Effects of short-term particulate air pollution and nitrogen dioxide on blood pressure in older women: Longitudinal data from the Women's Health Initiative

Tong Wen
The Pennsylvania State University College of Medicine: Penn State College of Medicine
Duanping Liao
The Pennsylvania State University College of Medicine: Penn State College of Medicine
Gregory A. Wellenius
Boston University School of Public Health
Eric A. Whitsel
University of North Carolina at Chapel Hill Gillings School of Global Public Health
Helene G. Margolis
University of California Davis
Leslie F. Tinker
Fred Hutchinson Cancer Research Center
James D. Stewart
University of North Carolina at Chapel Hill Gillings School of Global Public Health
Jeff D. Yanosky (JYanosky@phs.psu.edu)
Pennsylvania State University https://orcid.org/0000-0002-6196-655X

Research

Keywords: Air Pollution, Blood Pressure, Women's Health Initiative

Posted Date: October 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-952531/v1

Effects of short-term particulate air pollution and nitrogen dioxide on blood pressure in older women: Longitudinal data from the Women's Health Initiative

Tong Wen[1], Duanping Liao[1], Gregory A. Wellenius[2], Eric A. Whitsel[3, 4], Helene G. Margolis[5], Leslie F. Tinker[6], James D. Stewart[3], Jeff D. Yanosky[1*]

Affiliations:

[1] Penn State College of Medicine, Department of Public Health Sciences, Division of Epidemiology, Hershey, PA, USA

[2] Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA

[3] Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC, USA

[4] Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[5] Department of Internal Medicine, University of California, Davis, Davis, CA, USA

[6] Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington, USA

*Correspondence: jyanosky@phs.psu.edu

Abstract

Background: Short-term variations in particulate matter (PM) and traffic-related air pollutants (*e.g.*, nitrogen dioxide, NO_2) have been associated with daily mortality and cardiovascular health outcomes in previous studies. We aimed to evaluate whether short-term changes in PM in three size fractions ($PM_{2.5}$, $PM_{2.5-10}$, and PM_{10}) and NO_2 were associated with systolic and

diastolic arterial blood pressure (SBP and DBP, respectively) in the Women's Health Initiative Observational Study (OS) and Clinical Trials (CT).

Methods: We used linear mixed-effect models to estimate the association between short-term air pollution concentrations and repeated measures of arterial blood pressure.

Results: We found statistically significant positive associations between short-term measures (lag days 3-5) of $PM_{2.5}$ as well as NO_2 for both SBP and DBP in fully adjusted models when not controlling for calendar time. Also, in only the CT, PM_{10} and $PM_{2.5-10}$ were associated with DBP but not SBP. In fully adjusted models controlling for calendar time, associations with $PM_{2.5-10}$ and NO_2 remained statistically significant for DBP (except for $PM_{2.5-10}$ in the OS). Specifically, in the CT group, each IQR increase in lag 3-5 NO_2 exposure (9.88 ppb) was associated with a 0.13 mm Hg increase in DBP. Also, each IQR increase in lag 3-5 $PM_{2.5-10}$ exposure (8.46 $\mu g\ m^{-3}$) was associated with a 0.05 mm Hg increase in DBP. Effect modification was found for body mass index (BMI), socioeconomic position (SEP), diabetes, dietary sodium intake, combined fruit and vegetable consumption, and long-term $PM_{2.5}$ for $PM_{2.5}$, PM_{10}, and NO_2. Shorter lag periods (lag 0 through lag 2) typically exhibited lesser and, especially for SBP, sometimes negative associations. In two-pollutant models of exposures lagged over 3-5 days, NO_2 associations with DBP were stronger (0.20 mm Hg per IQR), but those for $PM_{2.5-10}$ were attenuated to null, as compared to single-pollutant models.

Conclusions: Our findings are consistent with short-term (lag days 3-5) $PM_{2.5-10}$ and NO_2 levels as risk factors for acute cardiovascular outcomes and cardiovascular disease, though two-pollutant model results suggest NO_2 is more likely responsible for the observed effects.

Keywords: Air Pollution, Blood Pressure, Women's Health Initiative

Introduction

Short-term variations (from days to weeks) in particulate matter (PM) and traffic-related air pollutants such as nitrogen dioxide (NO_2) have been associated with daily mortality and cardiovascular health outcomes in previous studies [1-3]. PM<2.5 μm ($PM_{2.5}$)-mediated arterial blood pressure (BP) elevation may potentially be an important part of the causal mechanism leading to acute cardiovascular outcomes [4, 5]. One recent study from Women's Health Initiative (WHI) suggests that long-term exposure to $PM_{2.5}$ and PM_{10} may be essential modifiable risk factors for hypertension in post-menopausal women [6].

Findings from earlier studies of the effects of repeated short-term air pollutant exposures on BP have been varied, though generally suggestive of positive associations [7-10]. One of these studies conducted in California found that $PM_{2.5}$ (specifically the $PM_{2.5}$ component primary organic carbon) was more strongly associated with BP measures than were gaseous pollutants [7]. Additionally, traffic-related exposure measures have been identified as important modifiers of the effect of $PM_{2.5}$ on arterial BP in a diverse population from the MESA study [11]. One randomized controlled trial in humans showed that short-term exposure to traffic-related air pollution (*i.e.*, diesel exhaust) was significantly associated with increased systolic BP (SBP) but not diastolic BP (DBP) [12]. Findings from many epidemiological studies of short-term air pollution effects on arterial BP have been analyzed using meta-analysis [13]; this meta-analysis showed overall significant positive though not robust short-term associations between several air pollutants ($PM_{2.5}$, PM<10 μm (PM_{10}), NO_2, and SO_2) and increases in SBP and DBP, as well as hypertension, an established risk factor for cardiovascular diseases. Blood pressure and air pollutant levels (in many areas of the US) have both decreased over the past several decades [14, 15]. Adar et al. found significant associations for both SBP and DBP with $PM_{2.5}$ as well as NO_2 for exposure averaging periods of seven days and longer in adjusted models that did not control for calendar time. However, when calendar time was included, those associations were attenuated to null [16].

Few previous studies have evaluated short-term effects of PM (in multiple size fractions, including $PM_{2.5}$ (which originates from primary emissions from combustion sources and from secondary formation in the atmosphere) and 2.5<PM<10 μm ($PM_{2.5-10}$) (which is typically generated from mechanical grinding or crushing, as well as from windblown dust)) and NO_2 on BP over the same short-term exposure period and those that have produced varied results [13]. Additionally, whether BMI, socioeconomic position (SEP), diabetes, combined fruit and vegetable consumption, or long-term average $PM_{2.5}$ levels may modify these effects is poorly understood. In this study, we estimated the effects of short-term PM ($PM_{2.5}$, 2.5<PM<10 μm ($PM_{2.5-10}$), and PM_{10}) and NO_2 on SBP and DBP using linear mixed effect models using data from the Observational Study (OS) and Clinical Trials (CT) components of the Women's Health Initiative (WHI) cohort. We evaluated effect modification by BMI, SEP, diabetes, dietary sodium intake, combined fruit and vegetable consumption, and long-term average $PM_{2.5}$ levels. Additionally, we used two-pollutant models examine confounding effects by co-pollutant on BP.

Methods

Study population

The Woman's Health Initiative (WHI) is a nationwide prospective U.S. cohort across 40 clinical centers in 24 states [17]. Post-menopausal women aged 50 to 79 years were recruited between 1993 and 1998, and followed through 2005. The WHI consists of two components, the observational study component (OS: n=93,696 participants) and the clinical trials component (CT: n=68,132 participants). We stratify our results by WHI cohort because of differences between study designs, population attributes, missing-ness of data, and results in this study. In the CT, repeated measurements were available from the screening visit and annual clinic visits (Years 1-11); in the OS, repeated measurements were available from the screening visit and the Year 3 visit. Our analysis was restricted to only those not currently taking anti-hypertensive medication (OS: n=69,490; CT: n=66,518) and therefore the final dataset contained 119,147

(OS group) and 407,563 (CT group) observations. Because $PM_{2.5}$ monitoring data were only available after 1999, and thus daily exposure models were unavailable prior to that date, about 66.8% of observations in the OS and 36.3% of observations in the CT were missing data on $PM_{2.5}$ exposure over the study period.

