

Short-Term Blood Pressure Responses to Ambient Fine Particulate Matter Exposures at the Extremes of Global Air Pollution Concentrations

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BACKGROUND

Fine particulate matter (PM_{2.5}) air pollution is a leading cause of global cardiovascular mortality. A key mechanism may be PM_{2.5}-induced blood pressure (BP) elevations. Whether consistent prohypertensive responses persist across the breadth of worldwide pollution concentrations has never been investigated.

METHODS

We evaluated the hemodynamic impact of short-term exposures to ambient PM_{2.5} in harmonized studies of healthy normotensive adults (4 BP measurements per participant) living in both a highly polluted (Beijing) and clean (Michigan) location.

RESULTS

Prior 7-day outdoor-ambient and 24-hour personal-level PM_{2.5} concentration averages were much higher in Beijing (86.7 ± 52.1 and 52.4 ± 79.2 μg/m³) compared to Michigan (9.1 ± 1.8 and 12.2 ± 17.0 μg/m³). In Beijing (n = 73), increased outdoor-ambient exposures (per 10 μg/m³) during the prior 1–7 days were associated with significant elevations in diastolic BP (0.15–0.17 mm Hg). In

overweight adults (body mass index ≥25 kg/m²), significant increases in both systolic (0.34–0.44 mm Hg) and diastolic (0.22–0.66 mm Hg) BP levels were observed. Prior 24-hour personal-level exposures also significantly increased BP (0.41/0.61 mm Hg) in overweight participants. Conversely, low PM_{2.5} concentrations in Michigan (n = 50), on average within Air Quality Guidelines, were not associated with BP elevations.

CONCLUSIONS

Our findings demonstrate that short-term exposures to ambient PM_{2.5} in a highly polluted environment can promote elevations in BP even among healthy adults. The fact that no adverse hemodynamic responses were observed in a clean location supports the key public health importance of international efforts to improve air quality as part of the global battle against hypertension.

Keywords: autonomic nervous system; blood pressure; environment; endothelial dysfunction; heart rate; hypertension.

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Fine particulate matter <2.5 μm (PM_{2.5}) air pollution is a leading cause of global morbidity and mortality.^{1–4} Over 90% of the population is exposed to levels above annual standards (<10 μg/m³) set by World Health Organization (WHO) Air Quality Guidelines (AQG).^{2,3} This translates into roughly 4.2 million deaths per year worldwide.³ However, large regional differences in ambient PM_{2.5} concentrations exist.^{2–6} In North America, less than 20% of individuals face

levels above AQG compared to more than 99% of those living in East and South Asia.⁵ Daily PM_{2.5} averages can exceed astounding levels (i.e., 500 μg/m³) in megacities such as Beijing,^{2,3,5,6} which are 10- to 50-fold those encountered in urban locations across the United States and Canada.^{3–5,7,8,9} Due to the enormous population facing extremely poor air quality, the largest public health burden (>50%) due to PM_{2.5} disproportionately impacts Asia.^{2,3} Nevertheless, recent

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studies compellingly demonstrate that even low levels of PM_{2.5} within AQG still pose significant risks for morbidity and mortality.^{4,7}

The greatest portion of adverse health effects from PM_{2.5} is from cardiovascular diseases.¹⁻³ Both short and long-term exposures are associated with increased risks for myocardial infarctions, strokes, and heart failure.^{1,10} Mounting studies by us and others have provided evidence that a key mechanistic explanation may be PM_{2.5}-mediated elevations in arterial blood pressure (BP).^{1,8,9,10-13} A number of air pollutants are capable of increasing BP over a few hours-to-days of exposure.^{8,9,11-18} Living in a more air polluted environment can even promote the onset of chronic hypertension.^{13,15,17} Several potentially responsible biological pathways have been elucidated including autonomic imbalance favoring sympathetic nervous system activation and vascular dysfunction.^{1,11,18-23}

