HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Environ Int. 2017 August ; 105: 79–85. doi:10.1016/j.envint.2017.05.009.

Long-term exposure to residential ambient fine and coarse particulate matter and incident hypertension in post-menopausal women

Trenton Honda[1,*], **Melissa N. Eliot**[2], **Charles B. Eaton**[2,3], **Eric Whitsel**[4,5], **James D. Stewart**[4,6], **Lina Mu**[7], **Helen Suh**[8], **Adam Szpiro**[9], **Joel D. Kaufman**[9], **Sverre Vedal**[9], and **Gregory A. Wellenius**[2]

[1]Department of Health Sciences, Northeastern University, Boston, MA

[2]Department of Epidemiology, School of Public Health, Brown University, Providence, RI

[3]Department of Family Medicine, Alpert Medical School of Brown University, Providence, RI

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

[5]Department of Medicine, School of Medicine, University of North Carolina Chapel Hill, NC

[6]Carolina Population Center, University of North Carolina Chapel Hill, Chapel Hill, NC

[7]School of Public Health and Health Professions, State University of New York, Buffalo, Buffalo, NY

[8]Department of Civil and Environmental Engineering, Tufts University, Medford, MA

[9]School of Public Health, University of Washington, Seattle, WA

Abstract

BACKGROUND—Long-term exposure to ambient particulate matter (PM) has been previously linked with higher risk of cardiovascular events. This association may be mediated, at least partly, by increasing the risk of incident hypertension, a key determinant of cardiovascular risk. However, whether long-term exposure to PM is associated with incident hypertension remains unclear.

METHODS—Using national geostatistical models incorporating geographic covariates and spatial smoothing, we estimated annual average concentrations of residential fine ($PM_{2.5}$), respirable (PM_{10}), and course ($PM_{10-2.5}$) fractions of particulate matter among 44,255 post-menopausal women free of hypertension enrolled in the Women's Health Initiative (WHI) clinical trials. We used time-varying Cox proportional hazards models to evaluate the association between long-term average residential pollutant concentrations and incident hypertension, adjusting for

[*]Corresponding author: t.honda@northeastern.edu, Mailing Address: Northeastern University, 202 Robinson Hall, 360 Huntington Ave, Boston MA 02115.

Competing Interests: The authors declare that they have no competing interests.

potential confounding by sociodemographic factors, medical history, neighborhood socioeconomic measures, WHI study clinical site, clinical trial, and randomization arm.

RESULTS—During 298,383 person-years of follow-up, 14,511 participants developed incident hypertension. The adjusted hazard ratios per interquartile range (IQR) increase in $PM_{2.5}$, PM_{10}, and $PM_{10\text{-}2.5}$ were 1.13 (95% CI: 1.08, 1.17), 1.06 (1.03, 1.10), and 1.01 (95% CI: 0.97, 1.04), respectively. Statistically significant concentration-response relationships were identified for $PM_{2.5}$ and PM_{10} fractions. The association between $PM_{2.5}$ and hypertension was more pronounced among non-white participants and those residing in the Northeastern United States.

CONCLUSIONS—In this cohort of post-menopausal women, ambient fine and respirable particulate matter exposures were associated with higher incidence rates of hypertension. These results suggest that particulate matter may be an important modifiable risk factor for hypertension.

INTRODUCTION

Air pollution, and especially fine particulate matter ($PM_{2.5}$) is an established risk factor for adverse cardiovascular health outcomes [1, 2] [3–6]. In 2012, the World Health Organization (WHO) attributed 7 million deaths worldwide - one of every eight deaths - to air pollution, with nearly 80% of these due to cardiovascular causes [7]. The elevated cardiovascular morbidity and mortality associated with $PM_{2.5}$ may be explained, in part, by its increasing the risk of hypertension.