Blood pressure measurements

Supine blood pressure was measured in the right arm after participants had been seated and at rest for at least three minutes. SBP and DBP were computed by averaging two measurements; if only one measurement was available, that single value was used.

Air pollution exposure assessment

Air pollution concentration estimates were available at geocoded residential locations of WHI participants from a daily lognormal kriging model [18] (Liao et al. 2006) for $PM_{2.5}$, PM_{10}, and NO_2. $PM_{2.5-10}$ was estimated by subtracting model-predicted $PM_{2.5}$ from model-predicted PM_{10}. This kriging model was validated using leave-one-out cross-validation and had a low average prediction error of 0.06 μg m^{-3}. Lagged exposure variables were calculated based on the index date of the BP measurement and the period one-week prior, from zero (day of the measurement; lag 0) to six days prior (lag 6) and were expressed as an interquartile range (IQR) change in the pollutant to afford comparisons among air pollutants. Moving averages were also calculated over corresponding lag periods (lag 0-1, lag 0-2, lag 0-3, etc.). Because the effect estimates for individual lag periods were similar and largest (*i.e.*, most positive) for lag days 3, 4 and 5, summary measures of the exposures were calculated by averaging lagged values from three to five days prior to the BP measurement (lag 3-5). Twelve-month moving-average $PM_{2.5}$ levels were estimated using spatio-temporal generalized additive mixed models (GAMMs) at geocoded residential locations of WHI participants [19]. This GAMM model was

validated using 10-set cross-validation and had high predictive accuracy with a cross-validation R^2 of 0.77.

Covariates

At baseline and during each annual follow-up visit, questionnaires were used to collect demographic data. 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), region (Northeast, South, Midwest, and West), day of the week, season (spring, summer, fall, and winter), neighborhood SEP (continuous z-score (higher z-score corresponds to higher SEP) calculated using six census tract-level variables [20] and categorized by tertile), BMI (<25 kg/m^2; 25-30 kg/m^2; 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, diabetes, long-term average $PM_{2.5}$ concentrations (categorized by tertile), and calendar time expressed as the number of years since baseline exam. For participants in the CT, treatment arm was also included as a categorical variable.

Statistical analysis

<u>Linear mixed-effects models:</u>

We used linear mixed-effect (LME) models to estimate the association of air pollutant exposure and arterial blood pressure. A compound symmetric variance matrix was specified in the models to control for correlated errors between repeated measures. To estimate associations between SBP and DBP measures and air pollutant exposure metrics, the following linear mixed-effects regression model was fit to the data:

$$y_{ij} = \beta_0 + \sum_{p=1}^{P} \beta_p X_p + \alpha_i + b_i Age_{ij} + e_{ij}$$

where y_{ij} represents either SBP or DBP measurements for subject i and visit j, β_p's are fixed-effect coefficients, X_p's are explanatory variables (including air pollutant concentrations, confounders, and calendar time expressed as years since baseline exam). α_i is a subject-specific random intercept included to account for the multiple observations available per subject, and b_i is a random slope for age. SAS v9.4 PROC MIXED was used for model fitting (except upon non-convergence, when PROC GLIMMIX was used). A significance level of 0.05 was used for all analyses.

Model selection:

First we evaluated unadjusted models between air pollutant concentrations ($PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, and NO_2) and arterial blood pressure (SBP, DBP) in both OS and CT. For each pollutant, the models included only a single lag period (lag days 0 to 6, in separate models) or a single moving average. Next we evaluated the effect of lag 3-5 exposures in the models, then added confounders, in sets, to form basic and adjusted models as described below. In basic models, confounders included age, race/ethnicity, arm group (only for CT), census region, day of the week, season, and a random slope for age. Next we added additional potential confounders to the basic model; if the percent change in the air pollutant effect estimate was >10%, then the variable was considered a confounder. If the percent change in the air pollutant effect estimate was <10%, we then evaluated whether the Akaike information criterion (AIC) was lowered upon inclusion of the variable and if so, the variable was considered a confounder. In adjusted models, we further controlled for BMI, SEP, pack-years of smoking, and diabetes. Next, to control for calendar time, we added the number of years since baseline exam to the fully adjusted models. We evaluated fully-adjusted models with and without adjustment for calendar time 1) to isolate the effect of controlling for calendar time and 2) to facilitate comparisons with previous analyses which may or may not have controlled for calendar time. To evaluate effect

modification, we fit fully adjusted models with interaction terms for the lag 3-5 air pollutant and each of BMI, SEP, diabetes, smoking, sodium intake, fruit and vegetable consumption, US Census Region ("Northeast", "Midwest", "South", "West"), and long-term $PM_{2.5}$ concentrations. When statistically significant effect modification was found (*p*-value for interaction term < 0.05), stratified analyses were conducted. For pollutants which were found to have statistically significant main effects in fully adjusted models controlling for calendar time, we further examined these pollutants in two-pollutant models.

Results

During the study period (1993-2005), a total of 136,008 participants (69,490 in OS and 66,518 in CT) were included in the analysis. Approximately 1 in 3 participants came from the western region of the US and most of participants were white (>80%). On average, participants were overweight (*i.e.*, BMI >= 25 kg m^{-2}), with higher mean BMI among participants in CT than in the OS, but this difference was not statistically significant. Characteristics of the study participants and air pollutant concentrations are presented in Table 1.

Unadjusted models:

Regression coefficients (listed in the columns headed with "β" in the tables) represent the change in BP per unit change in air pollution concentration (after transformation of the air pollutant concentration to the IQR scale). Results from unadjusted models using lag 3-5 exposures were varied and not consistent in direction. For SBP, unadjusted models using lag 3-5 exposures showed that short-term exposure to $PM_{2.5-10}$ and PM_{10} were significantly negatively associated in the OS and CT (except for $PM_{2.5-10}$ in OS), while NO_2 was significantly positively associated in both the OS and CT. For DBP, $PM_{2.5}$, $PM_{2.5-10}$, PM_{10} and NO_2 were significantly positively associated in both the OS and CT (except for PM_{10} in the OS group and a statistically significant negative association for $PM_{2.5-10}$ in the OS group) (Table 2).

Fully adjusted models:

Results from multivariable models with each potential confounder added showed that BMI, SEP, pack-years of smoking, and diabetes were important confounders (in addition to those in the basic models) among the three PM fractions as well as NO_2 and for both SBP and DBP, especially for $PM_{2.5}$ and NO_2 (Supplemental Material Table S1).

Results from basic and fully adjusted models without controlling for calendar time using single lag days (0-6) are presented in Supplemental Material Tables S2A and Table S2B. Shorter single lag periods (lag 0 through lag 2) showed significantly negative or null associations for PM ($PM_{2.5}$, $PM_{2.5-10}$ and PM_{10}) with both SBP and DBP (except for $PM_{2.5}$-DBP in OS group) as well as NO_2 with SBP. For longer lag periods, effects were consistent and largest (*i.e.*, most positive) for single lag periods 3, 4, and 5.

