause activation of the sympathetic and parasympathetic nervous system and to affect arterial tone.[7] Thus, we hypothesize that air pollutants would be positively associated with BP. However, we also note that nitrogen monoxide (NO; formerly referred to as nitric oxide) can cause vasodilation and therefore may cause decreases in BP.[8] Findings from earlier longitudinal studies of the associations between short-term air pollutant levels and BP have been inconsistent. Some studies have reported results suggestive of positive associations for $PM_{2.5}$.[9–12] Other findings suggest null or negative associations for $NO_2$,[13] $PM_{10}$,[13] and ozone.[11] One randomized controlled trial in humans showed that short-term (2-hour) exposure to traffic-related air pollution (specifically diesel exhaust) was associated with increased systolic BP (SBP)

but not diastolic BP (DBP).[14] Additionally, traffic-related exposure measures were identified as a modifier of the cross-sectional association between $PM_{2.5}$ and BP in a diverse population from the Multi-Ethnic Study of Atherosclerosis study, specifically the association between $PM_{2.5}$ and SBP was stronger in the presence of high $NO_2$ levels.[15] However, which specific component(s) of the air pollution mixture, including traffic-related air pollutants such as $NO_2$, are responsible for observed effects on BP and which are confounded by others remains poorly understood. To our knowledge few previous studies have evaluated short-term effects on BP of (1) PM in multiple size fractions [including $PM_{2.5}$ (which originates from primary emissions from combustion sources and from secondary formation in the atmosphere), PM > 2.5 and <10 μm ($PM_{2.5–10}$, which is typically generated from mechanical grinding or crushing, as well as from wind-blown dust), and $PM_{10}$] and (2) $NO_2$ over the same short-term exposure period. One recent meta-analysis showed overall positive though not robust short-term associations between several air pollutants ($PM_{2.5}$, $PM_{10}$, $NO_2$, and $SO_2$) and increases in SBP and DBP; meta-analysis of associations between $PM_{2.5-10}$ and BP was not available due to the limited number of studies.[16]

Air pollutant levels (in many areas of the United States) and population-average BP have both decreased over the past several decades.[17,18] Griffin et al.[19] and Adar et al.[20] suggest careful consideration of confounding factors by time-varying age and calendar time in longitudinal studies with time-trending exposures. Adar et al.[20] found positive associations for both $PM_{2.5}$ as well as $NO_2$ with SBP and DBP for exposure averaging periods of 7 days and longer in adjusted models that did not control for calendar time (years since the first examination date). However, when calendar time was included, those associations were attenuated to null.[20] A limitation of the exposure assessment approach used for short-term exposures in Adar et al.[20] was the use of area-wide averages of monitoring site concentrations, leading potentially to increased exposure measurement error and decreased exposure contrasts. Exposure models that reflect variation within a given urban area (intraurban gradients) and that are less influenced by missing data may offer benefits when evaluating associations between short-term air pollutant levels and BP.

In this study, by using data from a large nationally representative study and with an improved exposure assessment approach over previous studies, we aimed to estimate the associations between short-term PM ($PM_{2.5}$, $PM_{2.5-10}$, and $PM_{10}$) and $NO_2$ levels and SBP and DBP, adjusting for spatial and temporal confounders including assessment of calendar time, copollutants, and long-term pollutant levels. We investigated confounding by co-pollutant in two-pollutant models and associations of long-term (annual) $PM_{2.5}$ with SBP and DBP in models that included short-term $PM_{2.5}$.

## METHODS

### Study Population

The WHI is a nationwide prospective US cohort across 40 clinical centers in 24 states.[21] Postmenopausal women 50 to 79 years of age were recruited between 1993 and 1998. Our analysis contained data of follow-up from 2005. The WHI consisted of two components, the observational study (N = 93,696 participants) and the clinical trials (N = 68,132 participants). In the clinical trials, repeated measurements were available from the screening and annual clinic visits (years 1–11); in the observational study, repeated measurements were available from the screening and year 3 visits. In this study, we combined observational and clinical trial components together to investigate the longitudinal association between repeated measures of air pollution exposure and BP. We restricted our analysis to those with complete data on antihypertensive medication use, BP measurements, and potential confounders (listed in the covariates section). Institutional review boards at all participating institutions approved the WHI protocols, and we obtained informed consent from all participants.

### BP Measurements

BP was measured in the right arm with a conventional mercury sphygmomanometer after participants had been seated and at rest for 5 minutes. SBP and DBP were computed by averaging two measurements, obtained at least 30 seconds apart[22]; however, if only one measurement was available, that single value was used. To reduce outcome misclassification related to antihypertensive medication use, multiple imputation methods were used to impute nontreated BP among those using antihypertensive medication following methods described in McClelland et al.[23] Briefly, we used observed (treated) BP levels to estimate nontreated BP levels in a multiple linear regression model (with one observation per participant) that contained covariates for age, self-reported race–ethnicity, body mass index (BMI), self-reported diabetes status, pack–years of smoking, classes of antihypertensive medications, all two-way interactions of (1) each class of antihypertensive medication and (2) each category of self-reported race–ethnicity, as well as all two-way interactions of any two classes of antihypertensive medications in a dataset of participants who were not using medication at baseline but started medication use during follow-up. The model-estimated nontreated BP value and its standard error were used to characterize the mean and standard deviation (SD) of a normal distribution for each participant-measurement under treatment. We obtained 10 random samples from this distribution for each participant-measurement under treatment and combined them with measurements from participants who were not under treatment, then saved them in 10 datasets separately. Next, coefficient estimation of the association between air pollution and BP were analyzed by pooling (i.e., using inverse variance weighting) the 10 individual effect estimates to obtain a single coefficient and its standard error.