Nevertheless, several important questions regarding the prohypertensive actions of PM_{2.5} remain. Meta-analyses^{12,13} of heterogeneous studies each individually conducted in a single region have provided suggestive evidence that BP elevations might be prompted both by high^{16,17} and relatively low ambient levels.^{8,9,14,15} However, the nature and consistency of the hemodynamic actions of PM_{2.5} across the wide spectrum of global ambient concentrations has never been explicitly investigated in a single multicountry trial. In addition, most prior studies enrolled mixed or “susceptible” populations including elderly adults and patients with cardiovascular or metabolic disease.¹¹⁻¹³ The hemodynamic impact of PM_{2.5} specifically in a healthy young normotensive population therefore remains less well-described. In this context, we designed a 2-country harmonized trial to characterize the BP responses in healthy adults without hypertension of short-term exposures to very high (Beijing) as well as low (Michigan) ambient PM_{2.5} levels from a global air quality perspective. A secondary aim was to explore potential biological mechanisms, including vascular endothelial function and autonomic balance.

METHODS

This protocol was designed to evaluate the effect of ambient and personal-level PM_{2.5} exposures on BP changes among individuals living in both study locations (southeast Michigan and Beijing, China). Other outcomes were secondary endpoints. The study was approved by the Institutional Review Boards of the University of Michigan and Peking University and all participants signed a written informed consent during a screening visit. Participant inclusion criteria at both locations were healthy nonsmoking adults living in nonsmoking households (by self-report) aged 18–50 years without a history of cardiovascular disease or risk factors (screening visit BP <140/90 mm Hg and fasting glucose <126 mg/dl). Body mass index was calculated from height and weight measured at the most recent visit. Subjects were also excluded if they reported taking any medication (e.g., cholesterol or BP-lowering medication, fish oil, antioxidant) on a routine basis expected to alter study outcomes.

Qualifying participants ($n = 50$, Michigan; $n = 73$, Beijing) were enrolled into a repeated measures panel study conducted concomitantly from November 2014 until January 2016 in Beijing and from August 2014 until February 2016 in Michigan (online [Supplementary Figures S1 and S2](#)). There were up to 4 visits per participant in each study; however, the protocol was completed within 1 month in Michigan, whereas the study visits were conducted across 15 months on average for each participant in Beijing. For each study visit, participants came fasting ≥ 8 hours between 8 AM and 10 AM to a temperature-controlled outpatient research facility of the University of Michigan and Peking University Health Science Center (PUHSC). For a 24-hour period prior to all 4 visits in Beijing and 2 visits in Michigan, participants wore a personal environmental monitor during usual daily activities.

Cardiovascular outcomes

In Michigan, seated right upper arm BP and heart rate (HR) using an appropriate sized cuff were measured by an automated device (BPM-100; BpTRU) after participants rested unattended in the exam room for 5 minutes with their arm supported at mid-sternal level. The average of 5 BP readings (2nd to 6th levels using 1 minute intervals) was defined as the primary outcome. Participants next rested supine on a patient exam bed and continuous electrocardiogram monitoring was performed for 6 minutes using a Spacelabs evo Holter system. Time (SD of normal-to-normal intervals) and frequency domain (high frequency; low frequency) HR variability (HRV) metrics were analyzed using the Spacelabs Pathfinder system (<http://www.spacelabshealthcare.com/>). Thereafter, resting basal longitudinal brachial artery diameter images were measured at a standardized site on the right upper arm using a portable Terason ultrasound system and a 10 MHz linear array transducer (<http://www.terason.com/>). All images were captured by an electrocardiogram triggered on the R-wave. Conduit artery endothelial-dependent vasodilation was then measured using the standardized flow-mediated dilatation (FMD) method employing a 5-minute upper arm cuff occlusion technique. Brachial artery images were captured continuously for 2 minutes during reactive hyperemia. Digital images were analyzed offline using a software package employing an edge-detection system (Brachial Analyzer, Medical Imaging Applications; <http://www.mia-llc.com/>). FMD was calculated as the percent increase in brachial artery diameter from baseline at 50–90 seconds (FMD50-90) as well as the largest percent change (FMD peak) during the 2-minute reactive hyperemia period.