Fully adjusted models not controlling for calendar time and using lag 3-5 exposures included the following confounders: age, race/ethnicity, treatment arm (only for the CT group), region, day of the week, season, BMI, SEP, pack-years of smoking, and diabetes. In these fully adjusted models not controlling for calendar time, $PM_{2.5}$ and NO_2 were significantly associated with both SBP as well as DBP (regression coefficients from the LME models without effect modification are presented in Table 2). Effect sizes for NO_2 were largest among the pollutants considered for SBP and DBP, except for $PM_{2.5}$-SBP in the OS group. In the CT group, each IQR increase in lag 3-5 $PM_{2.5}$ exposure (an increment of 7.66 μg m^{-3}) was associated with a 0.07 mm Hg increase in SBP and a 0.06 mm Hg increase in DBP. By comparison, each IQR increase in lag 3-5 NO_2 exposure (an increment of 9.88 ppb) was associated with a 0.45 mm Hg increase in SBP and a 0.38 mm Hg increase in DBP. PM_{10} and $PM_{2.5-10}$ were significantly associated with DBP only in the CT group, again in fully adjusted models not controlling for calendar time.

In fully adjusted models controlling for calendar time, the association between NO_2 and DBP in both the OS and CT groups remained statistically significant, as did the association between $PM_{2.5-10}$ and DBP in only the CT group. Specifically, in the CT group, each IQR increase in lag 3-5 NO_2 exposure (9.88 ppb) was associated with a 0.13 mm Hg increase in DBP (Table 2). Also, each IQR increase in lag 3-5 $PM_{2.5-10}$ exposure (8.46 μg m^{-3}) was associated with a 0.05 mm Hg increase in DBP (Table 2). In the OS group, the effect size for lag 3-5 NO_2 exposure was larger and was 0.32 mm Hg.

Effect modification:

We evaluated effect modification in either 1) fully adjusted models not controlling for calendar time or 2) in fully adjusted models controlling for calendar time, depending on whether main effects were statistically significant in Table 2.

In fully adjusted models not controlling for calendar time, we found effect modification by BMI, SEP, diabetes, and long-term $PM_{2.5}$ levels for $PM_{2.5}$, PM_{10}, and NO_2 (*p*-value for interaction terms <0.05; Table 3).

Because $PM_{2.5-10}$-DBP and NO_2-DBP associations were statistically significant in the fully adjusted models controlling for calendar time, effect modification was evaluated in those models. For NO2-DBP, we found effect modification by BMI, SEP, diabetes, dietary sodium intake, and combined fruit and vegetable consumption (Table 4). No effect modification was found between $PM_{2.5-10}$ and DBP in the CT group.

Effect modification by BMI:

BMI modified the effects of lag 3-5 $PM_{2.5}$ exposure as well as lag 3-5 NO_2 exposure for SBP in only the CT group, in models not controlling for calendar time. Also, BMI modified the effects of lag 3-5 NO_2 exposure for DBP in the CT group, again in models controlling for calendar time. Stratified results showed both $PM_{2.5}$-SBP associations and NO_2-SBP associations were stronger

and more positive among participants with higher BMI; the $PM_{2.5}$-SBP association was statistically non-significant among those in the first (lowest) tertile of BMI (Table 3 & Table 4).

Effect modification by SEP:

SEP also significantly modified the effect of lag 3-5 $PM_{2.5}$ and NO_2 in both the CT and OS for both SBP and DBP, in models not controlling for calendar time (Table 3). For both $PM_{2.5}$-SBP and $PM_{2.5}$-DBP, stratified associations were lower among those with higher SEP. For NO_2-SBP, stratified associations were again lower among those with higher SEP.

For NO_2-DBP associations in models controlling for calendar time (Table 4), stratified associations also were lower among those with higher SEP in both the OS and CT groups.

Effect modification by other factors:

For $PM_{2.5}$, PM_{10}, and NO_2 lag 3-5 exposures, associations with SBP and DBP were stronger and more positive among participants with diabetes compared to those without, in models not controlling for calendar time (Table 3). Also, for lag 3-5 $PM_{2.5}$ exposures, stratified associations with DBP were stronger and more positive for the second and third tertiles of long-term $PM_{2.5}$ level in the CT group.

For NO_2-DBP associations in models controlling for calendar time, stratified associations were lower among those with higher fruit and vegetable consumption in the OS group. Also, stratified results by dietary sodium intake showed NO_2-DBP associations were stronger and more positive in the first and third tertile of sodium intake in the OS group, as compared to the second tertile (Table 4).

Two-pollutant models controlling for calendar time:

In Table 2, only $PM_{2.5-10}$ and NO_2 had statistically significant main effects in fully adjusted models controlling for calendar time and only for DBP, so only these two pollutants were used in two-

pollutant models. Though $PM_{2.5-10}$ and NO_2 were significantly correlated in our analysis, repeated measures correlation coefficients were low and ranged between 0.02 and 0.09 across the seven lag periods lag 0 to lag 6.

Regression coefficients from single-pollutant and two-pollutant fully adjusted models controlling for calendar time are presented in Table 5. For DBP, compared to single pollutant model results, NO_2 associations were stronger and more positive in two-pollutant models. However, those for $PM_{2.5-10}$ were attenuated to null. We also found effect modification by US Census Region in the fully adjusted two-pollutant model controlling for calendar time (Supplemental Material Table S3).

Discussion

Our findings indicate that short-term measures (lag days 3-5) of $PM_{2.5}$ as well as NO_2 are consistently associated with changes in SBP and DBP in models not controlling for calendar time. When evaluating $PM_{2.5}$ and NO_2 exposures averaged over lag days 3-5, patterns of association were consistent and robust with respect to the direction of association.

However, results for shorter exposure periods (lag days 0-2) were attenuated, null, or sometimes protective for PM in the three size fractions evaluated and for the NO_2-SBP association. These findings are similar to results from other studies in different populations showing protective or null short-term effects of PM [21-26] and NO_2 [21, 26] on blood pressure on the same day or the previous 1-3 days. Specifically, statistically significant negative associations were found between lag day 1, 2-, and 3 PM_{10} and SBP as well as lag day 2 PM_{10} and DBP, and between lag day 2 and 3 NO_2 and SBP. In contrast, statistically significant positive associations were found between lag day 1 and lag day 2 NO_2 and DBP among nonsmoking adults [21]. Statistically non-significant associations were also found between lag day 1 $PM_{2.5}$ with both SBP and DBP among elders with no anti-hypertensive medication use

[22]; similar results were found for $PM_{2.5}$ exposures immediately and 24-h after a 2 hr walk in close proximity to traffic for both SBP an DBP among healthy adults [23]. In children, statistically non-significant associations were found between lag day 0 (*i.e.*, same day) exposures to PM in three size fractions and SBP [24]; also statistically non-significant associations were found between lag day 1 exposures to $PM_{2.5}$ as well as NO_2 and both SBP and DBP in children [26]. Statistically significant negative associations were also found between lag day 1-3 exposures to $PM_{2.5}$ with SBP and DBP among young adults [25].

In our analysis, in models not controlling for calendar time, SEP, BMI, and diabetes were found to be statistically significant effect modifiers. Two prior studies also reported effect modification by BMI on the association between $PM_{2.5}$ and BP [7, 27]. We also found effect modification by long-term $PM_{2.5}$ level on short-term exposure to $PM_{2.5}$, a result consistent with earlier studies which showed that the association between short-term $PM_{2.5}$ and SBP was stronger in areas with higher long-term $PM_{2.5}$ levels [27, 28].

Our results for short-term (lag days 3-5) exposures, in models not controlling for calendar time, were broadly 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 [29]. Another panel study of 64 elderly subjects with history of coronary heart diseases [7] found that multiday (3-day, 5-day, and 7-day) averaged air pollution exposures were positively associated with increased SBP and DBP. In our single-pollutant models, lag 3-5 NO_2 had stronger effects on both SBP and DBP than did lag 3-5 $PM_{2.5}$, compared on an IQR basis. Stronger effects of NO_2 on BP than those of $PM_{2.5}$ have also been shown in another study from Canada [30].