### Air Pollution Exposure Assessment

Participants' residential addresses were collected during the screening visit and updated each follow-up visit. We estimated daily average concentrations of $PM_{2.5}$, $PM_{10}$, and

$NO_2$ at geocoded residential locations of WHI participants[24] using lognormal ordinal kriging models based on air quality monitoring data from the US Environmental Protection Agency's Air Quality System in the contiguous US during the study period.[25] $PM_{2.5}$ monitoring data were only available after 1999; therefore, daily exposure models were unavailable before that date for $PM_{2.5}$. We estimated $PM_{2.5\text{-}10}$ by subtracting model-predicted $PM_{2.5}$ from model-predicted $PM_{10}$. We validated the kriging models using leave-one-site-out cross-validation statistics including: (1) prediction error (PE): the average of the difference between the predicted and measured daily concentrations at each monitoring site; (2) standardized PE (SPE): the PE divided by its SE of estimation across all sites; and (3) root mean square standardized (RMSS): the SD of all SPEs across all sites. Details of the cross-validation statistics can be found in the literature.[25–27]

We calculated lagged exposure variables based on the index date of the BP measurement throughout the period 1-week prior, from 0 (day of the measurement; lag 0) to 6 days prior (lag 6). We expressed these values as an interquartile range (IQR) change in the pollutant concentration to afford comparisons among air pollutants. Long-term (annual) $PM_{2.5}$ concentrations were obtained by averaging monthly estimates from spatiotemporal generalized additive mixed models (GAMMs) at geocoded residential locations of WHI participants.[28] These GAMM models were validated using 10-set cross-validation and had high predictive accuracy with a cross-validation $R^2$ of 0.77 for $PM_{2.5}$. Long-term $PM_{2.5}$ levels were also calculated by averaging daily estimates from kriging models.

## Meteorologic Data

We obtained meteorologic data for the contiguous US from the National Climate Data Center.[29] We estimated daily mean ambient temperature (°C), dew point temperature (°C), barometric pressure (kPa), relative humidity (%), and wind speed (m $s^{-1}$) at each participant's geocoded address by averaging the daily mean measurements across all stations within 50 km. These meteorologic variables have been used in previous health studies,[27,30] and were calculated over the same time periods (i.e., the same lags) as the air pollutants, as described above.

## Covariates

At the screening and follow-up visits, questionnaires were used to collect demographic and residential location data. We identified potential confounders based on literature review and the following criteria: (1) whether each is hypothesized to be associated with air pollution; (2) whether it is a potential independent cause of changes in BP; and (3) that it is not likely in the causal pathway from air pollution exposure to BP. Covariates included in this analysis were age at visit, self-reported race–ethnicity (White, Hispanic/Latino, Black/African-American, Asian/Pacific Islander, American Indian/Alaskan Native, and other), educational attainment (individual-level rather than neighborhood, categories listed in Table 1), neighborhood socioeconomic position [SEP, calculated using six census tract-level variables (median household income; median value of housing units; the percentage of households receiving interest, dividend, or net rental income; the percentage of adults 25 years of age or older who had completed high school; the percentage of adults 25 years of age or older who had completed college; and the percentage of employed persons 16 years of age or older in executive, managerial, or professional specialty occupations), expressed as a continuous z-score, and then categorized by tertile, increasing values of which correspond to higher SEP],[31] BMI (<25; 25–30; and ≥30 $kg/m^2$), dietary sodium intake (mg/day and categorized by tertile), combined fruit and vegetable consumption (medium servings/day and categorized by tertile), pack–years of smoking (continuous), self-reported diabetes, US Census region (Northeast, South, Midwest, and West), day of the week, season (spring, summer, fall, and winter), long-term average $PM_{2.5}$ concentration (categorized by tertile), meteorologic variables, and calendar time expressed as the number of days since the screening visit. In addition, treatment arm (categorical variable with categories for the treatment arm of the clinical trials (separate categories in each arm for treatment and placebo) and a separate category for the observational studies) was included as a covariate.

## Statistical Analyses

### Linear Mixed-effects Models

We used linear mixed-effects (LME) models to estimate the association of air pollutant exposure and SBP and DBP. The following LME regression model was fit to the data:

$$y_{ij} = \beta_0 + \sum_{p=1}^{P} \beta_p X_{i,j,p} + b_i Age_{ij} + e_{ij}$$

In this formula, $y_{ij}$ represents either SBP or DBP measurements for subject $i$ and visit $j$, $\beta_p$ is the fixed-effect coefficients, and $X_p$ is the explanatory variables (including air pollutant concentrations, time-varying and time-invariant confounders, and calendar time). $b_i$ is a random slope for age. An auto-regressive model was used to account for serial correlations between repeated measures on each participant. SAS v9.4 PROC MIXED was used for model fitting (except upon nonconvergence due to infinite likelihood, when PROC GLIMMIX was used).

From among the potential confounders identified above (except for meteorologic variables), we kept only those for which the Akaike information criterion (AIC) was lowered upon inclusion of each covariate in separate models (not stepwise; though we note this did not exclude any confounders). We included all available meteorologic variables in preliminary models, and then removed a meteorologic variable if it was not statistically significant in any of the four models (one for each air pollutant) for SBP and DBP separately. In this

