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The Benefits of Intensive Versus Standard Blood Pressure Treatment According to Fine Particulate Matter Air Pollution Exposure: A Post Hoc Analysis of SPRINT

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Abstract

Fine particulate matter <2.5 μm ($PM_{2.5}$) air pollution is implicated in global mortality, especially from cardiovascular causes. A large body of evidence suggests a link between $PM_{2.5}$ and elevation in blood pressure (BP), with the latter implicated as a potential mediator of cardiovascular events. We sought to determine if the outcomes of intensive BP lowering (systolic BP < 120 mm Hg) on cardiovascular events are modified by $PM_{2.5}$ exposure in in the Systolic Blood Pressure Intervention Trial (SPRINT). We linked annual $PM_{2.5}$ exposure estimates derived from

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an integrated model to subjects participating in SPRINT. We evaluated the effect of intensive BP-lowering by $PM_{2.5}$ exposure on the primary outcome in SPRINT using cox-proportional hazard models. A total of 9286 participants were linked to $PM_{2.5}$ levels (mean age 68±9 years). Intensive BP-lowering decreased risk of the primary outcome more among patients exposed to higher $PM_{2.5}$ ($P_{interaction}$=0.047). The estimate for lowering of primary outcome was numerically lower in highest than in the lower quintiles. The benefits of intensive BP-lowering were larger among patients chronically exposed to $PM_{2.5}$ levels above U.S. National Ambient Air Quality Standards of 12 μg/m^3 (HR 0.47, 95% CI: 0.29–0.74) compared to those living in cleaner locations (HR 0.81, 95% CI: 0.68–0.97), $P_{interaction}$=0.037. This exploratory non-prespecified post-hoc analysis of SPRINT suggests that the benefits of intensive BP lowering on the primary outcome was greater in patients exposed to higher $PM_{2.5}$, suggesting that the magnitude of benefit may depend upon the magnitude of antecedent $PM_{2.5}$ exposure.

Summary:

Air pollution has been implicated in cardiovascular risk, partly through effects on blood pressure. We sought to determine if intensive blood pressure lowering (systolic blood pressure < 120 mm Hg) on cardiovascular events is modified by air pollution exposure in the SPRINT trial. SPRINT participants (n=9,286) were linked with annual $PM_{2.5}$ exposure. We showed that intensive BP-lowering decreased risk of the composite cardiovascular outcome in higher $PM_{2.5}$ more than cleaner areas ($P_{interaction}$=0.047). Thus, this analysis of SPRINT suggests that the magnitude of cardiovascular benefit of intensive blood pressure lowering may depend upon the magnitude of antecedent $PM_{2.5}$ exposure

Keywords

Air pollution; particulate matter; hypertension; cardiovascular disease

Introduction

A considerable body of evidence implicates particulate matter <2.5 microns ($PM_{2.5}$) as the principal air pollutant posing the greatest threat to global health.[1–6] An estimated 8.9 million avoidable deaths in 2015 were attributable to ambient air pollution alone[7], 120% larger than the estimates in the Global Burden of Disease (GBD) study which attributed 4.2 million deaths to ambient air pollution.[8] Prior studies have shown that exposure to $PM_{2.5}$ is associated with acute and chronic elevations in blood pressure (BP)[9] as well as incident hypertension[10]. It has indeed been hypothesized that a portion of the cardiovascular morbidity and mortality from air pollution may in part be mediated by elevations in BP, and that this may help explain the large global footprint of mortality and disability attributable to air pollution.[11, 12] Compelling data in the United States and Canada continue to demonstrate that even low levels of $PM_{2.5}$ pose health risks, with recent studies showing a continuous relationship between mortality and $PM_{2.5}$ at levels below current annual National Ambient Air Quality Standards (NAAQS) of <12 ug/m.[3,13–15] Empirical evidence from time series analyses also continue to suggest a relationship between blood pressure and extreme levels of air pollution, such as that encountered in China, implying a relationship across a broad range of exposures.[16, 17]

If high BP is truly a mediator of the health effects from $PM_{2.5}$ exposures (i.e., part of the causal-pathway), strategies that lower $PM_{2.5}$ should lower BP, as has indeed been shown in a growing number of short-term intervention studies.[18–2021] Conversely given that $PM_{2.5}$ adversely affects individuals with prior cardiovascular disease and/or those with multiple risk factors, it is also possible that individuals with high levels of blood pressure may be disproportionately affected and that the benefits of BP-lowering may be differentially influenced by the magnitude of concomitant exposure to ambient $PM_{2.5}$. In this exploratory, non-prespecified post-hoc study, we sought to test the hypothesis that the effect of BP-lowering strategies on cardiovascular outcomes is influenced by on $PM_{2.5}$ exposure levels, using a contemporary trial of intensive BP lowering, the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods

All data and materials have been made publicly available at the National Heart, Lung and Blood Institute online data repository and can be accessed at https://biolincc.nhlbi.nih.gov.