Hypertension is a highly prevalent, established risk factor for cardiovascular disease [8]. As of 2009–2012, 70 million American adults had hypertension, and an additional 33% had pre-hypertension [9]. Hypertension is known to increase the risk of death by myocardial infarction, stroke, heart failure and kidney disease, with 360,000 deaths directly or indirectly attributable to hypertension in 2013 [10]. While a number of modifiable (obesity, physical inactivity, poor diet, alcohol and tobacco use) and non-modifiable (age, family history) hypertension risk factors have been described [11], a growing body of evidence implicates air pollution as a possible risk factor. Specifically, several studies have identified positive associations between markers of long-term exposure to $PM_{2.5}$ and hypertension prevalence [12, 13] or blood pressure elevations [14, 15], while others have found no association [16, 17]. A separate body of literature has evaluated the association between daily changes in pollutant levels and blood pressure measures [18, 19]. However, only a few previous studies have investigated links between long-term air pollution and incident hypertension [17, 20–22]. Of these studies, only one has been performed in the context of a large, national US cohort, and that study examined associations with self-reported hypertension [20]. As hypertension is an established risk factor for adverse cardiovascular health outcomes [8], additional research is needed to further elucidate the association between $PM_{2.5}$ and the risk of incident hypertension. Additionally, while a number of studies have linked $PM_{2.5}$ to hypertension and blood pressure, much less is known about the potential associations of long-term exposure to other particulate matter size fractions (i.e. $PM_{10\text{-}2.5}$, PM_{10}), which may or may not be associated with hypertension risk [23–28].

To address these gaps in the literature, we examined the association between long-term exposure to various particulate matter size fractions ($PM_{2.5}$, $PM_{10-2.5}$, PM_{10}) and the risk of incident hypertension in a prospective cohort of post-menopausal women.

METHODS

Population

Data from the Women's Health Initiative clinical trials (WHI CT) was used to quantify the association between incident hypertension and air pollution exposure. The WHI is a large, national, prospective cohort study of post-menopausal women aged 50-79 years at enrollment focused on investigating strategies for the prevention of heart disease, cancer, and osteoporosis morbidity and mortality [29]. The WHI CT included 68,132 women recruited between 1993 and 1998; randomized into trials evaluating the effects of hormone replacement therapy (n=27,347), dietary modification (n=48,835), and calcium/vitamin D supplementation (n=36,282) and followed until 2005 (see Supplemental Material for additional details of the study inclusion/exclusion criteria and recruitment details). A subsequent five-year extension (2005–2010) was conducted during which 82.4% of the original WHI cohort (n=52,174) continued to be followed. Our study followed participants originally enrolled in all WHI CTs from enrollment (1993–1998) through the end of the first study extension (2010). Participants who did not have data on follow-up time in the first extension (n=221) were excluded, affording 67,911 participants for the current analysis.

Exposure Assessment

Daily $PM_{2.5}$ measurements obtained from the US Environmental Protection Agency's (EPA) AQS and IMPROVE networks were used to calculate annual averages of $PM_{2.5}$ [30, 31]. Using these data, partial least-squares regression models incorporating a number of geographic covariates were used in a national, universal kriging model to estimate average $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ concentrations across the United States for each participant. The geocoded address history of all WHI participants from baseline through 2010, accounting for changes of address, at baseline, and for each year of follow-up, were linked with specific exposure estimates using geographic information systems software [32]. The model has previously been shown to predict concentrations with high cross-validation accuracy for both $PM_{2.5}$ (R^2=0.88) and PM_{10} (R^2=0.40–0.63) [33, 34]. Estimates of coarse particulate matter exposure ($PM_{10-2.5}$) were calculated by subtracting the estimated $PM_{2.5}$ for a given time interval from the estimated PM_{10}. Annual moving average estimates of $PM_{2.5}$, PM_{10}, and PM_{10}-2.5 were calculated for 1980–2010.

Outcome assessment

At baseline and then annually through 2005, blood pressure was ascertained at WHI clinical centers after participants had been seated for five minutes using standardized procedures [29, 35]. Two separate measurements were taken ≥30 seconds apart from the right arm in all participants with a conventional mercury blood pressure cuff at baseline and at each subsequent visit [29, 35]. The mean of the two measurements from each visit were calculated for use in analyses.

At the time of study enrollment, WHI participants were queried whether they have been diagnosed with high blood pressure or hypertension by a physician and/or whether they were taking medications prescribed to treat hypertension. As in previous studies from WHI [36], participants were considered to have prevalent hypertension if at enrollment they had: a systolic blood pressure (SBP) ≥140 mm Hg, a diastolic blood pressure (DBP) ≥90 mm Hg, a history of physician-diagnosed hypertension, or reported use of anti-hypertension medication. Based upon these criteria, 34.8% of participants (n=23,656) were identified as having hypertension at baseline and were thus excluded from analysis. From 1993–2005, presence or absence of hypertension was assessed annually for each participant using both conventional sphygmomanometer measurements and self-reported anti-hypertensive medication use (participants were queried: “Do you now take pills for high blood pressure”). Blood pressure was measured annually using standard procedures (described above). From 2005–2010, participants self-reported new diagnoses of hypertension and/or new use of medication prescribed for hypertension on standardized questionnaires. As in previous studies [37, 38], we defined incident hypertension as first self-report of medication prescribed for hypertension, SBP ≥ 140 mm Hg, or DBP ≥ 90 mm Hg.