**TABLE 1.** Summary Statistics on WHI Participants' Characteristics, Air Pollution Exposure Metrics, and BP Measurements in Our Analysis Dataset

| Variables | Total |
|---|---|
| Participants, N | 143,658 |
| Observations (with complete data for $PM_{10}$ and $NO_2$), n | 356,319 |
| Observations (with complete data for $PM_{2.5}$ and $PM_{2.5\text{-}10}$), n | 157,983 |
| Age at visit, years, mean (SD) | 65.4 (7.4) |
| US Census region, N (%) | |
| Northeast | 34,399 (24.0) |
| Midwest | 32,107 (22.4) |
| South | 37,510 (26.1) |
| West | 39,642 (27.6) |
| Race–ethnicity, N (%) | |
| American Indian or Alaskan Native | 614 (0.4) |
| Asian or Pacific Islander | 1,700 (1.2) |
| Black or African-American | 12,806 (8.9) |
| Hispanic/Latino | 5,798 (4.0) |
| White (not of Hispanic origin) | 121,373 (84.5) |
| Other | 1,367 (1.0) |
| Neighborhood SEP, N (%) | |
| Tertile 1 | 49,169 (34.2) |
| Tertile 2 | 47,067 (32.8) |
| Tertile 3 | 47,422 (33.0) |
| Mean (SD) | 0.2 (5.3) |
| Educational attainment, N (%) | |
| Did not go to school | 113 (0.1) |
| Grade school (1–4 years) | 513 (0.4) |
| Grade school (5–8 years) | 1,617 (1.1) |
| Some high school (9–11 years) | 5,177 (3.5) |
| High school diploma or GED | 24,637 (17.2) |
| Vocational or training school | 14,439 (10.1) |
| Some college or Associate Degree | 39,955 (27.8) |
| College graduate or Baccalaureate Degree | 15,897 (11.1) |
| Some post-graduate or professional | 16,301 (11.4) |
| Master's degree | 21,421 (14.9) |
| Doctoral degree | 3,588 (2.5) |
| BMI ($kg/m^2$), n (%) | |
| BMI < 25 | 115, 664 (32.5) |
| BMI ≥ 25 and <30 | 125, 413 (35.2) |
| BMI ≥ 30 | 115, 242 (32.3) |
| Mean (SD) | 28.3 (5.9) |
| Dietary sodium intake (mg), mean (SD), n (%) | |
| Tertile 1 | 1,527 (380), 83,717 (23.5) |
| Tertile 2 | 2,466 (247), 84,043 (23.6) |
| Tertile 3 | 3,896 (1,105), 84,246 (23.6) |
| Missing | 104,313 (29.3) |
| Mean (SD) | 2,632 (1193) |
| Combined fruit and vegetable consumption (medium servings per day), mean (SD), n (%) | |
| Tertile 1 | 2.0 (0.6), 83,412 (23.4) |
| Tertile 2 | 3.9 (0.6), 84,599 (23.7) |
| Tertile 3 | 6.7 (1.6), 83,995 (23.6) |
| Missing | 104,313 (29.3) |
| Mean (SD) | 4.2 (2.2) |
| Pack–years of smoking, mean (SD) | 9.9 (18.4) |
| Diabetes present, n (%) | |
| Yes | 25,130 (7.1) |
| No | 331,189 (92.9) |
| Any antihypertensive medication use, n (%) | |
| Yes | 123,873 (34.8) |
| No | 232,446 (65.2) |
| SBP (mmHg), mean (SD) | |
| Observed | 126.2 (17.3) |
| Observed + imputed among those with medication use | 128.9 (18.4) |
| DBP (mmHg), mean (SD) | |
| Observed | 73.7 (9.3) |
| Observed + imputed among those with medication use | 75.8 (9.8) |
| Air pollutants, lag 0-6 day[a], mean (SD) | |
| $PM_{2.5}$ ($\mu g/m^3$) | 13.7 (5.6) |
| $PM_{2.5\text{-}10}$ ($\mu g/m^3$) | 13.4 (6.6) |
| $PM_{10}$ ($\mu g/m^3$) | 27.4 (8.2) |
| $NO_2$ (ppb) | 18.7 (7.1) |
| Air pollutants, lag 3-5 day[b], mean (SD) | |
| $PM_{2.5}$ ($\mu g/m^3$), IQR = 7.7 | 13.7 (6.8) |
| $PM_{2.5\text{-}10}$ ($\mu g/m^3$), IQR = 8.5 | 12.8 (7.7) |
| $PM_{10}$ ($\mu g/m^3$), IQR = 12.3 | 26.9 (9.8) |
| $NO_2$ (ppb), IQR = 9.9 | 18.3 (7.7) |
| Long-term $PM_{2.5}$ ($\mu g/m^3$), mean (SD); n (%) | |
| Tertile 1 | 9.5 (1.6); 127,086 (35.7) |
| Tertile 2 | 13.3 (0.9); 124,550 (35.0) |
| Tertile 3 | 17.8 (3.0); 104,683 (29.4) |
| Mean (SD), IQR = 4.8 | 13.3 (3.9) |

[a]Lag 0-6 day: Average of lag day 0, lag day 1… and lag day 6.
[b]Lag 3-5 day: Average of lag day 3, lag day 4, and lag day 5.

way, for a given outcome, we used a stable, fixed set of meteorologic variables in final analyses. We also evaluated whether the air pollution–BP associations differed by the following variables: BMI, neighborhood SEP, diabetes, dietary sodium intake, combined fruit and vegetable consumption, US Census region, and long-term average $PM_{2.5}$ concentration. To do this, we fit adjusted models with interaction terms for air pollutant concentration and each modifier separately, then stratified analyses were conducted and the results reported. Additionally, we used two-pollutant models to examine confounding effects among copollutants on BP. Finally, we also included both short-term and long-term $PM_{2.5}$ in the same model to investigate (partial, because short-term is part of long-term) confounding of short-term effects by long-term.