In Beijing, at each clinic visit, participants rested for at least 5 minutes prior to measuring seated BP and HR in the right upper arm using an appropriate sized cuff with an automated device (Omron HEM-7200). The average of 3 BP readings and HR was used as the primary outcome. Thereafter, resting supine microvascular endothelial-dependent vasodilatation (reactive hyperemia index) was measured in the right index finger using the standard protocol with a commercially available methodology (<http://www.itamar-medical.com/endopat-main/>). The day prior to each clinic visit, participants were fitted with an

ambulatory electrocardiogram monitor (Model MGY H7; <http://meigaoyi.en.ec21.com/>), which they wore for 24 hours. Time and frequency domain HRV metrics were analyzed for the 24-hour period using PC-based software (Holter System version 12.Netfor Windows, DM Software).

Environmental exposure outcomes

The Michigan Department of Environmental Quality operates tapered element oscillating microbalance samplers (Rupprecht & Patashnick TEOM 1400a) to monitor continuous PM_{2.5} levels across Michigan. Outdoor-ambient temperature and PM_{2.5} data were averaged over 24-hour periods from the monitoring site in Ypsilanti, Michigan (ID: 261610008; 42.2406 -83.59972; <http://www.michigan.gov/deq/>). For assessing outdoor-ambient exposure, each patient had their own unique multiple 24-hour long ambient exposure epochs calculated starting retrospectively from the time in the morning at the start of each of the 4 study visit days. Seven individual 24-hour lag periods were calculated for each patient from each study visit day. In addition, the rolling average of exposures from 1 to 7 days in duration was calculated. Personal-level exposures and temperatures were recorded using a battery-powered active personal particulate monitor (pDR-1500; Thermo Scientific). Averages were recorded for the 24-hour period prior to the start of visit day 2 in each study block. Average personal exposure to PM_{2.5} mass was calculated from gravimetric determinations using a microbalance (MT-5, Mettler Toledo, Columbus, OH) in a temperature/humidity-controlled environment. Sample handling, processing, and analysis took place in a Class 100 ultraclean room. In Beijing, outdoor-ambient temperature and PM_{2.5} levels were measured continuously by a temperature sensor of MetOne G1475 and a MetOne BAM-1020, which were set up at PUHSC on campus fixed monitoring station. Personal-level exposures and temperatures were recorded using a battery-powered active personal particulate monitor (pDR-1500; Thermo Scientific).

Statistical methods

Summary statistics were computed for continuous measures as mean \pm SD, as well as median (interquartile range), and for categorical variables as frequency and proportion (%). All outcomes were evaluated for normality of distribution using the Shapiro–Wilk normality test. We analyzed the associations of longitudinal health measurements repetitively obtained with 24-hour average outdoor-ambient (4 associations per patient for each lag day and rolling average lag periods) and personal-level temperature exposures (2 associations per patient) using mixed-effect models. Random effects were included to account for within subject correlations. The outcomes of this model are the longitudinal health parameters (e.g., systolic BP): Outcome_{it} = b₀ + b_i + b₁ * Temp_{it} + b₂ * PM_{it} + other covariates + random errors; where *i* represents the *i*th individual, *t* represents the *t*th repeated measurement, b_i represents the random intercept for participant *i*, PM represents the PM_{2.5} exposure (either each lag day and rolling average lag periods for ambient exposure, or personal exposure), and Temp represents the temperature exposure. Models were adjusted for several a priori determined covariates including patient age, sex, dichotomized body mass index (≥ 25 kg/m²), and study block (1 vs. 2 in Michigan) or study visit (1–4 in Beijing). An interaction term [body mass index ≥ 25 kg/m² (*n* = 22) * fine particulate matter] was also added to the models to evaluate the effect modifications. All analyses were performed using the statistical software package R (version 3.2.5).