In models controlling for calendar time, our results are broadly consistent with those in Adar et al. [16]. However in that analysis associations attenuated to null after controlling for calendar

time (for exposure averaging periods of seven days, for example), whereas in the present study associations for lag 3-5 $PM_{2.5-10}$ and NO_2 remained statistically significant for DBP. Despite remaining statistically significant, the effect sizes are small. However, they may still be clinically relevant: Across the (somewhat skewed) distribution of exposure to NO_2, comparing the most highly-exposed individuals to the least, they may experience a change in exposure of approximately three IQRs, and therefore the corresponding effect size would, using the larger effect estimate from the OS, be 3*0.32=0.96 mm Hg in DBP. In these models, we found effect modification by SEP, BMI, and diabetes in the NO_2-DBP association, suggesting that participants with high BMI, low SEP, and diabetes may be particularly susceptible to the effects of short-term NO_2 on DBP. We also found that participants with more fruit and vegetable consumption were less susceptible to the effects of NO_2 on DBP, suggesting potential dietary intervention to mitigate air pollution-induced CVD risk [31]. We also noted effect modification by dietary sodium intake, but the non-monotonic pattern in these associations does not support meaningful causal interpretation.

Further, in two-pollutant models controlling for calendar time, associations of DBP with NO_2 became stronger than those in single-pollutant models, whereas $PM_{2.5-10}$ associations were attenuated to null. Zhao et al. [10] reported similar findings: In two-pollutant models including both 1-day averaged $PM_{2.5}$ and NO_2, the statistically significant positive association between $PM_{2.5}$ exposure and SBP attenuated to non-significant. We also note effect modification by US Census Region consistent with results in Adar et al. [16], with the effects of lag 3-5 NO_2 in the two-pollutant model stronger in the South and West US Census Regions as compared to the others.

However, some results from our analysis differ from earlier studies. Our study showed statistically significant negative or null associations between individual lag day 0-2 air pollutant exposures and both SBP and DBP. These negative associations persisted even when

controlling for calendar time. In contrast, a panel study of 74 patients undergoing cardiac rehabilitation [32] found a statistically significant positive association between 0-5 hour moving-average $PM_{2.5}$ exposure and SBP, with each IQR increase corresponding to an increase of 0.94 mm Hg (95%CI: 0.02-1.87). They also found statistically non-significant associations between $PM_{2.5}$ in individual lag periods (evaluating lag days 0, 1, 2, 3, and 4 separately) and DBP, which is inconsistent with our findings. In another study, Dvonch et al. [28] reported that short-term exposure (*i.e.*, lag day 2) to $PM_{2.5}$ was positively associated with SBP among all subjects, suggesting a positive effect more acute than in our findings. These differences could be due to differences in study population or to different exposure estimation procedures. A recent meta-analysis of air pollution exposure and blood pressure reported substantial heterogeneity in effect estimates on blood pressure for $PM_{2.5}$, PM_{10}, and NO_2; also, NO_2 had a larger meta-estimated association with DBP than $PM_{2.5}$ [13]. Their analysis also provided evidence of publication bias for the association between NO_2 and DBP. Also, earlier studies have documented evidence of spatial and temporal variability of particulate pollution with regard to sources and chemical composition [33, 34], 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.

This study has several strengths. One is the large sample size and recruitment from many areas of the US which allowed us to perform stratified analysis with sufficient statistical power; also the longitudinal study design using repeated measurements of blood pressure increased statistical power to detect associations between air pollution exposures and BP measures. Secondly, the estimates of air pollution exposure from daily lognormal kriging models contain greater temporal (*i.e.*, daily) and spatial (including urban-scale gradients) resolution than in previous studies using conventional exposure assessment methods. Our study also has several limitations. The first concerns the lack of $PM_{2.5}$ monitoring before 1999. Second, we were unable to control for other potential confounders such as physical activity and occupational

exposure. The third is exposure error; a small amount of spatial error is unavoidable when performing spatial interpolation and kriging models did not include very local, micro- to neighborhood-scale information (or their proxies) on air pollutant levels. Of course, where monitoring was sparse, interpolation was based on distant measurements. The fourth is limited generalizability. The findings from this study may not be generalizable to males, nor to younger, pre-menopausal women in the U.S.

In conclusion, our findings are consistent with short-term (lag days 3-5) $PM_{2.5-10}$ and NO_2 levels as risk factors for acute cardiovascular outcomes and cardiovascular disease, though two-pollutant model results suggest NO_2 is more likely responsible for the observed effects among elderly women not taking anti-hypertensive medication.

Supplementary information

Additional file 1: Table S1. Effects of an IQR change in air pollutant concentration on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in basic models with varying levels of adjustment in the WHI Observational Study (OS) and Clinical Trials (CT) components. **Table S2A.** Associations between an IQR change in air pollutant concentration and systolic blood pressure (SBP) and diastolic blood pressure (DBP) for single lag days (0-6) based on basic models. **Table S2B.** Associations between an IQR change in air pollutant concentration and systolic blood pressure (SBP) and diastolic blood pressure (DBP) for single lag days (0-6) based on fully adjusted models. **Table S3.** Single- and two-pollutant models of lag 3-5 day air pollutant exposures based on fully adjusted models + calendar time stratified by US Census Region.

Abbreviations

PM: Particulate matter; $PM_{2.5}$: Particulate matter <2.5μm; $PM_{2.5-10}$: Particulate matter >2.5μm and <10μm; PM_{10}: Particulate matter <10μm; NO_2: nitrogen dioxide; BP: Blood pressure; SBP:

Systolic blood pressure; DBP: diastolic blood pressure; WHI: Women's Health Initiative; OS: Observational Study; CT: Clinical Trials; BMI: Body mass index; SEP: Socioeconomic position; IQR: Interquartile range; GAMM: Generalized additive mixed models; LME: Linear mixed effect models.

Funding

This study was supported by National Institutes of Health grant #1 R01 ES020871-01A1.

Acknowledgements

The authors would like to thank the contribution from all WHI investigators and participants.

Authors' contributions

Gregory A. Wellenius, Eric A. Whitsel, Duanping Liao, Jeff D. Yanosky, Leslie F. Tinker, and James D. Stewart helped secure funding for the project. Jeff D. Yanosky and Tong Wen conducted data analysis and manuscript writing. Eric A. Whitsel and James D. Stewart contributed to data collection and data cleaning. Eric A. Whitsel, Helene G. Margolis, Duanping Liao, Leslie F. Tinker, and Gregory A. Wellenius provided suggestions to the data analysis, reviewed, and revised the manuscript. The authors read and approved the final manuscript.

Availability of data and materials

Supporting data is not available.

Ethics approval and consent to participate

Informed consent was provided from all study participants.

Consent for publication

The authors consent to publication.

Competing interests

The authors, with the exception of Gregory A. Wellenius, declare that they have no competing interests. Dr. Wellenius serves as a paid consultant for the Health Effects Institute (Boston, MA) and Google, LLC (Mountain View, CA).

Authors' information

Tong Wen, Penn State College of Medicine, Department of Public Health Sciences, Division of Epidemiology, Hershey, PA, USA, twen@phs.psu.edu; Duanping Liao, Penn State College of Medicine, Department of Public Health Sciences, Division of Epidemiology, Hershey, PA, USA, dliao@phs.psu.edu; Gregory A. Wellenius, Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA, wellenius@bu.edu; Eric A. Whitsel, Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC, USA, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, eric_whitsel@med.unc.edu; Helene G. Margolis, Department of Internal Medicine, University of California, Davis, Davis, CA, USA, hgmargolis@ucdavis.edu; Leslie F. Tinker, Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington, USA, ltinker@WHI.org; James D. Stewart, Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC, USA, j.stewart@unc.edu; Jeff D. Yanosky, Penn State College of Medicine, Department of Public Health Sciences, Division of Epidemiology, Hershey, PA, USA, jyanosky@phs.psu.edu.

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Table 1. Demographic and physiologic characteristics of 136,008 participants in the WHI Observational Study (OS) and Clinical Trial (CT) components and air pollution exposure metrics throughout follow-up (1993-2005).