## Sensitivity Analyses

We conducted sensitivity analyses to evaluate (1) the approach used to reduce outcome misclassification from medication use using multiple imputation versus adding a

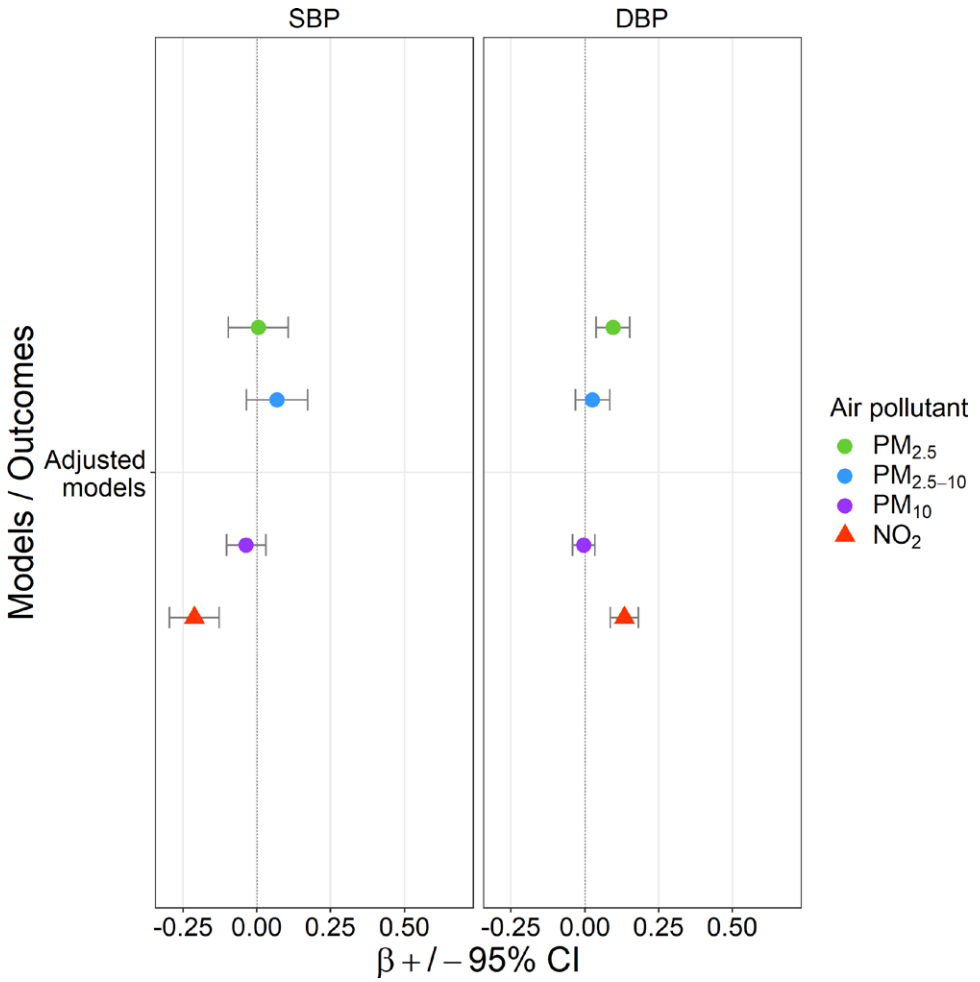


**FIGURE 1.** Associations of an IQR change in lag 3-5 day air pollutant exposure metrics and SBP and DBP in the WHI (data from Table 2). The IQR for $PM_{2.5}$, $PM_{2.5\text{-}10}$, $PM_{10}$, and $NO_2$ was 7.7, 8.5, 12.3 μg/m$^3$, and 9.9 ppb, respectively.

**TABLE 2.** Associations[a] Between IQR Changes in Short-term (Lag 3-5 Day) and Long-term (Annual) $PM_{2.5}$ in the Same Model and BP in the WHI

| Health Outcome | Air Pollutant[b] | n | β[c] | 95% CI | |
|---|---|---|---|---|---|
| SBP | Short-term $PM_{2.5}$ | 123,062 | 0.04 | −0.08 | 0.16 |
| | Long-term $PM_{2.5}$[d] | 123,062 | −0.39 | −0.52 | −0.26 |
| DBP | Short-term $PM_{2.5}$ | 123,062 | 0.10 | 0.03 | 0.17 |
| | Long-term $PM_{2.5}$[d] | 123,062 | 0.12 | 0.05 | 0.19 |

The IQR for long-term $PM_{2.5}$ and short-term $PM_{2.5}$ is 4.8 μg/m$^3$ and 7.7 μg/m$^3$, respectively.

[a]Models adjusted for age at visit, self-reported race–ethnicity, education, treatment arms, US Census region, day of the week, season, BMI, neighborhood SEP, pack-year of smoking, diabetes, calendar time, temperature, dew point temperature, relative humidity, wind speed, and a random slope for age. Models for DBP additionally adjusted for barometric pressure.

[b]The Pearson correlation between short-term and long-term $PM_{2.5}$ is 0.26.

[c]β represents changes in SBP and DBP per IQR change in short-term and long-term $PM_{2.5}$ concentrations.

[d]Long-term $PM_{2.5}$ estimated from spatiotemporal GAMMs.

constant of 10 mmHg to SBP and DBP, (2) whether control for seasonality was adequate, (3) whether the choice of exposure model used for long-term $PM_{2.5}$ affected our results, and (4) whether restricting to complete data on $PM_{2.5}$ affected our results. To do this, we compared our main results using multiple imputation with those not using multiple imputation but instead, to estimate nontreatment BP levels for those reporting antihypertensive medication use, adding a fixed constant of 10 mmHg to observed SBP and DBP.[32] Second, we replaced the four-category season variable (using three degree of freedom) with 12 monthly indicator variables. Third, in models using long-term (annual) $PM_{2.5}$, we compared results using

long-term $PM_{2.5}$ estimates from GAMMs obtained by averaging monthly estimates to those obtained by averaging daily estimates from kriging models. Fourth, for $PM_{10}$ and $NO_2$, we restricted to complete data on $PM_{2.5}$ (which effectively limits by time period after 1999).