Covariates

Potential confounders were assessed by self-administered questionnaires at time of study enrollment and annually thereafter. Demographic covariates included age and race/ethnicity (Asian, Hispanic, Native American/Alaskan Native, Black, White). Socioeconomic covariates included educational attainment (completed graduate school, completed college/vocational school versus other), household income (>$100,000 per year, $50,000–$100,000 per year versus <$50,000 per year), employment status (current versus other), insurance coverage (current versus other), and a U.S. Census tract-level, neighborhood socioeconomic status (SES) summary Z-Score of wealth/income, education and occupation [39]. Health behavior covariates included smoking status (current/historical or never), self-reported sodium intake and physical activity level (quantified as average metabolic equivalents per week). Health status variables included body mass index (BMI), self-reported history of coronary artery disease, diabetes and high cholesterol. Additionally, indicator variables for 36 unique WHI study clinical sites were included to control for potential geospatial confounding. Information on participation in one or more randomized WHI clinical trials (Diet Modification trial, Hormone Replacement trial, Calcium and Vitamin D trial) and treatment arm of clinical trial (treatment versus control) was also collected.

STATISTICAL ANALYSIS

Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for hypertension incidence associated with time-varying estimates of geocoded address-specific concentrations of each pollutant. Models controlled for variables which have previously been shown to be associated with air pollution and/or hypertension, including: age at enrollment, BMI, education, race/ethnicity, smoking status, physical activity, sodium intake, neighborhood socioeconomic summary z-score, household income, employment status, insurance status, history of high cholesterol, history of cardiovascular disease, history of diabetes, dietary sodium intake, clinical trial study arm and

WHI study clinical site. Associations were examined in single-pollutant and two-pollutant ($PM_{2.5}$ and $PM_{10-2.5}$) models. We additionally tested for exposure-response relationships utilizing indicator variables for quintiles of exposure.

Several sensitivity analyses were performed to assess the robustness of our results to various model specifications. First, we repeated the main analyses without adjustment for BMI, history of coronary artery disease and/or type 2 diabetes mellitus at enrollment, as these factors may represent intermediate factors on the causal chain linking air pollution and incident hypertension [40]. Second, as the exposure period that is most etiologically relevant to the development of chronic diseases such as hypertension is not well known, and pollutant measurements in the US tend to trend downward over time, we repeated the primary analyses using time-fixed Cox models to examine the association between incident hypertension and exposure estimated at baseline [41]. Last, the analyses were repeated using interval survival regression to account for the one-year interval censoring nature of the hypertension outcome data [42].

In secondary analyses we examined whether the associations between each pollutant and incident hypertension varied by categories of age, BMI, history of diabetes, WHI study region, smoking status, physical activity, education, neighborhood SES Z-Score and race/ethnicity by including multiplicative terms between pollutant measures and the variables of interest in the models. As the majority (84.8%) of participants were White, race/ethnicity was evaluated as a dichotomized variable (White versus non-White) as well as by individual ethnic background (Black, Asian/Pacific Islander, Hispanic/Latino). Finally, for comparison with prior studies of hypertension prevalence, we used logistic regression to estimate the cross-sectional association between pollutant levels at baseline and prevalence-odds ratios (POR) and 95% CIs of prevalent hypertension at enrollment.

The proportion of missing data was generally low, with most covariates missing less than 2% of data. Higher levels of missingness were observed for covariates relating to work history (11.2%) income (5.8%), physical activity (9.4%), history of cardiovascular disease (10.5%) and high cholesterol (10.7%). Missing data were imputed by multiple imputation using chained equations to create ten datasets with complete data [43]. Analyses were carried out using R version 3.2.1 [44].