Study Design and Analytical Plan:

The trial design, inclusion and exclusion criteria, assessments and outcomes for SPRINT are published elsewhere[22, 23]. Briefly, SPRINT included patients with hypertension, age 50 years or older, systolic BP (SBP) 130–180 mm Hg with one or more of the following CVD risk factors: history of clinical or subclinical CVD other than stroke, estimated glomerular filtration rate (eGFR) of 20–59 mL/min/1.73 m^2 using the four-variable MDRD equation, 10-year risk for CVD ≥15% calculated using the Framingham Risk Score, or age ≥75 years. Main exclusion criteria included diabetes, a history of stroke, heart failure, proteinuria ≥1 g/day, or eGFR <20 mL/min/1.73 m^2. Eligible participants were randomly assigned to either an SBP target of <120 mm Hg or one of <140 mm Hg. All major classes of antihypertensive medications were included in the SPRINT formulary. Participants were seen monthly for the first 3 months and then every 3 months thereafter. Intensive participants were also seen monthly to titrate medications until SBP goal was reached or the investigator decided to not titrate further.

In this exploratory, non-prespecified, post-hoc analysis of SPRINT we proposed investigating the association between $PM_{2.5}$ and cardiovascular events and study the heterogeneity of treatment benefit by $PM_{2.5}$ exposure. The original proposal and analysis plan were approved by the SPRINT steering committee (Data Supplement) and incorporated primary outcomes per $PM_{2.5}$ increments (in quartiles) and by study randomization. We performed several subsequent exploratory analysis, where we examined the occurrence of the outcomes in SPRINT in relation to $PM_{2.5}$ both as a continuous variable, in quintiles (vs proposed quartiles, due to narrow range of $PM_{2.5}$ in the linked dataset) and in relationship to a binary threshold value of the annual United States National Ambient Air Quality Standards (NAAQS) threshold. We were particularly interested in the differential effects of the treatment arms in SPRINT according to the magnitude of concomitant exposure to ambient $PM_{2.5}$ given the known relationship between $PM_{2.5}$ and blood pressure. Additional details are provided in the Statistical Analytical Plan (see below).

Exposure characterization:

We linked annual $PM_{2.5}$ exposure derived from an integrated model (satellite aerosol optical depth with chemical transport) to participants in SPRINT using ZIP code of residence, preserving confidentiality. The U.S. National Ambient Air Quality Standards (NAAQS) has set average annual $PM_{2.5}$ at 12 ug/m^3. We studied the impact of intensive BP lowering by quintiles of $PM_{2.5}$ exposure during the calendar year of trial enrollment, with respect to the primary outcome (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or cardiovascular death). The primary exposure of interest was ZIP-level average annual $PM_{2.5}$. Each patient was assigned the average annual $PM_{2.5}$ using ZIP code of residence of the calendar year at trial entry. Modelled $PM_{2.5}$ level measures are highly correlated over time (trial year 1 vs year 2, Spearman's rho=0.90; year 2 vs year 3: Spearman's rho=0.96), and therefore the entry $PM_{2.5}$ is a rough approximation of the level of exposure that an individual experienced over the study period.

$PM_{2.5}$ estimates were obtained from a validated integrated exposure model that estimated $PM_{2.5}$ by combining aerosol optical depth retrievals from multiple sources (NASA MODIS, MISR, and SeaWIFS instruments) with chemical transport model estimates (GEOS-Chem), and subsequently calibrated against global ground-based observations of $PM_{2.5}$, using geographically-weighted regression[24]. The data thus obtained corresponded to grids of 0.01×0.01 degrees (~1×1 km). The data were imported in QGIS and mapped to the 2013 ZIP shapefiles available from (www.census.gov) and mean (area-average) ZIP-level $PM_{2.5}$ was calculated using zonal statistics.

Study Measurements:

Participant demographics were collected at baseline. Clinical and laboratory data were collected at baseline, and every 3 months thereafter. BPs in SPRINT were measured at each visit by trained staff with an automated device (Omron-HEM-907 XL) using standardized procedures[23]. Seated BP measurements (X3) were conducted early in the visit after 5 min rest and proper positioning of the participant in a chair with back support and proper cuff size determination, but before stressful exam components such as blood draws and questionnaires. Self-reported CVD outcomes were collected every 3 months using structured interviews in both treatment arms of the study.

Study Outcomes:

The primary outcome in SPRINT was a composite CVD outcome of myocardial infarction (MI), acute coronary syndrome (other than MI), stroke, acute decompensated heart failure, or death from CVD causes. Secondary outcomes included the individual components of the primary outcome, death from any cause, and the composite of the primary outcome or death from any cause. An adjudication committee blinded to treatment assignment adjudicated all outcomes using a prespecified protocol.