## RESULTS

During the study period (1993–2005), we include a total of 143,658 participants in the analysis. Participants were approximately equally distributed across four regions of the United States and most of participants were white (84.5 %). On average, participants were overweight (i.e., BMI ≥ 25 kg/$m^2$). Characteristics of the study participants, air pollutant concentrations, and BP levels are presented in Table 1.

Results from adjusted models not controlling for calendar time using single-lag days (0–6) are presented in eTable 1; http://links.lww.com/EDE/B996. Shorter single-lag periods (lag 0 through lag 2) showed negative or null associations for $PM_{2.5}$, $PM_{2.5\text{-}10}$, and $PM_{10}$ with SBP, and for $PM_{2.5\text{-}10}$ and $PM_{10}$ with DBP. Because the BP model coefficient estimates for individual lag periods were generally consistent and most positive or negative for lag days 3, 4 and 5, we calculated a summary measure of the PM and $NO_2$ exposures that met the model screening criteria by averaging lagged values from 3 to 5 days before the BP measurement (referred to hereafter as lag 3-5 day). For $PM_{2.5\text{-}10}$ and $PM_{10}$ with DBP, lag 6 effects were also elevated. In models with lag 3-5 day air pollutant concentrations not controlling for calendar time, but adjusted for other confounders, $PM_{2.5}$, $PM_{10}$, and $NO_2$ were positively associated with both SBP and DBP (eTable 2; http://links.lww.com/EDE/B996). Comparisons between adjusted models with and without control for calendar time are presented in eFigure 1; http://links.lww.com/EDE/B996. The Pearson correlation between age at visit and calendar time in our analysis was 0.28. However, the independent variability in these two variables is largely due to differences in age at baseline. Once differences in age at baseline are removed, the correlation increases to 0.94, which raises concern that models controlling for calendar time suffer from overadjustment. Results from adjusted models (with control for calendar time) are shown in Figure 1, eTables 2 and 3; http://links.lww.com/EDE/B996 (for single-lag days). Regression coefficients (listed in the columns headed with "β" in eTable 3; http://links.lww.com/EDE/B996) represent the change in BP per IQR change in lag 3-5 day air pollutant concentration. $NO_2$ was negatively associated with SBP (each IQR increase in lag 3-5 day $NO_2$ concentration (an increment of 9.9 ppb) was associated with a −0.21 mmHg [95% confidence interval (CI): −0.30, −0.13] change but positively associated with DBP [0.13 mmHg (95% CI: 0.09, 0.18)]. $PM_{2.5}$ was not associated with SBP, but was positively associated with DBP [each IQR increase in lag 3-5 day $PM_{2.5}$ concentration (an increment of 7.7 μg $m^{-3}$) was associated with a 0.10 mmHg (95% CI: 0.04, 0.15) change].

When including both short-term (lag 3-5 day) and long-term (annual) $PM_{2.5}$ levels in the same model, long-term $PM_{2.5}$ was negatively associated with SBP, but short-term showed no association (Table 2). For DBP, both long-term and short-term $PM_{2.5}$ were positively associated, with the association of long-term stronger than that for short-term. In this study, the

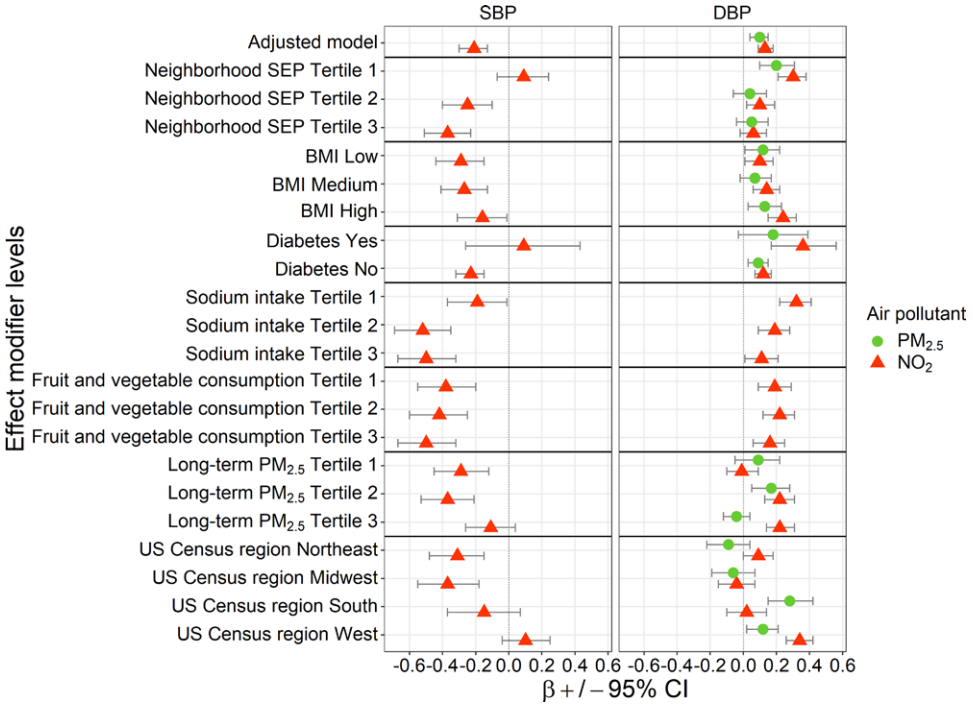


**FIGURE 2.** Adjusted and stratified associations of an IQR change in lag 3-5 day air pollutant exposure metrics and SBP and DBP showing effect modification by BMI, neighborhood SEP, diabetes, sodium intake, and US Census region. (We did not analyze effect modification by sodium intake and fruit and vegetable consumption for the $PM_{2.5}$–DBP associations due to missing $PM_{2.5}$ data before 1999.) The IQR for $PM_{2.5}$ is 7.7 μg/$m^3$ and for $NO_2$ is 9.9 ppb.