RESULTS

At enrollment 23,656 participants (34.8%) met the criteria for prevalent hypertension and were excluded from the main analysis. Among participants free of prevalent hypertension at baseline (n=44,255), the average age was 62.0 years (standard deviation, SD 7.0). The average baseline BMI was 27.9 kg/m^2 (SD 5.5) with 36% of participants meeting the definition of obese. The majority of participants (85%) were White, followed by Black (7%) and 47% reported historical or current smoking (Table 1). Over the course of the original study (1995–2005) and the first extension (2005–2010) there were a total of 298,383 person-years of follow-up during which 14,511 participants developed incident hypertension. The average incidence rate of hypertension was 48.6/1000 person-years. The average particulate matter concentrations for participants over the course of the study were: $PM_{2.5}$: 13.2 $\mu g/m^3$

(SD 3.0), PM_{10}: 22.9 μg/m^3 (SD 5.6), and $PM_{10-2.5}$: 9.8 μg/m^3 (SD 4.6). $PM_{2.5}$ and PM_{10} estimates were moderately correlated (r=0.56), $PM_{2.5}$ and $PM_{10-2.5}$ were not correlated (r=0.03) and $PM_{10-2.5}$ and PM_{10} were highly correlated (r=0.84).

Table 2 presents the associations between one-year average $PM_{2.5}$ and risk of incident hypertension. In fully adjusted models, an IQR (3.98 μg/m^3) increase in $PM_{2.5}$ exposure was associated with 1.13 (95% CI 1.08, 1.17) times the rate of incident hypertension. A monotonic exposure-response relationship was also identified, with individuals in the highest versus lowest quintile of exposure having a 23% (hazard ratio [HR]: 1.23, 95% CI: 1.12, 1.34) higher rate of incident hypertension (p-for-trend <0.001).

In two-pollutant models examining hypertension risk associated with $PM_{10-2.5}$ controlling for $PM_{2.5}$, we observed no evidence of a linear association (HR 1.01, 95% CI: 0.97, 1.04, per IQR increment of 5.27 μg/m^3) (Table 2). In models of quintiles of exposure, only the top quintile of exposure was statistically significantly associated with higher risk of hypertension (HR: 1.10, 95% CI: 1.01, 1.19), but the overall test of linear trend was not statistically significant (p=0.081).

In investigations of the association between increases in PM_{10}, we found that an IQR (6.17 μg/m^3) shift was associated with a hazard ratio of incident hypertension of 1.06 (95% CI: 1.03, 1.10) (Table 2). Models of quintiles of PM_{10} show a significant exposure-response relationship (p-for trend <0.001), with an 18.9% (95% CI: 10.1%, 28.4%) higher risk of incident hypertension in the highest versus lowest quintile of exposure.

In logistic regression models examining the cross-sectional association between PM size fractions and hypertension prevalence at enrollment we found no evidence of significant association (Supplement 1).

Sensitivity Analyses

We performed several sensitivity analyses assess the robustness of our findings to various model assumptions (Supplement 2). First, results were essentially unchanged in models excluding variables potentially lying on the causal pathway between air pollution and hypertension (coronary artery disease, diabetes, hyperlipidemia and BMI). Second, our results were also not materially different when using semi-parametric interval regression to account for the interval censored nature of the data. Finally, in analyses using time-fixed Cox models investigating association between exposure at enrollment and incident hypertension, associations were attenuated and not statistically significant.

Effect Modification

We evaluated whether the association between PM size fractions and incident hypertension varied by participant characteristics. While we observed some statistically significant heterogeneity for specific PM size fractions, we found no characteristic that was systematically associated with a stronger association across PM size fractions. For example, the association between $PM_{2.5}$ and incident hypertension was more pronounced among non-Whites (HR of 1.21 versus 1.12; p=0.009), those in the Northeast study region (HR of 1.32 in Northeast versus 1.03 to 1.27 in other regions; p<0.001) and among obese participants

(1.15 versus 1.10; p=0.051), but did not vary by categories of age, smoking status, physical activity, education or neighborhood SES Z-score (Table 3). When considering $PM_{10-2.5}$, we also observed heterogeneity by race/ethnicity but with a stronger association observed among white participants and by region, with the strongest association observed among those living in the Midwest. Stronger associations in the Midwest were also observed for PM_{10} models. We found that the association between PM and incident hypertension was statistically significantly different by age category when considering PM_{10} and $PM_{10-2.5}$, and not different when considering $PM_{2.5}$.

DISCUSSION

We observed that long-term exposures to $PM_{2.5}$ and PM_{10}, but not $PM_{10-2.5}$, were associated with increased risk of incident hypertension in a national cohort of post-menopausal women. An IQR increase in one-year average $PM_{2.5}$ exposure was associated with 1.13 (95% CI: 1.08, 1.17) times the risk of incident hypertension. This statistically significant increased risk persisted after additionally controlling for PM_{10}-2.5 in two-pollutant models. A statistically significant dose-response relationship was also observed in models of quintiles of exposure (*p*-for trend<0.001) with the highest quintile of exposure associated with a 23% increased risk relative to the lowest quintile of exposure. Models examining the association with quintiles of $PM_{10-2.5}$ did not differ from the null except for the highest quintile of exposure. Last, statistically significant, positive associations were also identified for PM_{10} (HR 1.06, 95% CI: 1.03, 1.10 per IQR), with a monotonic positive association observed across quintiles of exposure.