	OS	CT
Participants, N	69,490	66,518
Observations, n	119,147	407,563
Age at visit, years, Mean ± SD	64.24 ± 7.49	66.09 ± 7.31
Region, %		
Northeast	21.85	23.23
South	26.07	24.32
Midwest	21.15	22.51
West	30.92	29.95
Race/Ethnicity, %		
American Indian or Alaskan Native	0.47	0.39
Asian or Pacific Islander	2.87	2.25
Black or African-American	5.91	8.59
Hispanic/Latino	4.09	4.02
White (not of Hispanic origin)	85.6	83.71
Other	1.07	1.05
Neighborhood-level SEP, Mean ± SD	0.35 ± 5.33	0.26 ± 5.28
Tertile 1	31.52	32.31
Tertile 2	32.81	33.52
Tertile 3	35.67	34.17
Body mass index (BMI), kg/m^2, Mean ± SD, %		
At baseline	26.53 ± 5.49	28.19 ± 5.59
BMI <25	46.61	31.74
BMI >=25 and <30	33.18	36.64
BMI >=30	20.21	31.62
Across all visits	26.53 ± 5.44	28.60 ± 5.84
BMI <25	46.19	29.9
BMI >=25 and <30	33.47	35.71
BMI >=30	20.34	34.4
Dietary sodium intake (mg), Mean ± SD, %	2546.92 ± 1183.68	2688.62 ± 1160.83
Tertile 1	1510.84 ± 388.86, 36.55	1552.67 ± 362.79, 30.55
Tertile 2	2461.08 ± 245.75, 32.89	2470.48 ± 246.37, 33.71
Tertile 3	3866.13 ± 1149.87, 30.56	3883.00 ± 1024.69, 35.74
Combined fruit and vegetable consumption, medium servings per day, %	4.34 ± 2.26	4.12 ± 2.17
Tertile 1	2.00 ± 0.66, 31.58	2.01 ± 0.64, 34.85
Tertile 2	3.90 ± 0.56, 33.08	3.88 ± 0.56, 33.57
Tertile 3	6.76 ± 1.66, 35.34	6.71 ± 1.59, 31.58

Pack-years of smoking	9.38 ± 17.78	9.61 ± 17.95
Diabetes present , %		
Yes	3.73	7.19
No	96.27	92.81
Systolic blood pressure (SBP), mm Hg		
Across all visits	123.45 ± 16.72	125.61 ± 16.91
Baseline visit	126.96 ± 17.96	127.97 ± 17.40
Diastolic blood pressure (DBP), mm Hg		
Across all visits	73.33 ± 9.00	72.72 ± 9.30
Baseline visit	74.73 ± 9.33	75.88 ± 9.12
Air pollutants, lag days 0-6, Mean ± SD		
$PM_{2.5}$ ($\mu g/m^3$)	13.92 ± 5.69	13.45 ± 5.64
$PM_{2.5-10}$ ($\mu g/m^3$)	14.14 ± 7.12	13.39 ± 6.61
PM_{10} ($\mu g/m^3$)	27.99 ± 8.65	27.07 ± 8.04
NO_2 (ppb)	19.04 ± 7.36	17.84 ± 7.03
Air pollutants, lag days 0-2, Mean ± SD		
$PM_{2.5}$ ($\mu g/m^3$)	13.87 ± 6.70	13.39 ± 6.63
$PM_{2.5-10}$ ($\mu g/m^3$)	14.49 ± 8.35	13.67 ± 7.85
PM_{10} ($\mu g/m^3$)	28.27 ± 10.33	27.28 ± 9.83
NO_2 (ppb)	19.28 ± 8.12	18.01 ± 7.74
Air pollutants, lag days 3-5, Mean ± SD		
$PM_{2.5}$ ($\mu g/m^3$) IQR=7.66	13.88 ± 6.75	13.45 ± 6.75
$PM_{2.5}$ in IQR units	1.81 ± 0.88	1.76 ± 0.88
$PM_{2.5-10}$ ($\mu g/m^3$) IQR=8.46	13.51 ± 8.18	12.82 ± 7.60
$PM_{2.5-10}$ in IQR units	1.60 ± 0.97	1.52 ± 0.90
PM_{10} ($\mu g/m^3$) IQR=12.14	27.38 ± 10.06	26.55 ± 9.62
PM_{10} in IQR units	2.26 ± 0.83	2.19 ± 0.79
NO_2 (ppb) IQR=9.88	18.45 ±7.82	17.41 ± 7.60
NO_2 in IQR units	1.87 ± 0.79	1.76 ± 0.77
Long-term $PM_{2.5}$, $\mu g/m^3$, Mean ± SD, %	13.02 ± 3.74	13.84 ± 4.23
Tertile 1	9.49 ± 1.62, 37.92	9.50 ±1.63, 32.43
Tertile 2	13.32 ± 0.89, 35.63	13.38 ± 0.91, 32.02
Tertile 3	17.67 ± 2.93, 26.45	18.22 ± 3.24, 35.55

Table 2. Main effects of an IQR change in lag 3-5 day air pollutant exposure metrics on systolic and diastolic blood pressure in the WHI Observational Study (OS) and Clinical Trials (CT) components for $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, and NO_2.

Health Outcome	Models	Air pollutants	OS				CT			
			N	β	SE	*p*-value	N	β	SE	*p*-value
SBP	Unadjusted	**$PM_{2.5}$**	39,537	0.02	0.093	0.846	259,571	-0.01	0.031	0.843
		$PM_{2.5-10}$	39,537	-0.12	0.085	0.151	259,571	**-0.08**	**0.031**	**0.008**
		PM_{10}	105,214	**-0.20**	**0.054**	**0.0003**	385,740	**-0.09**	**0.027**	**0.001**
		NO_2	105,214	**0.12**	**0.062**	**0.046**	385,740	**0.17**	**0.034**	**<0.0001**
	Basic	**$PM_{2.5}$**	39,425	0.09	0.091	0.320	259,035	0.06	0.032	0.062
		$PM_{2.5-10}$	39,425	-0.04	0.088	0.680	259,035	0.01	0.032	0.685
		PM_{10}	104,916	-0.05	0.055	0.379	384,953	0.03	0.027	0.271
		NO_2	104,916	0.01	0.066	0.859	384,953	**0.37**	**0.037**	**<0.0001**
	Fully adjusted	**$PM_{2.5}$**	37,646	**0.18**	**0.092**	**0.045**	248,334	**0.07**	**0.032**	**0.026**
		$PM_{2.5-10}$	37,646	-0.12	0.089	0.178	248,334	0.01	0.033	0.719
		PM_{10}	100,041	-0.07	0.056	0.205	369,230	0.04	0.028	0.117
		NO_2	100,041	**0.16**	**0.067**	**0.020**	369,230	**0.45**	**0.037**	**<0.0001**
	Fully adjusted + calendar time	**$PM_{2.5}$**	37,646	0.13	0.092	0.175	248,334	-0.06	0.032	0.067
		$PM_{2.5-10}$	37,646	-0.06	0.089	0.514	248,334	-0.04	0.033	0.284
		PM_{10}	100,041	-0.07	0.056	0.202	369,230	-0.05	0.028	0.064
		NO_2	100,041	-0.13	0.067	0.061	369,230	-0.02	0.038	0.608
DBP	Unadjusted	**$PM_{2.5}$**	39,537	**0.22**	**0.051**	**<0.0001**	259,571	**0.15**	**0.018**	**<0.0001**
		$PM_{2.5-10}$	39,537	**-0.13**	**0.047**	**0.004**	259,571	**0.04**	**0.018**	**0.032**
		PM_{10}	105,214	-0.02	0.030	0.444	385,740	**0.12**	**0.016**	**<0.0001**
		NO_2	105,214	**0.45**	**0.034**	**<0.0001**	385,740	**0.77**	**0.020**	**<0.0001**
	Basic	**$PM_{2.5}$**	39,425	**0.14**	**0.052**	**0.006**	259,035	**0.06**	**0.018**	**0.001**
		$PM_{2.5-10}$	39,425	0.01	0.050	0.894	259,035	**0.07**	**0.019**	**0.000**
		PM_{10}	104,916	0.00	0.032	0.878	384,953	**0.06**	**0.016**	**0.000**