Statistical Analysis:

We used Cox proportional hazards regression models stratified according to clinic, to estimate the Hazard Ratios and 95% confidence intervals for first occurrence of the primary outcome and its subcomponents for intensive vs standard treatment arms (referent) by $PM_{2.5}$

exposure quintile. There were no violations for the proportional hazards assumptions. To assess for effect modification of treatment arm among SPRINT participants by $PM_{2.5}$, we included the product term (SBP treatment arm × $PM_{2.5}$ quintile (as an ordinal variable or as a continuous variable)) in the Cox proportional hazards regression in the full sample. This was repeated for secondary outcomes separately without correction for multiple testing. Measures of interaction and p-values for the primary outcome are presented along with hazard ratios for subgroups by quintile of $PM_{2.5}$ exposure. We additionally assessed interaction between $PM_{2.5}$ (< vs ≥ 12 ug/m3, categorical variable) and treatment effect, using the NAAQS threshold. We also constructed a Cox proportional hazard model including an interaction term between study treatment arm and $PM_{2.5}$ quintile (treated as nominal variable) for the incidence of the primary outcome. All analyses were performed using Statistical Package for Social Sciences (version 20) and R project 3.4.2

Results

Population characteristics

Among 9,361 trial participants, 9,286 were linked to $PM_{2.5}$ levels. Mean average annual exposure among SPRINT participants was 9.5 ± 2.7 $\mu g/m^3$, with 1328 (14.3%) facing levels at or above annual NAAQS of 12 $\mu g/m^3$. Supplemental figure S1 shows the histogram of $PM_{2.5}$ exposure among the study participants. The characteristics of patients by $PM_{2.5}$ exposures are shown in Table 1. Participants exposed to higher $PM_{2.5}$ were more likely to be African American, free of pre-existing cardiovascular disease, and not on statin therapy. There were no clinically-important differences in baseline SBP, DBP, or number of antihypertensive agents. When patients were stratified by quintile of $PM_{2.5}$ and trial assignment, all characteristics (with 3 minor exceptions) were balanced between the arms within each quintile (Supplemental Table S1).

Effects of Intensive BP-lowering by $PM_{2.5}$ Levels on Cardiovascular Events

We followed participants for a median of 3.3 years (range 2.9 – 3.9) with 559 total primary outcome events over the study period. The number of events for each of the outcomes by quintile of $PM_{2.5}$ and study assignment are shown in Supplemental Table S2. When $PM_{2.5}$ was treated as a continuous variable, the higher the $PM_{2.5}$ the greater the reduction in the primary outcome by more intense BP reduction ($P_{interaction}$=0.047), Figure 1A. Given the lower limit of detection of the $PM_{2.5}$ model of 3 $\mu g/m^3$ (likely reflecting participants in Puerto Rico), we performed additional analyses excluding patients living in areas with $PM_{2.5} \leq 3$ $\mu g/m^3$ (Figure 1B) using $PM_{2.5}$ as a continuous variable. In this subset, the treatment effect was stronger in participants exposed to higher $PM_{2.5}$ with respect to primary outcome ($PM_{2.5}$ × assignment $P_{interaction}$ = 0.011).

The effect of intensive BP control on the primary outcome although smaller, persisted among patients residing in areas with low $PM_{2.5}$ classified by using a binary threshold of 12 $\mu g/m^3$ which corresponds to the US NAAQS annual standard (<12 $\mu g/m^3$: HR 0.81, 95% CI: 0.68–0.97) relative to patients exposed to higher levels (≥12 $\mu g/m^3$: HR 0.46, 95% CI: 0.29–0.74), ($P_{interaction}$=0.037), Figure 2.

When stratified by $PM_{2.5}$ quintiles, (Q1: HR 1.00 [0.72–1.41]; Q2: 0.77 [0.51–1.18]; Q3: HR 0.92 [0.62–1.37]; Q4: HR 0.63 [0.44–0.91] and Q5: HR 0.53 [0.36–0.79]) (Figure 3), the interaction with intervention was not significant, ($P_{interaction}$=0.099). When categorized into upper two quintiles (Q4-Q5 grouped) vs lower 3 quintiles (Q1-Q3 grouped), there was an interaction between $PM_{2.5}$ group and study treatment: $P_{interaction}$=0.013 for Q4-Q5 vs Q1-Q3). Analyses of $PM_{2.5}$ quintiles and P values for interaction term ($PM_{2.5}$ × study assignment) as nominal variable and in different models separately are shown in table 2.