Relatively few studies have investigated the association between long-term exposure to particulate matter and incident hypertension, but those that have are generally consistent with our findings. Chen et al. (2013) evaluated the association of six-year mean concentration of $PM_{2.5}$ exposure with incident hypertension among 35,303 Canadian participants observed between 1996 and 2010 and reported a relative risk of 1.13 (95% CI: 1.05,1.22) for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ [22]. For comparison, the effect estimate from our study scaled to a 10 $\mu g/m^3$ increase in $PM_{2.5}$ is somewhat larger (HR 1.36, 95% CI: 1.21, 1.48). In a smaller study (n=3,236) of younger, African American women, Coogan et al. (2012) found a relative risk of hypertension of 1.48 (95% CI: 0.95, 2.31) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ [21]. This is similar to our results for Black participants rescaled to 10 $\mu g/m^3$ (HR 1.58, 95% CI: 1.13, 2.09). Zhang et al. (2016) reported a pattern of significant findings similar but weaker than ours, with a 10 $\mu g/m^3$ increase in 24-month average $PM_{2.5}$ (HR 1.04, 95% CI: 1.00, 1.07), $PM_{10-2.5}$ (1.03, 95% CI: 1.00, 1.07) and PM_{10} (HR 1.02, 95% CI: 1.00, 1.04) all associated with self-reported incident hypertension in an analysis of the Nurses Health Study [20]. Interestingly, Zhang et al. reported significant interactions by BMI, as well as higher risk among individuals younger than 65 years, which is consistent with our findings for $PM_{2.5}$ and PM_{10}, respectively.

Relatively more studies have evaluated the cross-sectional association between markers of long-term pollutant levels and hypertension prevalence with mixed results. For example, Fuks et al. (2011) found no significant association between an IQR increment increase in one-year moving average of $PM_{2.5}$ (IQR 2.4 $\mu g/m^3$) or PM_{10} (IQR 3.9 $\mu g/m^3$) and prevalent

hypertension [16]. Similarly, Chen at al. (2015) found no association between one-year moving average $PM_{2.5}$ (OR 0.99, 95% CI: 0.96, 1.02 per 5 μg/m^3), $PM_{10-2.5}$ (OR 1.00, 95% CI: 0.96, 1.03 per 5 μg/m^3) or PM_{10} (OR 1.00, 95% CI:0.94, 1.07 per 10 μg/m^3) and prevalent hypertension in a cross-sectional study in Taiwan [45]. In contrast to these studies, Babisch et al. (2014) found a 1 μg/m^3 increase in $PM_{2.5}$ was associated with a significantly higher prevalence of hypertension (OR: 1.15, 95% CI: 1.02, 1.30) in a smaller (n=4,166) German cohort [13]. Dong et al. (2013) found statistically significant associations with prevalent hypertension for three-year average PM_{10} in a Chinese population (OR: 1.12, 95% CI: 1.08, 1.16 per 19 μg/m^3) [12]. More recently, Lin et al. (2017) observed a 10 μg/m^3 increase in one-year average $PM_{2.5}$ associated with higher odds of hypertension (OR 1.14, 95% CI: 1.07, 1.22) and Liu et al. (2017) found an IQR increase (41.7 μg/m^3) in 9-month average $PM_{2.5}$ to be associated with 1.11 (95% CI: 1.05, 1.17) times the odds of hypertension [46, 47].

Residential distance to nearest major roadway has sometimes been used as a proxy for long-term exposure to traffic-related pollutants, including fine particles. For example, Fuks et al. [16] found no association between residential distance to the nearest major roadway and prevalent hypertension using baseline data from 4,291 participants from the Heinz Nixdorf Recall Study in Germany. In contrast, Kirwa et al. (2014) used data from the San Diego cohort of the WHI and found that residential proximity to major roadways was associated with statistically significant increase in prevalence odds of hypertension [48] while Kingsley et al. (2015) found among WHI CT participants that living close to major roadways was associated with incident hypertension [37].