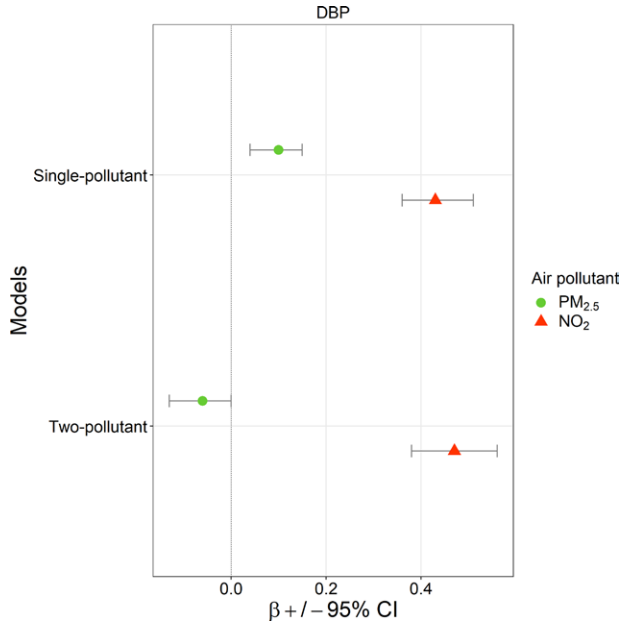


**FIGURE 3.** Adjusted associations of an IQR change in lag 3-5 day air pollutant exposure metrics and DBP in the WHI from single-pollutant and two-pollutant models. The IQR for $PM_{2.5}$ is 7.7 μg/m$^3$ and for $NO_2$ is 9.9 ppb.

Pearson correlation between short-term and long-term $PM_{2.5}$ is 0.26.

## Effect Modification

Overall, we found effect modification by BMI, neighborhood SEP, diabetes, dietary sodium intake, and US Census region for $NO_2$–SBP and $NO_2$–DBP associations (Figure 2 and eTable 4; http://links.lww.com/EDE/B996). Because lag 3-5 day $PM_{2.5}$ was not associated with SBP (Figure 1), we did not assess whether BMI, neighborhood SEP, diabetes, or US Census region modified the $PM_{2.5}$–SBP association. Summary statistics on the distributions of lag 3-5 day air pollutant concentrations across levels of the effect modifiers are presented in eTables 5 and 6; http://links.lww.com/EDE/B996.

BMI and neighborhood SEP modified associations of lag 3-5 day $NO_2$ for SBP and DBP. Stratified results showed that $NO_2$–SBP associations were stronger and more negative among participants with lower BMI and higher neighborhood SEP; while $NO_2$–DBP associations were stronger and more positive among participants with higher BMI and lower neighborhood SEP.

We also found effect modification for diabetes; $NO_2$–DBP associations were more strongly positive among those with diabetes. For SBP, stratified results suggested a negative $NO_2$–SBP association among those without diabetes and a null association for those with diabetes, but CIs were overlapping. Also, stratified results by dietary sodium intake showed $NO_2$–DBP associations were stronger and more positive among those with lower sodium intake, while $NO_2$–SBP associations were stronger and more negative among those with higher sodium intake.

## Two-pollutant Models

In Table 2, both $PM_{2.5}$ and $NO_2$ were associated with DBP. Resultantly, these pollutants were analyzed in two-pollutant models (Figure 3 and eTable 7; http://links.lww.com/EDE/B996). $PM_{2.5}$ and $NO_2$ were correlated in our analysis, although the Pearson correlation was not strong at 0.44. In two-pollutant models, the $NO_2$ association with DBP became slightly stronger, but for $PM_{2.5}$ became weaker, as compared with single-pollutant models. We also found effect modification by US Census region in the adjusted two-pollutant models (which also controlled for calendar time; eTable 8; http://links.lww.com/EDE/B996). The associations between $NO_2$ and DBP were stronger in the South and West US Census regions, with an IQR change corresponding to increases in DBP of 1.12 mmHg (95% CI: 0.89, 1.36) for the South and 0.64 mmHg (95% CI: 0.50, 0.78) for the West, compared to the other regions (Northeast and Midwest).

## Sensitivity Analyses

Compared to our main analysis, associations across all air pollutants were similar after adding a fixed constant of 10 mmHg to observed BP levels among those using antihypertensive medication and upon the addition of additional degrees of freedom for seasonality (eTables 9 and 10; http://links.lww.com/EDE/B996). However, results did differ between the two exposure models used for long-term $PM_{2.5}$ levels: In models including only long-term $PM_{2.5}$, for SBP, the association when using GAMMs was more strongly negative than that from kriging models (eTable 11; http://links.lww.com/EDE/B996). For DBP, the association for long-term $PM_{2.5}$ from kriging models was more strongly positive than that from GAMMs. In BP models that included both long- and short-term $PM_{2.5}$, we found a positive association between long-term $PM_{2.5}$ estimated from kriging models and DBP. In contrast, the same association was not present when using long-term $PM_{2.5}$ estimated from GAMMs (eTable 12; http://links.lww.com/EDE/B996). When restricting the time period to that with complete data on $PM_{2.5}$ and comparing the results with the main analysis in Figure 1, the association for lag 3-5 day $NO_2$ and SBP was similar, whereas the association for lag 3-5 day $NO_2$ and DBP was larger (eTable 13; http://links.lww.com/EDE/B996). Because we observed generally negative associations with SBP and positive associations with DBP, we also evaluated alternative outcomes of pulse pressure and mean arterial pressure. The results are shown in eTable 14; http://links.lww.com/EDE/B996.