	NO_2	104,916	**0.36**	**0.038**	**<0.0001**	384,953	**0.35**	**0.021**	**<0.0001**
Fully adjusted	**$PM_{2.5}$**	37,646	**0.16**	**0.052**	**0.002**	248,334	**0.06**	**0.019**	**0.001**
	$PM_{2.5-10}$	37,646	0.00	0.051	1.000	248,334	**0.08**	**0.019**	**<0.0001**
	PM_{10}	100,041	0.01	0.039	0.898	369,230	**0.07**	**0.016**	**<0.0001**
	NO_2	100,041	**0.41**	**0.038**	**<0.0001**	369,230	**0.38**	**0.022**	**<0.0001**
Fully adjusted + calendar time	**$PM_{2.5}$**	37,646	0.09	0.052	0.086	248,334	-0.02	0.019	0.362
	$PM_{2.5-10}$	37,646	0.07	0.051	0.146	248,334	**0.05**	**0.019**	**0.013**
	PM_{10}	100,041	0.01	0.032	0.837	369,230	0.02	0.016	0.268
	NO_2	100,041	**0.32**	**0.039**	**<0.0001**	369,230	**0.13**	**0.022**	**<0.0001**

*: Basic model adjusted for age, race/ethnicity, arm group (for CT), region, day of the week, season and random slope for age; Fully adjusted model adjusted for age, race/ethnicity, arm group (for CT), region, day of the week, season, BMI, SEP, pack- year of smoking, diabetes and random slope for age.

**: PM is particulate matter; $PM_{2.5}$ is PM < 2.5 μm; $PM_{2.5-10}$ is 2.5 μm < PM < 10 μm; PM_{10} is PM < 10 μm; NO_2 is nitrogen dioxide.

Table 3. Effect modification of lag 3-5 day air pollutant exposures assessed using stratification by BMI, SEP, diabetes, and long-term $PM_{2.5}$ level based on fully adjusted models not controlling for calendar time (when interaction terms were significant in Table 2).*

Health Outcome	Air pollutant	Effect modifier and strata**		OS					CT				
				N	β	SE	*p*-value	*p*-value for interaction term	N	β	SE	*p*-value	*p*-value for interaction term
SBP	**$PM_{2.5}$**	SEP	Tertile 1	12,085	**0.52**	**0.174**	**0.003**	**0.002**	81,411	**0.16**	**0.060**	**0.009**	**0.0002**
			Tertile 2	12,312	0.19	0.161	0.230		83,977	**0.12**	**0.056**	**0.034**	
			Tertile 3	13,249	-0.10	0.148	0.501		82,946	-0.04	0.051	0.456	
		BMI	Low						69,063	-0.02	0.060	0.718	**0.026**
			Medium						89,311	**0.13**	**0.054**	**0.013**	
			High						89,960	**0.12**	**0.055**	**0.030**	
		Diabetes	No						227,817	0.05	0.033	0.144	**0.0029**
			Yes						20,517	**0.27**	**0.126**	**0.035**	
	NO_2	SEP	Tertile 1	31,923	**0.63**	**0.126**	**<0.0001**	**<0.0001**	120,928	**0.61**	**0.070**	**<0.0001**	**0.0006**
			Tertile 2	32,813	0.21	0.118	0.070		124,057	**0.53**	**0.066**	**<0.0001**	
			Tertile 3	35,305	**-0.22**	**0.109**	**0.040**		124,245	**0.33**	**0.060**	**<0.0001**	
		BMI	Low						106,919	**0.38**	**0.068**	**<0.0001**	**<0.0001**
			Medium						133,384	**0.43**	**0.062**	**<0.0001**	
			High						128,927	**0.62**	**0.065**	**<0.0001**	
		Diabetes	No						343,000	**0.40**	**0.039**	**<0.0001**	**<0.0001**
			Yes						26,230	**0.92**	**0.155**	**<0.0001**	
DBP	**$PM_{2.5}$**	SEP	Tertile 1	12,085	**0.39**	**0.098**	**<0.0001**	**0.0125**					
			Tertile 2	12,312	0.08	0.092	0.402						
			Tertile 3	13,249	0.07	0.084	0.416						
		Diabetes	No						227,817	**0.05**	**0.019**	**0.005**	**0.0049**
			Yes						20,517	**0.18**	**0.072**	**0.010**	
		Long-term $PM_{2.5}$	Tertile 1						63,559	-0.01	0.046	0.811	**0.0133**
			Tertile 2						74,311	**0.09**	**0.038**	**0.024**	
			Tertile 3						110,464	**0.05**	**0.026**	**0.039**	

PM_{10}	Diabetes	No	343,000	**0.06**	**0.017**	**0.001**	**0.0012**
		Yes	26,230	**0.20**	**0.067**	**0.003**	

Note: Effect modification for NO_2 – DBP association was evaluated in fully-adjusted models + calendar time. These results are presented in Table 5.

*Models adjusted for age, race/ethnicity, arm group (for CT), region, day of the week, season, BMI, SEP, pack-years of smoking, diabetes, and random slope for age.

**Categorized by tertile of SEP score, BMI, and/or long-term $PM_{2.5}$ level score separately.

Table 4. Effect modification of lag 3-5 day air pollutant exposures assessed using stratification by BMI, SEP, diabetes, sodium intake, and fruit and vegetable consumption based on fully-adjusted + calendar time models*.

Health Outcome	Air pollutant	Effect modifier and strata**		OS					CT				
				N	β	SE	*p*-value	*p*-value for interaction term	N	β	SE	*p*-value	*p*-value for interaction term
DBP	**NO_2**	SEP	Tertile 1	31,923	**0.58**	**0.071**	**<0.0001**	**<0.0001**	120,928	**0.22**	**0.041**	**<0.0001**	**<0.0001**
			Tertile 2	32,813	**0.30**	**0.068**	**<0.0001**		124,057	**0.14**	**0.039**	**0.001**	
			Tertile 3	35,305	**0.18**	**0.063**	**0.004**		124,245	**0.10**	**0.036**	**0.005**	
		BMI	Low						106,919	**0.13**	**0.040**	**0.001**	**<0.0001**
			Medium						133,384	**0.13**	**0.036**	**0.000**	
			High						128,927	**0.24**	**0.039**	**<0.0001**	
		Diabetes	No						343,000	**0.12**	**0.023**	**<0.0001**	**<0.0001**
			Yes						26,230	**0.38**	**0.090**	**<0.0001**	
		Sodium intake	Tertile 1	34,448	**0.42**	**0.065**	**<0.0001**	**0.0311**					
			Tertile 2	32,371	**0.25**	**0.068**	**0.0002**						
			Tertile 3	29,469	**0.33**	**0.072**	**<0.0001**						
		Fruit and vegetable consumption	Tertile 1	29,434	**0.47**	**0.072**	**<0.0001**	**0.0426**					
			Tertile 2	31,970	**0.32**	**0.069**	**<0.0001**						
			Tertile 3	34,884	**0.24**	**0.065**	**0.0002**						

*Fully adjusted + calendar time models included the main effect for each effect modifier (even if not identified as a confounder).

**Categorized by tertile of SEP score, BMI, sodium intake, and fruit and vegetable consumption separately.

Table 5. Single- and two-pollutant models of lag 3-5 day air pollutant exposures based on fully-adjusted + calendar time models*.