We found no evidence of an association between baseline exposure and prevalent hypertension, but consistent, positive results with time-varying pollution estimates and incident hypertension. It is possible then, that some of the heterogeneity in the literature on prevalent hypertension is due to air pollution having a more pronounced effect on hypertension incidence than prevalence in some populations. Alternatively, associations observed with prevalent hypertension may be influenced to varying degrees by reverse causation and/or survival bias.

An additional, possible explanation for our findings is that $PM_{2.5}$ and PM_{10} may act, at least partially, as surrogate measures for smaller, ultrafine particles (UFP), traffic related pollutants such as nitrogen dioxide, or roadway noise, all of which have been previously found to be associated with adverse cardiovascular health [19, 49, 50].

We evaluated whether the association between PM size fractions and incident hypertension varied by participant characteristics, but did not identify any characteristics that were systematically associated with a stronger association across PM size fractions. The strongest evidence of heterogeneity was observed for race/ethnicity with non-white participants exhibiting a stronger association between $PM_{2.5}$ and incident hypertension as compared to white participants. In models stratified further by race/ethnicity, the greatest risk from all PM size fractions was seen among Asian/Pacific Islanders. Prevalence of hypertension in the US has been previously shown to differ by racial background [51]. In any such analysis, it is likely that race/ethnicity is serving at least in part as a proxy for a number of dietary,

socioeconomic or geographic variables. The potential for chance findings must also be acknowledged.

We also found that WHI study region modified the associations of PM, although this varied by size fraction. For $PM_{2.5}$, those living in the Northeast were at the highest relative risk (HR 1.32, 95% CI: 1.05, 1.55) while those living in the West were at the lowest (HR 1.03, 95% CI: 0.83, 1.28). For $PM_{10\text{-}2.5}$ (HR 1.13, 95% CI: 1.03, 1.23) and PM_{10} (HR 1.18, 95% CI: 1.09, 1.28), the largest associations were observed in the Midwest. This observed heterogeneity may reflect regional differences in particulate matter sources, constituents or components, as has been previously described in the US [52].

Our study has a number of limitations. First, while our PM estimates have been previously validated [34], the estimates are for outdoor pollution concentrations and do not estimate personal exposures *per se*. However, previous studies show moderately strong correlations between outdoor particulate matter concentrations and corresponding personal exposures in older populations [53–55] providing some support for our use of outdoor home $PM_{2.5}$, PM_{10} and $PM_{10\text{-}2.5}$ as our exposure measure. Second, outcome misclassification is possible, as we relied upon self-report of new medication used to treat hypertension as one criterion in our outcome definition. It is possible that at least some individuals were unaware they were taking medications for hypertension. These sources of exposure and/or outcome misclassification may have biased our results either towards or away from the null hypothesis of no association. Third, despite controlling for a number of individual and neighborhood socioeconomic measures, the possibility of residual confounding by socioeconomic factors remains. Fourth, our study was limited to postmenopausal women in the US, limiting the generalizability of these findings to other geographic regions, younger women, or men.

On the other hand, our study had several important strengths. Our study is among the first to examine the association of long-term exposure to different fractions of particulate matter and incident hypertension, and only the second to examine the association in a large, national US cohort. We employed pollution estimates that have been shown to have high accuracy and precision in cross-validation studies [34] and we were able to control for an extensive list of potential confounders. Last, associations were robust to a number of sensitivity analyses.

CONCLUSIONS

Long term exposures to ambient fine and respirable particulate matter ($PM_{2.5}$ and PM_{10}) were associated with higher incidence rates of hypertension in a large, national cohort of post-menopausal women. Additionally, statistically significant dose-response relationships were identified for $PM_{2.5}$ and PM_{10}. Associations for $PM_{2.5}$ were more pronounced in participants who were non-white, lived in the Midwest, and were obese. If the associations we observe are causal, air pollution may be an important and modifiable risk factor for hypertension. Furthermore, the association of air pollution with hypertension might explain some of the increased cardiovascular morbidity and mortality that has been consistently associated with exposure to high concentrations of air pollution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We wish to thank the WHI investigators, staff, program office and clinical/academic centers, including but not limited to: Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller. Clinical Coordinating Center: Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg. Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner; (University of Minnesota, Minneapolis, MN) Karen L. Margolis. Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland.

We also thank the WHI participants for their contributions and commitment to the WHI program.

Funding: This report was supported by grant R01-ES020871 from the National Institute of Environmental Health Sciences (NIEHS), NIH. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. The development of the exposure models was also supported by EPA Grants RD831697 and K24ES13195. The contents of this report are solely the responsibility of the authors and do not necessarily represent the official views of the sponsoring institutions.