Adjusting for race (Black vs non-Black) did not alter the interaction term between $PM_{2.5}$ and study assignment with respect to primary outcome ($PM_{2.5}$ × study assignment, $P_{interaction}$=0.047). The interaction between study assignment and $PM_{2.5}$ with respect to primary outcome remained statistically significant, when only including Black participants ($PM_{2.5}$ × study assignment, $P_{interaction}$=0.035).

Secondary outcomes: When $PM_{2.5}$ was modelled as a continuous variable, there was a significant interaction between study arm and $PM_{2.5}$ with respect to stroke ($P_{interaction}$=0.026), but not other secondary outcomes (Supplemental table S3). In the subset excluding $PM_{2.5} \leq 3$ μg/m^3, the treatment effect was stronger in participants exposed to higher $PM_{2.5}$ with respect to non-MI ACS ($PM_{2.5}$ × assignment $P_{interaction}$ = 0.027), and stroke ($PM_{2.5}$ × assignment $P_{interaction}$ = 0.007), but not other secondary outcomes. When $PM_{2.5}$ was modelled as categorical (above or below NAAQS threshold of 12 μg/m^3), there was a similar finding with stroke ($PM_{2.5}$ <12 μg/m^3: HR 0.68 [0.49–0.96] vs $PM_{2.5}$ ≥12 μg/m^3: HR 0.27 [0.10–0.72], $P_{interaction}$=0.046).

When $PM_{2.5}$ quintiles were treated as ordinal variable, the numerical relationship between higher levels of $PM_{2.5}$ exposure were also observed individually with stroke [Q1: HR 1.47 (0.74–2.92); Q2: HR 1.03 (0.47–2.27); Q3: HR 1.12 (0.51–2.48); Q4: HR 0.54 (0.25–1.19); and Q5; HR 0.34 (0.12–0.94), $P_{interaction}$=0.01; and non-MI ACS [Q1: HR 1.50 (0.61–3.67); Q2: HR 1.43 (0.40–5.09); Q3: HR 1.73 (0.68–4.40); Q4: HR 0.69 (0.25–1.96) and Q5: HR 0.36 (0.11–1.14), $P_{interaction}$=0.025; $PM_{2.5}$ quintiles treated as ordinal variable], but not with heart failure, CV death, or myocardial infarction. Hazard ratios of intensive vs standard BP in each quintile are shown in Figure 3.

Discussion

The results from this post-hoc analysis of SPRINT suggests that intensive BP-lowering decreased the primary outcome in patients with the highest $PM_{2.5}$ exposure. Notably the benefits of intensive BP-lowering were larger among patients exposed to $PM_{2.5}$ levels above the NAAQS annual standard of 12 μg/m^3, compared to those living in cleaner locations, although benefits of intensive BP lowering persisted in patients exposed to levels below NAAQS limits.

The experimental design of SPRINT provided a unique opportunity to study the relationship between annual $PM_{2.5}$ levels and CVD outcomes. Participants in SPRINT were randomized and treated to two different BP levels, resulting in a 13 mm Hg average SBP separation during the average 3.26 years of follow-up, allowing a platform to examine the effect of

antecedent chronic $PM_{2.5}$ exposure at two separate BP levels, and its effect on the benefits of intensive BP-lowering. These exploratory analyses suggest linear trend in the benefit of intensive BP-lowering influenced by ambient $PM_{2.5}$, such that SPRINT participants exposed to higher levels of $PM_{2.5}$ had larger benefits with intensive lowering of BP. Those living in areas with air pollution levels below the NAAQS annual limit of 12 $\mu g/m^3$ showed lower albeit significant, persistent reduction in the primary endpoint with intensive BP-lowering compared with those living above the NAAQS limit.

The association between increase in air pollutants (in particular $PM_{2.5}$) and rise in blood pressure is well known, and has been documented extensively including in 4 recent meta-analyses.[9, 10, 25, 26] Short term increases in ambient $PM_{2.5}$ by 10 $\mu g/m^3$ are consistently reported to be associated with 1 to 3 mm Hg elevations in both systolic and diastolic BP over the ensuing few days[9]. Longer-term exposures have been associated with chronic elevations in BP and with an increased prevalence or incidence of hypertension, although results are less consistent.[27–29] A growing number of short-term intervention studies have also provided corroborative evidence, supporting a causal-relationship, by showing that reductions in $PM_{2.5}$ levels result in a lowering of BP.[30, 31] As such, elevations in BP may mediate some of the adverse cardiovascular health effects of $PM_{2.5}$.[31–33] A large body of evidence also implicates exposure to $PM_{2.5}$ in cardiovascular events such as cardiovascular mortality, acute myocardial infarction, stroke and heart failure. Time-series and case-crossover studies across the globe have explored the association between short-term changes in air pollution and daily changes in stroke, MI and heart failure. Indeed, increases in $PM_{2.5}$ have been associated with all 3 outcomes.[31] In a systematic review and meta-analysis of 94 studies until 2014, involving 28 countries, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10} concentration was associated with 1% increase in relative risks for admission to the hospital with stroke and stroke mortality[34]. In an analysis of the ESCAPE cohort from Europe, there was an association between annual $PM_{2.5}$ and stroke among subjects ≥ 60 years of age (hazard ratio [HR]: 1.40; 95% CI: 1.05 to 1.87 per 5 $\mu g/m^3$ increase in $PM_{2.5}$.