# DISCUSSION

In our study of postmenopausal older US women, short-term (lag 3-5 day) $NO_2$ concentrations were associated with decreased SBP and increased DBP. In addition, lag 3-5 day $PM_{2.5}$ concentrations were associated with increased DBP.

Results from two-pollutant models suggest $NO_2$ is more likely responsible for observed associations than is $PM_{2.5}$. In models with both short- and long-term (annual) averages of $PM_{2.5}$, associations with both SBP and DBP were stronger for long-term than short-term.

Our results showed that lag 3-5 $NO_2$ had stronger effects on both SBP (more negative) and DBP (more positive) than did lag 3-5 $PM_{2.5}$, compared on an IQR basis. Stronger effects of $NO_2$ on BP compared to those of $PM_{2.5}$ have also been shown in a study in Canada.[33] Another study, conducted among pregnant women, found a negative association between $NO_2$ levels (lag day 1, lag day 5 and averaged 7-day) and SBP. Also in this study, $PM_{10}$ was associated with increased SBP during the first trimester; and with decreased SBP later in pregnancy.[13] With regard to our two-pollutant model results, Zhao et al.[12] reported similar findings: In two-pollutant models including both 1-day averaged $PM_{2.5}$ and $NO_2$, they found that the association between $PM_{2.5}$ exposure and SBP was attenuated to null. Sun et al.[27] also found the strongest associations for $NO_2$ among several air pollutants considered, including $PM_{2.5}$, when examining risk of hemorrhagic stroke in the WHI population.

Evidence from a meta-analysis showed that a small sustained reduction in BP (10 mmHg for SBP and 5 mmHg for DBP) has been established as lowering long-term risk of cardiovascular events.[34] At the population level, even 2 mmHg lower in SBP could decrease about 10% stroke mortality and 7% other vascular disease in middle age, for example.[34] Also, short-term (24 hours) elevations in ambulatory BP have been identified as increasing acute risk of cardiovascular disease events including stroke and myocardial infarction.[35] The effect sizes (increase in BP per unit change in short-term air pollution exposure) in our study are small, and whether they are clinically relevant remains uncertain. However, they are relevant from a public health perspective. Across the (admittedly skewed) distribution of exposure to $NO_2$, comparing the most highly exposed individuals (max = 92.7 ppb) to the least (min = 1.9 ppb) which would correspond to a change in exposure of approximately nine IQRs ($90.9/9.9 \approx 9.2$), the corresponding change in DBP would, using the larger coefficient estimate from the $NO_2$–DBP association in the West US Census region, be: $9 \times 0.34 = 3.1$ (95% CI: 2.4, 3.9) mmHg.

We found effect modification by BMI, neighborhood SEP, and diabetes, consistent with the hypothesis that participants with high BMI, low neighborhood SEP, and diabetes may be particularly susceptible to the effects of short-term air pollution on BP. One study also reported effect modification by BMI on the association between $PM_{2.5}$ and BP, and association was stronger among obese subjects.[9] We also noted effect modification by dietary sodium intake, in that associations with DBP were more pronounced among those with lower sodium intake. We caution this may be attributable to residual information bias from medication use, despite our attempt to reduce it (we note that our multiple imputation model did not include medication dosage as a covariate as data were unavailable). The potential effect modification of sodium intake with air pollution on BP deserves further attention.

We note effect modification by US Census region, consistent with results in Adar et al.[20], with associations of lag 3-5 day $NO_2$ in two-pollutant models stronger in the South and West as compared to other regions. Variation in PM composition may partly explain the heterogeneity of the observed health effect estimates by the US Census region. One study suggested that exposure location reflecting different components in air pollutants could be an important determinant of health consequences.[36] Also, spatial errors could partially contribute to heterogeneity in health effect estimates across air pollutants. Therefore, including PM composition in future analyses may reduce regional heterogeneity in observed health effect estimates. Using daily exposure estimates with greater spatial resolution, possibly leveraging local geographic and meteorologic information, also would likely further reduce exposure errors.

We also note that associations of long-term $PM_{2.5}$ and SBP were more strongly negative when using GAMMs than kriging models, which is consistent with the hypothesis of a vasodilatory effect of exposure to NO from primary traffic-related emissions,[37] because GAMM estimates contain information on local road gradients, whereas kriging models do not. Thus, we hypothesize that confounding of $PM_{2.5}$ (and possibly $NO_2$) effects by NO may be partly responsible for the negative associations with SBP observed in our study. Also, we cannot dismiss the possibility of overcontrol for exposure from having age and calendar time in the same model and note that the associations between $PM_{2.5}$, $PM_{10}$, and $NO_2$ and SBP were positive in adjusted models not controlling for calendar time.

In adjusted models, both when controlling for calendar time and when not, our results for lag 3-5 day air pollutants are broadly consistent with the short-term (7-day average) associations in Adar et al.[20] except that, in that study, associations between 7-day average $NO_2$ and $PM_{2.5}$ were attenuated to null after controlling for calendar time, whereas in the present study associations for lag 3-5 day $PM_{2.5}$ and $NO_2$ remained extant for DBP as well as for lag 3-5 day $NO_2$ and SBP. Differences between our results and those of Adar et al. may be due to (1) smaller exposure errors in our study due to the use of log-normal kriging models reflecting greater within-urban area spatial variability than area-wide averages of monitor values, (2) larger sample size, or (3) differences in study population. In addition, our results emphasize the importance of controlling for calendar time in this setting: In models not controlling for calendar time, for SBP, associations with $PM_{2.5}$ and $NO_2$ were positive, but after control for calendar time were null or negative. While we believe that adjustment for calendar time is appropriate in our analysis because it can account for long-term time trends in BP that are not related to air pollution and provides some additional information in controlling for these