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Highlights

1. Long-term ambient $PM_{2.5}$ and PM_{10} exposures were associated with higher incidence rates of hypertension in post-menopausal women.
2. The association between $PM_{2.5}$ and hypertension was more pronounced among non-white participants and those living in the Northeast.
3. Coarse particulate matter was not associated with hypertension.

Table 1

Participant Characteristics

Characteristics	No History of Hypertension at Enrollment Mean ± SD or n (%)	Developed incident Hypertension during study Mean ± SD or n (%)
N	44,255	14,511
Age (years)	62.0 ± 7.0	62.9 ± 7.0
BMI (kg/M2)	27.9 ± 5.5	29.4 ± 5.8
Physical activity (MET/week)	11.3 ± 13.0	10.5 ± 12.5
Ever smoked	20,974 (47%)	6,717 (46%)
RACE/ETHNICITY		
-White (non-Hispanic)	37,518 (85%)	11,998
-Black	3,088 (7%)	1,373
-Other race	3,564 (8%)	1,140
SOCIOECONOMIC VARIABLES		
-Education		
-High school or less	9,780 (22%)	3,655 (25%)
-College or vocational school	21,980 (50%)	7,276 (50%)
-Grad school	12,199 (28%)	3,580 (25%)
-Household income		
-<$49,999	25,524 (58%)	9,632 (66%)
-$50,000–$99,999	12,484 (28%)	3,841 (26%)
->$100,000	3,732 (8%)	1,038 (7%)
-Currently employed	16,639 (38%)	4,940 (34%)
-Insurance coverage	41,018 (93%)	13,490 (93%)
-Neighborhood SES Z-Score	0.4 ± 5.3	0.0 ± 5.3
HEALTH HISTORY		
-Hyperlipidemia	3,599 (8%)	1,369 (9%)
-Cardiovascular disease	4,781 (11%)	1,676
RCT PARTICIPATION		
-DM-Treatment arm	12,689 (29%)	3,939 (27%)
-DM-Control arm	18,750 (42%)	6,221 (43%)
-HRT-Treatment arm	9,056 (21%)	3340 (23%)
-HRT-Control arm	8,862 (20%)	2,353 (16%)
-CaD-Treatment arm	12,070 (27%)	4,121 (28%)
-CaD-Control arm	12,035 (27%)	4,110 (28%)
POLLUTANTS		
-PM2.5 ($\mu g/m^3$)	13.2 ± 3.0	13.1 ± 3.0
-PM10 ($\mu g/m^3$)	22.9 ± 5.6	22.9 ± 5.6
-PM10-2.5 ($\mu g/m^3$)	9.8 ± 4.6	9.8 ± 4.6

Table 2

Long-term exposure to $PM_{2.5}$, PM_{10}-2.5 and PM_{10} and risk of incident hypertension

PM exposure	Hazard Ratio (95% Confident Interval)		
	$PM_{2.5}$[a]	$PM_{10-2.5}$[a,b]	PM_{10}[a]
per IQR increment[c]	1.13 (1.08, 1.17)	1.01 (0.97, 1.04)	1.06 (1.03, 1.10)
1st quintile	–	–	–
2nd quintile	1.06 (1.00, 1.12)	0.99 (0.94, 1.05)	1.04 (0.98, 1.09)
3rd quintile	1.13 (1.06, 1.21)	0.99 (0.93, 1.07)	1.08 (1.02, 1.15)
4th quintile	1.18 (1.09, 1.27)	1.02 (0.95, 1.09)	1.12 (1.05, 1.19)
5th quintile	1.23 (1.12, 1.34)	1.10 (1.01, 1.19)	1.19 (1.10, 1.28)
P for trend	<0.001	0.081	<0.001

[a] Model controls for age, BMI, education, ethnicity, smoking status, physical activity, sodium intake, neighborhood SES Z-score, household income, employment status, insurance status, history of high cholesterol, history of cardiovascular disease, history of diabetes, clinical trial study arm and WHI clinical site.

[b] Additionally controlling for $PM_{2.5}$

[c] IQR: $PM_{2.5}$ 3.98 $\mu g/m^3$, $PM_{10-2.5}$ 5.27 $\mu g/m^3$, PM_{10} 6.17 $\mu g/m^3$

Environ Int. Author manuscript; available in PMC 2018 August 01.