The results of the current analysis, if confirmed in other trials, may have important implications for preventive therapies for individuals living in locations with high levels of $PM_{2.5}$. Our findings suggest that intensive blood pressure lowering may be particularly important in populations facing $PM_{2.5}$ levels higher than the current NAAQS standard of 12 $\mu g/m^3$ and that these patients could benefit even more from intensive BP-lowering. The role for preventive therapies in areas associated with high levels of air pollution levels has been an important question for which there is not much evidence in terms of randomized controlled clinical trials and/or clinical outcomes. Position statements by the American Heart Association (AHA) and the European Society of Cardiology have generally advocated primary and secondary preventive measures, but have been constrained by a general paucity of evidence for reduction in hard events with control of risk factors.[35, 36] There is some evidence that therapeutic interventions such as statins and dietary components such as ω3 fatty acids may reduce the impact of air pollution on surrogate measures[37]. In a recent study of more than half a million persons in the National Institutes of Health–American Association for Retired Persons Diet and Health Study, followed for 17 years, the association between fine particulate matter and nitric oxide exposure with cardiovascular events was modified by Mediterranean diet intake, as measured by Mediterranean diet

index.[38] The association between air pollutants ($PM_{2.5}$ and NO_2) and cardiovascular events was no longer present in patients who had highest consumption of Mediterranean diet.

This study has several limitations that must be acknowledged. As a non-prespecified post-hoc analysis of a randomized trial, our findings should merit abundant caution and require confirmation in future studies. The relatively narrow $PM_{2.5}$ range and the low statistical power, especially for secondary outcomes may require caution in the interpretation of the results of $PM_{2.5}$ on secondary outcomes such as stroke and ACS. Exposure misclassification is always a concern, given the fact that this was modelled based on residential zip code, which may not reflect the location where the trial participants may have spent the majority of time. Another limitation is the fact that $PM_{2.5}$ exposure could be a marker of socioeconomic status or other poorly defined social determinant(s) that co-segregate with exposure. The correlations between $PM_{2.5}$ and socioeconomic factors and $PM_{2.5}$ exposure is high, limiting our ability to make firm conclusions with more research needed to define this relationship. Residual confounding from spatially covarying risk factors is always a possibility and it is possible that poorly characterized social determinants could co-segregate with exposures, and contribute to the current observations. However, in multiple previous studies, adjustment of factors such as education, socioeconomic status and other demographic variables failed to eliminate the relationship between $PM_{2.5}$ and health risks.[39, 40] Air pollutants rarely occur in isolation to each other or in the absence of other environmental exposures (e.g., noise, temperature). As a prominent example, near-roadway environments lead to exposures to noise, particulate and gaseous traffic-related air pollution, as well as psychological stressors.[11] The independent and potentially additive (or synergistic) cardiovascular risks posed by these multiple exposures, impacting most of the world's population on a daily basis has yet to be fully understood. Regardless, $PM_{2.5}$ is acknowledged as the single largest triggering event for myocardial infarction worldwide and the leading environmental cause for preventable morbidity and mortality.[41] As such, there is a critical need for treatments that lower the risk posed by air pollution. The importance as well as the putative design and plausibility of clinical trials to mitigate exposures have been previously reviewed.[42, 43] Positive results and confirmation of these findings from SPRINT would provide much-needed scientific evidence to protect public health and provide yet another line of evidence supporting a "causal role" for $PM_{2.5}$ in CVD.

Conclusions

This exploratory non-prespecified post-hoc analysis of SPRINT suggests that the cardiovascular benefit of intensive BP-lowering could be dependent upon the level of $PM_{2.5}$ exposure. Benefits of BP lowering, however, persisted in patients exposed to $PM_{2.5}$ lower than NAAQS threshold. Further research is needed to identify strategies to mitigate risk of $PM_{2.5}$ exposure in high-risk individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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https://www.sprinttrial.org/public/dspScience.cfm

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Perspectives

Intensive blood pressure lowering is effective in reducing cardiovascular risk in patients exposed to high levels of air pollution. Intensive blood pressure lowering (goal SBP <120 mmHg) can be beneficial in selected patients with who live in neighborhoods with elevated air pollution exposure. Although this is a post-hoc analysis of a large randomized controlled trial, results show a linear trend in the benefit of intensive BP lowering with air pollution exposure. The mechanisms of the interaction between air pollution and benefit of intensive BP lowering need to be further investigated.