Model	Health Outcome	Air pollutant	CT			
			N	β	SE	*p*-value
Single-pollutant	DBP	$PM_{2.5-10}$	248,334	**0.05**	**0.019**	**0.013**
		NO_2	369,230	**0.13**	**0.022**	**<0.0001**
Two-pollutant**	DBP	$PM_{2.5-10}$	248,334	0.03	0.019	0.083
		NO_2	248,334	**0.20**	**0.028**	**<0.0001**

*: Models adjusted for age, race/ethnicity, arm group (for CT), region, day of the week, season, BMI, SEP, pack-years of smoking, diabetes, random slope for age and calendar time.

**: The two-pollutant model includes $PM_{2.5-10}$ and NO_2 in the same model.

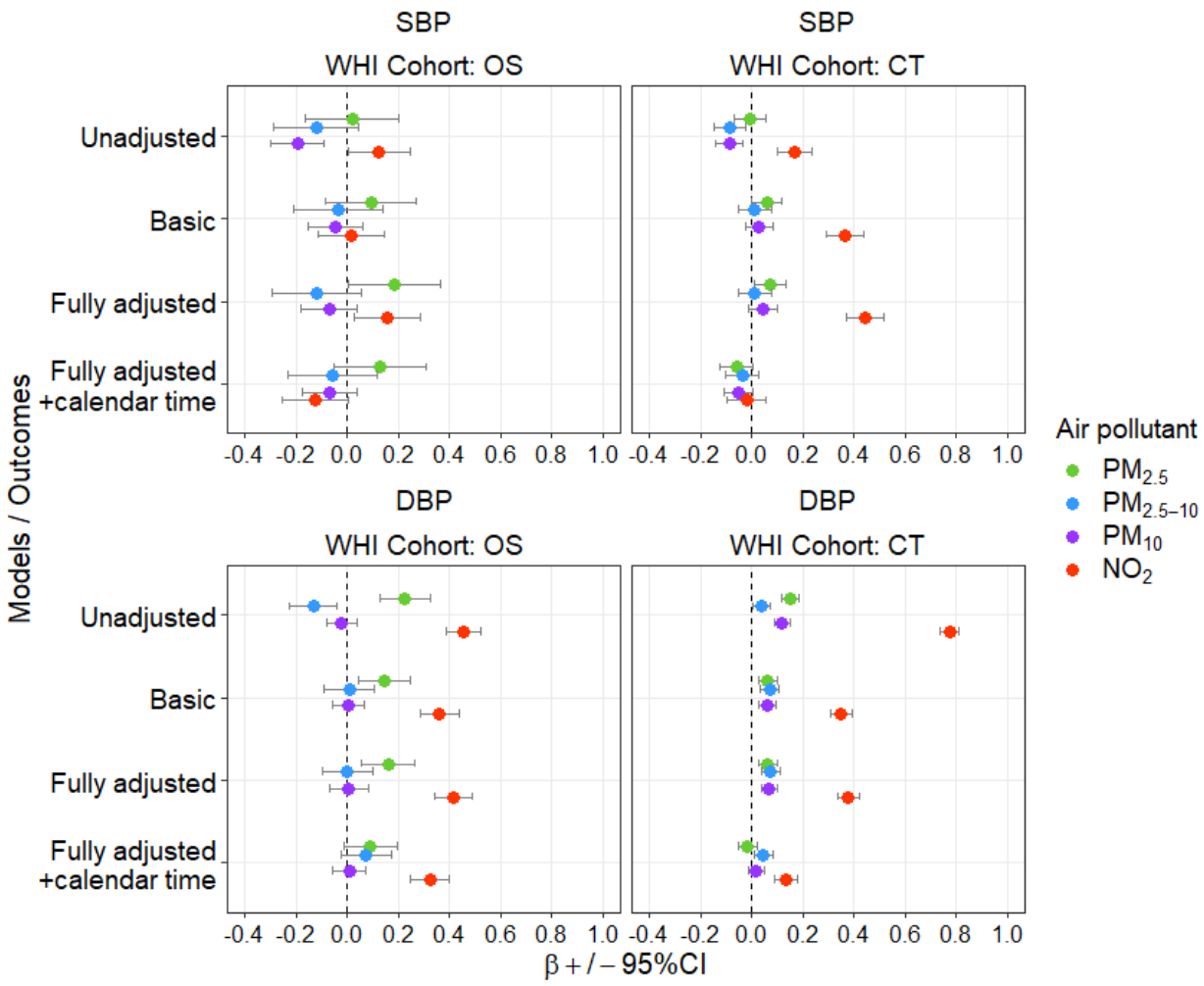

Figure 1. Main effects of an IQR change in exposure metrics averaged over lag days 3-5 on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the WHI Observational Study (OS) and Clinical Trial (CT) components for unadjusted, basic, fully adjusted, and fully adjusted + calendar time models using data from Table 2. Note: CI is confidence interval.

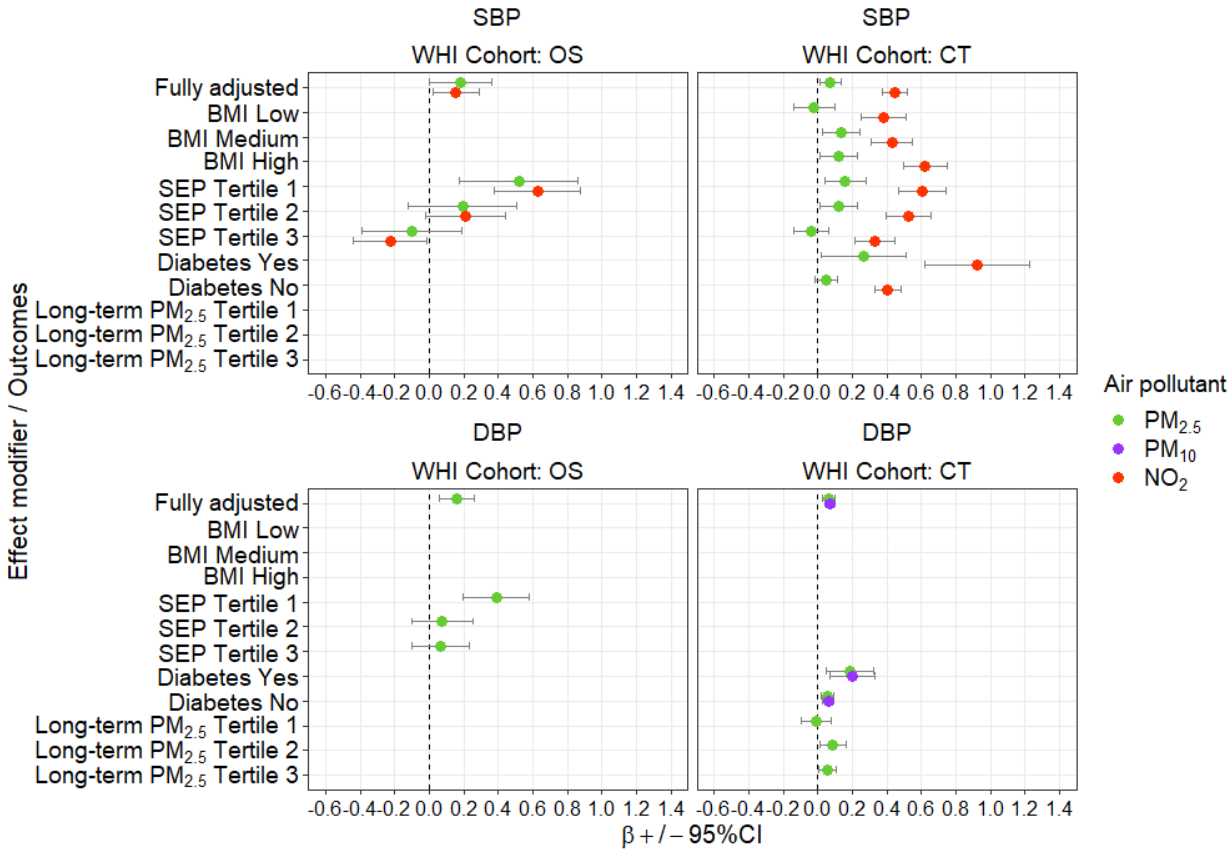

Figure 2. Fully adjusted and stratified effects of an IQR change in exposure metrics averaged over lag days 3-5 on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in models not controlling for calendar time across WHI Observational Study (OS) and Clinical Trials (CT) groups showing effect modification by body mass index (BMI), socioeconomic position (SEP), diabetes, and long-term $PM_{2.5}$ level based on results in Table 3. Note: CI is confidence interval.