Table 3

Association between IQR increment of PM size fractions, and incident hypertension, stratified by participant characteristics[a,b]

Characteristics	$PM_{2.5}$ HR (95% CI)	Inter-a ction P value	$PM_{10\text{-}2.5}$[c] HR (95% CI)	Inter-a ction P value	PM_{10} HR (95% CI)	Inter-a ction P value
Age		0.289		0.046		0.021
Below Median (61)	1.14 (1.09, 1.20)		1.03 (0.99, 1.07)		1.09 (1.05, 1.13)	
Above Median (61)	1.12 (1.02, 1.22)		0.99 (0.91, 1.07)		1.05 (0.97, 1.13)	
BMI		0.051		0.850		0.184
<30	1.10 (1.05, 1.16)		1.01 (0.97, 1.05)		1.05 (1.02, 1.09)	
>=30	1.15 (1.05, 1.25)		1.01 (0.93, 1.09)		1.08 (1.01, 1.15)	
Diabetes		0.751		0.743		0.926
No	1.13 (1.08, 1.18)		1.01 (0.97, 1.04)		1.06 (1.03, 1.10)	
Yes	1.11 (0.96, 1.26)	<0.00	1.02 (0.90, 1.13)	0.004	1.07 (0.95, 1.18)	<0.00
Region		1				1
Midwest	1.20 (1.09, 1.32)		1.13 (1.03, 1.23)		1.18 (1.09, 1.28)	
Northeast	1.32 (1.05, 1.55)		1.06 (0.85, 1.29)		1.16 (0.97, 1.37)	
South	1.27 (1.02, 1.51)		1.00 (0.78, 1.23)		1.13 (0.94, 1.35)	
West	1.03 (0.83, 1.28)		0.96 (0.77, 1.16)		1.00 (0.83, 1.20)	
Smoker		0.186		0.785		0.346
Current or Former	1.11 (1.02, 1.21)		1.00 (0.93, 1.08)		1.05 (0.98, 1.13)	
Never	1.14 (1.09, 1.20)		1.01 (0.97, 1.05)		1.07 (1.03, 1.11)	
Physical Activity		0.631		0.223		0.463
<7.5MET hrs/week	1.14 (1.08, 1.20)		0.99 (0.94, 1.04)		1.05 (1.01, 1.10)	
>7.5MET hrs/week	1.12 (1.01, 1.24)		1.02 (0.93, 1.11)		1.07 (0.99, 1.16)	
Education		0.724		0.111		0.142
<College degree	1.12 (1.07, 1.17)		1.00 (0.96, 1.03)		1.06 (1.02, 1.09)	
>=College degree	1.13 (1.03, 1.23)		1.03 (0.95, 1.11)		1.09 (1.01, 1.16)	
Neighborhood SES Z-Score		0.968		0.512		0.727
>0	1.13 (1.03, 1.23)		1.02 (0.94, 1.09)		1.07 (1.00, 1.15)	
<=0	1.13 (1.08, 1.18)		1.00 (0.96, 1.04)		1.06 (1.03, 1.10)	
Ethnicity		0.009		0.018		0.520
White	1.12 (0.99, 1.27)		1.02 (0.91, 1.13)		1.07 (0.96, 1.18)	

Characteristics	$PM_{2.5}$ HR (95% CI)	Inter-a ction P value	$PM_{10-2.5}$[c] HR (95% CI)	Inter-a ction P value	PM_{10} HR (95% CI)	Inter-a ction P value
Non-White	1.21 (1.13, 1.29)		0.95 (0.90, 1.01)		1.05 (1.00, 1.11)	
-Black	1.20 (1.05, 1.34)		0.98 (0.86, 1.11)		1.08 (0.97, 1.19)	
-Asian/Pacific Islander	1.26 (1.00, 1.48)		1.04 (0.83, 1.24)		1.13 (0.95, 1.30)	
-Hispanic/Latino	1.14 (0.99, 1.29)		1.01 (0.89, 1.13)		1.07 (0.95, .19)	

[a]Model controls for age, BMI, education, ethnicity, smoking status, physical activity, sodium intake, neighborhood SES Z-score, household income, employment status, insurance status, history of high cholesterol, history of cardiovascular disease, history of diabetes, clinical trial study arm and WHI clinical site.

[b]IQR: $PM_{2.5}$ 3.98 μg/m^3, $PM_{10-2.5}$ 5.27 μg/m^3, PM_{10} 6.17 μg/m^3

[c]Additionally controlling for $PM_{2.5}$