Novelty and Significance

What is new? This study suggests that the cardiovascular benefit of intensive BP-lowering could be dependent upon the level of $PM_{2.5}$ exposure.

What is relevant? Patients with hypertension exposed to high $PM_{2.5}$ may derive strong cardiovascular benefit from intensive lowering of blood pressure to goal systolic blood pressure of less than 120 mmHg.

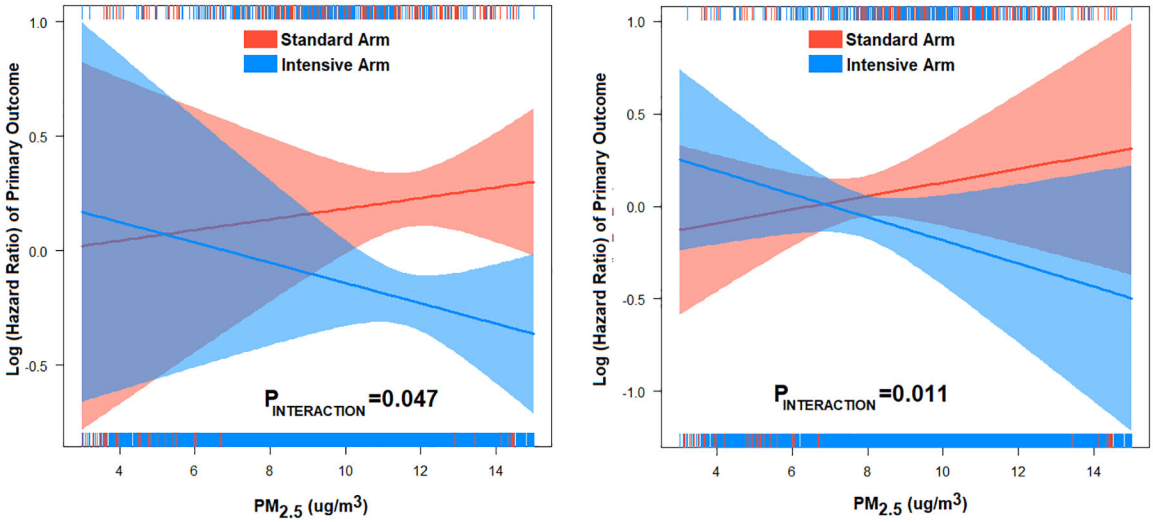

Figure 1:

Association between $PM_{2.5}$ (continuous variable) and hazard ratio (Log) of primary outcome in in the intensive vs standard BP in the (A) entire cohort (n=9,286) and (B) excluding $PM_{2.5} \leq 3$ μg/m^3 (n=8,718). $P_{INTERACTION}$ is between $PM_{2.5}$ and study assignment. The association between $PM_{2.5}$ and primary outcome was not statistically significant in the standard arm or the intensive arm.