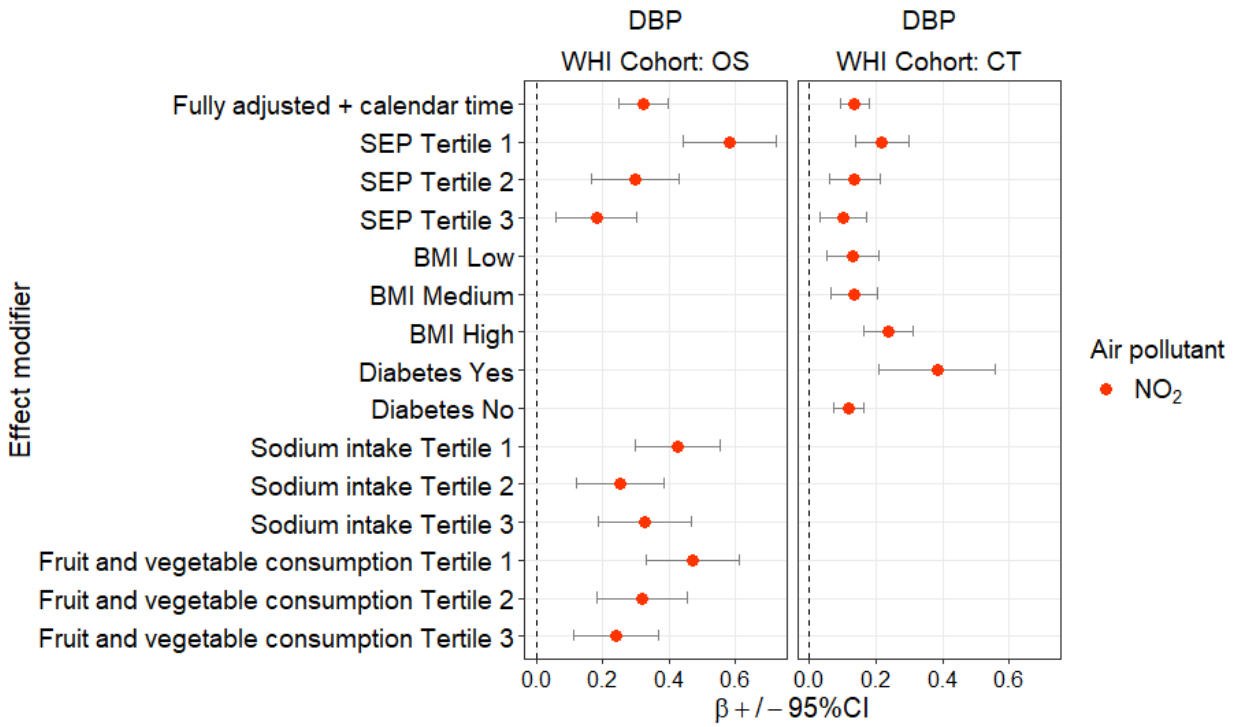

Figure 3. Fully adjusted + calendar time and stratified effects of an IQR change in exposure metrics averaged over lag days 3-5 on diastolic blood pressure (DBP) in the WHI Observational Study (OS) and Clinical Trials (CT) components showing effect modification by BMI, (socioeconomic position) SEP, diabetes, sodium intake, and fruit and vegetable consumption based on results in Table 5. Note: CI is confidence interval.

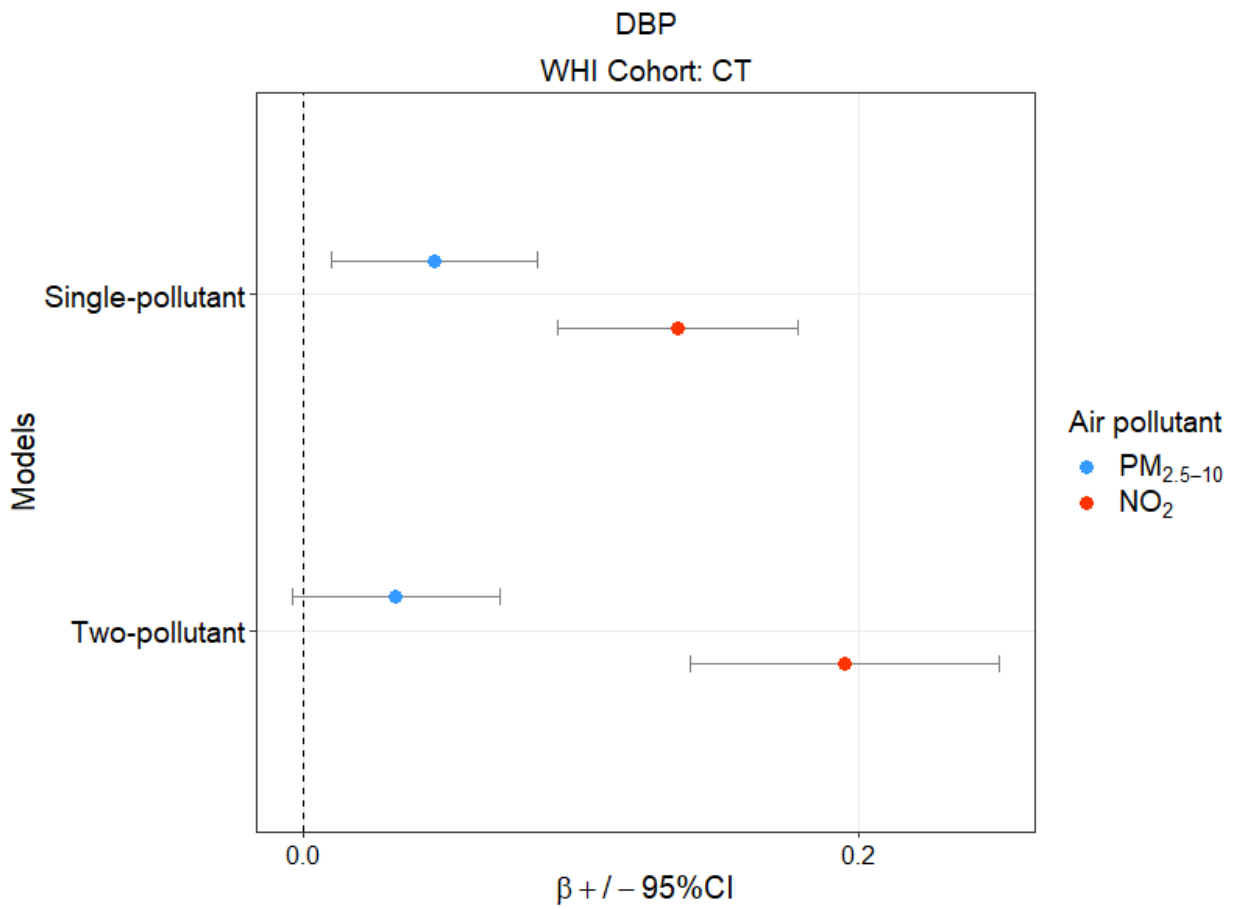

Figure 4. Fully adjusted + calendar time effects of an IQR change in exposure metrics averaged over lag days 3-5 on diastolic blood pressure (DBP) in the WHI Clinical Trial (CT) group from single-pollutant and two-pollutant models. Note: CI is confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalfilesforWHIBPEH20210930.pdf