trends, as mentioned previously, we cannot dismiss the possibility of overcontrol for exposure by having age and calendar time in the same model. Whether or not a previously published result was adjusted for calendar time may explain, in part, the inconsistent findings (sometimes negative, sometimes null, sometimes positive) regarding $PM_{2.5}$ and $NO_2$ in the literature, along with other differences in study design. In addition, our results for long-term (annual) $PM_{2.5}$ concentrations showed a negative association with SBP but a positive association with DBP (in models controlling for calendar time). However, Adar et al.[20] found no association between long-term (annual) $PM_{2.5}$ and both SBP and DBP (also in models controlling for calendar time). Our results using long-term (annual) $PM_{2.5}$ are consistent with a previous analysis of incident hypertension in the WHI[6] for DBP, though not so for SBP.

Our results for short-term (lag 3-5 day) concentrations for PM in the three size fractions and $NO_2$ with DBP were partially consistent with those from previous studies. One panel study of 62 cardiac rehabilitation patients showed a positive association between moving-average (over the previous 5 days) $PM_{2.5}$ exposure and SBP, as well as moving averages of the previous 4-, and 5-day $PM_{2.5}$ exposure levels and DBP.[10] Another panel study of 64 elderly subjects with history of coronary heart diseases found that multiday (3, 5, and 7 days) averaged air pollution exposures were positively associated with increased SBP and DBP.[9]

Our findings showed that associations between PM in the three size fractions evaluated and BP (SBP and DBP) for lag days 0, 1, and 2 were attenuated, null, or sometimes negative (with no clear biologic explanation for observed negative findings). These results are broadly consistent with other studies. One study in Antwerp, Belgium, found no associations between lag day 1 $PM_{2.5}$ for either SBP or DBP among elders with no antihypertensive medication use.[38] Similar results were found for $PM_{2.5}$ exposures immediately and 24 hours after a 2-hour walk in close proximity to traffic for both SBP and DBP among healthy adults.[39] In another study in children, no associations were found between lag day 0 (i.e., same day) exposures to PM in three size fractions and SBP.[40] In another study among young adults, negative associations were found between lag 1-3 day exposures to $PM_{2.5}$ with SBP and DBP.[41] In contrast, a panel study of 74 patients undergoing cardiac rehabilitation found a positive association between 0 and 5 hours moving-average $PM_{2.5}$ exposure and SBP[42]; They also found null associations between $PM_{2.5}$ in individual lag periods (evaluating lag days 0, 1, 2, 3, and 4 separately) and DBP, which is partially inconsistent with our findings, though this discrepancy may be due to differences in sample size. Furthermore, one meta-analysis reported substantial heterogeneity in effect estimates of BP for short-term levels of $PM_{2.5}$, $PM_{10}$, and $NO_2$, and also provided evidence of publication bias for the association between $NO_2$ and DBP.[16] In addition, earlier studies have documented evidence of spatial and temporal variability of PM pollution with regard to sources and chemical composition,[43,44] and as such differences in PM composition, as discussed in Giorgini et al.,[5] could be another reason our findings differ from those in earlier studies conducted in different areas.

This study has several strengths. One is the large sample size and recruitment from many areas of the United States, which allowed us to perform stratified analysis with sufficient statistical power; also the longitudinal study design using repeated measurements provides increased statistical power to detect associations between air pollution levels and BP as compared to a cross-sectional design. Second, the estimates of air pollution exposure are from daily lognormal kriging models, which have advantages in terms of spatial resolution and reducing error in exposure estimation over traditional area-average or nearest-neighbor approaches, namely: (1) They provide better spatial resolution in reflecting within-urban-area variation in situations where more than one monitor is present in a given urban area and (2) On days when a given nearest-neighbor value is missing, interpolating the available data using kriging is expected to result in less exposure error than using the next nearest monitor's data, which itself may be distant.

This study also has several limitations. The first concerns the lack of $PM_{2.5}$ monitoring before 1999. Second, $PM_{2.5-10}$ was estimated by subtracting model-predicted $PM_{2.5}$ from model-predicted $PM_{10}$. Although the $PM_{2.5}$ and $PM_{10}$ models were validated separately, $PM_{2.5-10}$ was not, and as such exposure errors will be larger for $PM_{2.5-10}$. The third is spatial error arising from the spatial misalignment of monitors and participant residences. The fourth is that kriging models did not include very local, micro- to neighborhood-scale information (or their proxies) on air pollutant levels, as discussed above. In addition, the exposure error could be larger for $NO_2$ due to limited monitor density across the contiguous US. The fifth is related to the lack of personal exposure data and/or outdoor time-activity data, which contributes to exposure error in our study. Sixth, we were unable to stratify by those participants with underlying cardiovascular diseases (these data were not present in our analysis dataset), and these cardiovascular health conditions may modify the associations between air pollutant levels and BP. Finally, generalizability is limited. In postmenopausal women, changes in hormone levels may affect the cardiovascular system and, at least potentially, modify air pollution effects. Therefore, the findings from this study may not be generalizable to males, non-white postmenopausal women, or to younger US women.

## CONCLUSION

In conclusion, our findings are consistent with short-term (lag 3-5 day) $PM_{2.5}$ and $NO_2$ levels being associated with increases in DBP among postmenopausal US older women, though two-pollutant model results suggest $NO_2$ is more likely responsible for the observed associations. Associations for long-term (annual) $PM_{2.5}$ were larger than those for short-term.

In models containing both short-term and long-term (annual) $PM_{2.5}$ levels, we found an association with long-term but not short-term.

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