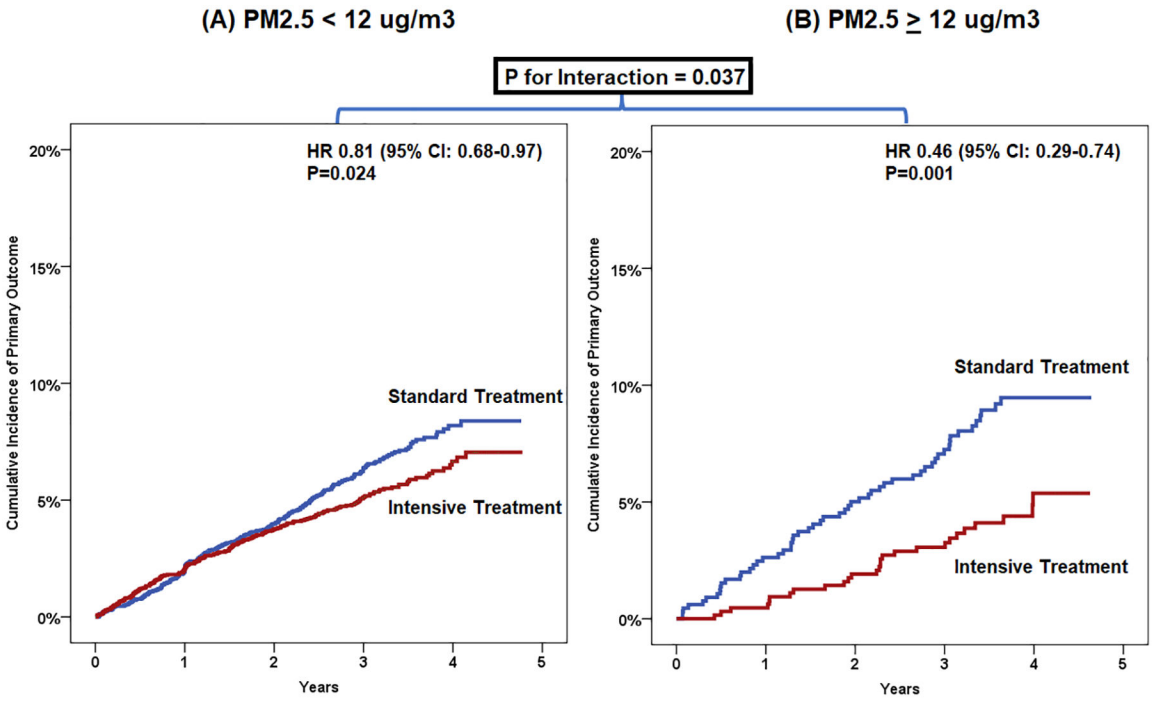

Figure 2:

Primary outcome with intensive treatment vs standard treatment stratified by $PM_{2.5}$ exposure category (above or below the NAAQS cut-off of $PM_{2.5}$ of 12 ug/m^3, nominal variable)

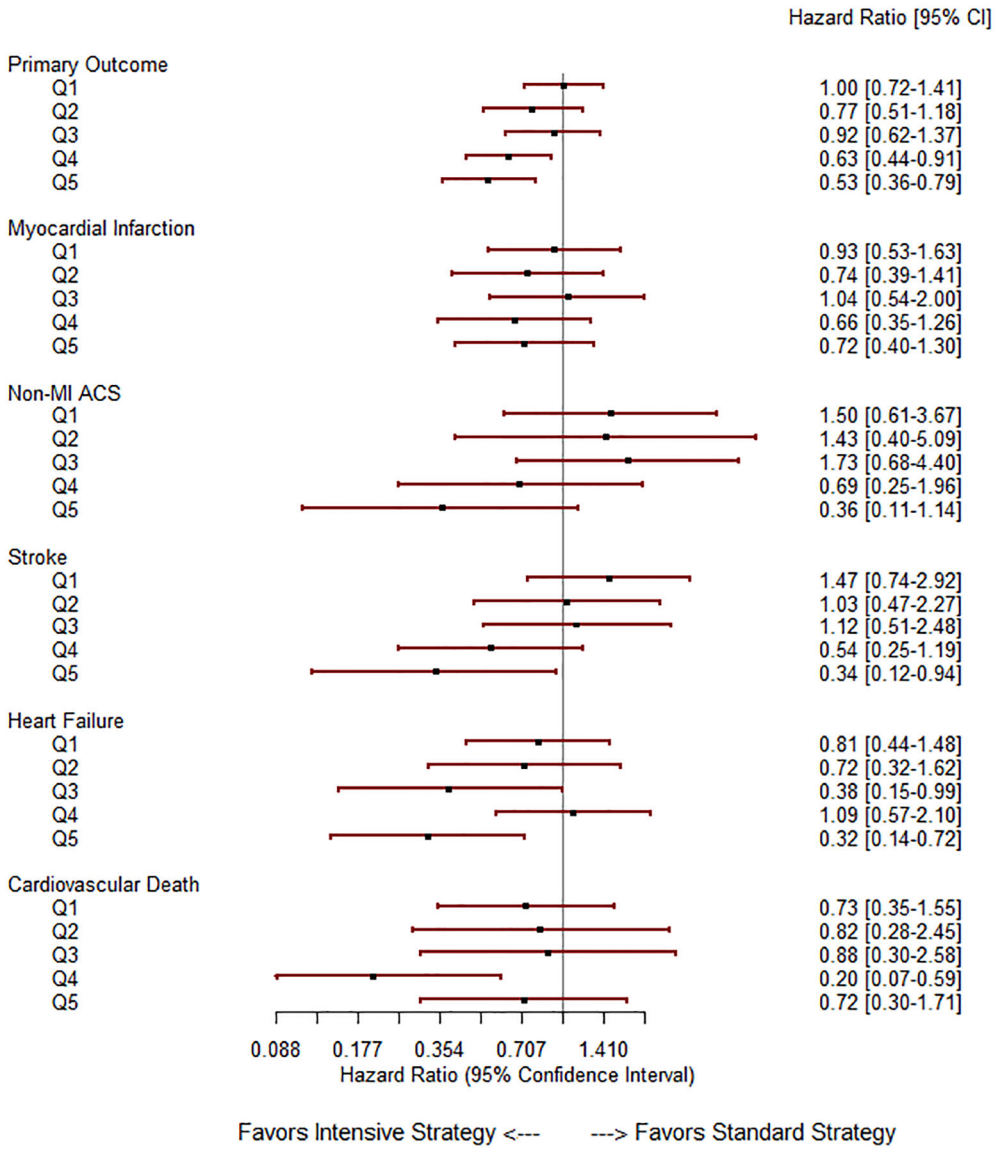

Figure 3:

Forest plot depicting the effect of intensive BP lowering by $PM_{2.5}$ exposure quintile. Statistical tests for varying effect of treatment by $PM_{2.5}$ level were performed using Cox PH models and corresponding p-values (for interaction term, $PM_{2.5}$ (ordinal variable) × study assignment) are displayed in the right-hand column. The solid lines represent no difference in the effect and values to the left of the HR 1.0-line favor intensive BP lowering

Table 1:

Characteristics of study participants by $PM_{2.5}$ quintile

Characteristic	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Number of patients	1858	1857	1857	1857	1857
PM2.5 (μg/m^3)	5.3 ± 1.9	8.7 ± 0.4	9.7 ± 0.3	10.8 ± 0.3	12.8 ± 1.1
Age, years	68.1 ± 9.6	68.2 ± 9.3	67 ± 9.6	68 ± 9.3	68 ± 9.1
Female, n (%)	601 (32%)	637 (34%)	630 (34%)	719 (39%)	717 (39%)
Black Race, n (%)	348 (19%)	434 (23%)	657 (35%)	686 (37%)	797 (43%)
Current Smoker, n (%)	219 (12%)	225 (12%)	257 (14%)	244 (13%)	285 (15%)
History of clinical CVD, n (%)	389 (21%)	302 (16%)	283 (15%)	300 (16%)	277 (15%)
History of subclinical CVD, n (%)	118 (6.4%)	72 (3.9%)	92 (5.0%)	89 (4.8%)	113 (6.1%)
Statin, n (%)	884 (48%)	827 (45%)	793 (43%)	762 (41%)	767 (42%)
Aspirin, n (%)	933 (50%)	980 (53%)	935 (51%)	940 (51%)	945 (51%)
Assigned to Intensive lowering strategy	931 (50%)	946 (51%)	915 (49%)	916 (49%)	927 (50%)
Chronic Kidney Disease, n (%)	504 (27%)	613 (33%)	474 (26%)	543 (29%)	497 (27%)
eGFR, ml/min/1.73 m2	73 ± 21	69 ± 20	73 ± 21	71 ± 20	72 ± 20
Framingham 10-year risk	20.4 ± 11.2	20.8 ± 11.0	20.4 ± 11.2	19.6 ± 10.4	19.2 ± 10.2
Body Mass Index	29.4 ± 5.4	29.7 ± 5.7	30.1 ± 5.9	29.9 ± 5.8	30.2 ± 6.0
Baseline Blood Pressure (mm Hg)					
Systolic	139 ± 15	141 ± 16	140 ± 15	139 ± 16	139 ± 16
Diastolic	77 ± 12	79 ± 12	79 ± 12	78 ± 12	79 ± 12
Number of antihypertensives	1.8 ± 1.0	1.8 ± 1.1	1.9 ± 1.1	1.9 ± 1.0	1.9 ± 1.0
Not on antihypertensives	150 (8.1%)	198 (11%)	196 (11%)	171 (9%)	158 (9%)
Fasting Laboratory (mg/dL)					
Total cholesterol	187 ± 41	190 ± 42	192 ± 41	191 ± 41	190 ± 41
HDL cholesterol	52 ± 14	53 ± 15	53 ± 15	54 ± 14	54 ± 15
Triglycerides	132 ± 93	128 ± 88	126 ± 80	123 ± 87	120 ± 103
Glucose	98 ± 12	100 ± 14	99 ± 13	98 ± 14	99 ± 14

Table 2:

Analyses of the interaction between $PM_{2.5}$ (treated as continuous, ordinal, and nominal), and study treatment for the incidence of the primary outcome

Treatment of $PM_{2.5}$ Variable	**P Value for interaction between $PM_{2.5}$ and Study Assignment**
$PM_{2.5}$ treated as continuous	0.047
$PM_{2.5}$ Quintiles treated as continuous	0.01
$PM_{2.5}$ Quintiles treated as nominal (all in one model)	
Overall	0.099
Q2 vs Q1	0.27
Q3 vs Q1	0.76
Q4 vs Q1	0.066
Q5 vs Q1	0.016
$PM_{2.5}$ Quintiles treated as nominal (separate analyses)	
Q2 vs Q1	0.33
Q3 vs Q1	0.81
Q4 vs Q1	0.068
Q5 vs Q1	0.017
Q4–5 vs Q1–3	0.013