RESULTS

All physiological parameters including BP levels were on-average normal among participants at both locations (Tables 1 and 2). Exposures to outdoor-ambient and personal-level PM_{2.5} concentrations were substantially higher at Beijing compared to Michigan (Tables 3 and 4). Personal-level temperatures were only available at Michigan and were warmer

Table 1 Participant characteristics in Beijing (*n* = 73; 48 females; 100% Asian)

Variable	Obs	Mean \pm SD	Min	25 th Percentile	Median	75 th Percentile	Max
Age (years)	73	23.3 \pm 5.4	18.0	20.0	23.0	24.0	50.0
BMI (kg/m ²)	255	22.1 \pm 3.3	16.9	19.7	21.3	24.7	32.9
SBP (mm Hg)	250	110.5 \pm 10.9	85	102	110	118	144
DBP (mm Hg)	250	65.0 \pm 7.9	50	59	64	70	89
HR (beats/min)	249	70.8 \pm 10.9	48	63	70	78	113
SDNN (msec)	252	66.5 \pm 16.5	21.2	54.7	65.1	76.5	109.3
LF (msec ²)	252	900 \pm 392	77	608	869	1126	2186
HF (msec ²)	252	517 \pm 374	10	257	423	640	2158
LF/HF	252	2.27 \pm 1.13	0.64	1.43	2.03	2.79	7.49
RHI	241	1.80 \pm 0.59	0.82	1.37	1.64	2.14	4.52

Results represent the values averaged from each study visit for all patients. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HF, high frequency power; HR, heart rate; LF, low-frequency power variability; max, maximal value; min, minimal value; Obs, number of observations; RHI, reactive hyperemia index (finger microvascular endothelial-dependent vasodilatation); SBP, systolic blood pressure; SDNN, SD of normal-to-normal intervals.

Table 2. Participant characteristics in Michigan (*n* = 50; 34 females; 46 white, 2 black, 2 latino, 2 unreported)

Variable	Obs	Mean ± SD	Min	25 th Percentile	Median	75 th Percentile	Max
Age (years)	50	32.1 ± 9.6	19.0	24.0	28.5	41.0	50.0
BMI (kg/m ²)	50	26.1 ± 5.7	19.0	21.7	24.9	29.1	43.5
SBP (mm Hg)	200	107.8 ± 13.3	86	99	105	112	161
DBP (mm Hg)	200	70.2 ± 9.4	50	65	69	75	107
HR (beats/min)	200	70.6 ± 11.3	44	63	71	78	111
SDNN (msec)	194	79.0 ± 37.1	19.1	53.9	70.1	92.0	225.8
LF (msec ²)	189	1,829 ± 1,900	66	597	1,174	2,325	14,329
HF (msec ²)	189	2,224 ± 4,364	23	403	949	1,758	38,256
LF/HF	189	2.11 ± 2.71	0.13	0.72	1.33	2.58	28.2
FMD 50–90 (%)	185	4.14 ± 2.39	0.00	2.35	3.86	5.85	10.71
FMD peak (%)	185	7.35 ± 2.79	1.53	4.93	7.19	9.56	14.80
BAD (cm)	185	3.73 ± 0.77	2.32	3.11	3.64	4.41	5.22

Results represent the values averaged from each study visit for all patients. Abbreviations: BAD, brachial artery diameter; DBP, diastolic blood pressure; FMD, flow-mediated dilatation (brachial artery endothelial-dependent vasodilatation); HF, high frequency power; HR, heart rate; LF, low-frequency power variability; max, maximal value; min, minimal value; Obs, number of observations; SBP, systolic blood pressure; SDNN, SD of normal-to-normal intervals.

and less variable than outdoor levels, whereas outdoor temperatures were slightly cooler than in Beijing.

In the entire Beijing cohort, BP trended to increase in relation to higher outdoor-ambient PM_{2.5} concentrations (per 10 µg/m³) with some associations reaching statistical significance for diastolic levels (0.15–0.17 mm Hg) (Figure 1). In overweight adults (body mass index ≥25 kg/m³), higher outdoor-ambient PM_{2.5} concentrations during the prior 1–7 days were associated with significant elevations in both systolic (0.34–0.44 mm Hg) and diastolic (0.22–0.66 mm Hg) BP (Figure 2a). In addition, personal-level exposure during the prior 24-hours also significantly increased BP (0.41/0.61 mm Hg) in overweight adults (Figure 2b). In a real-world context, the BP changes per interquartile range increase in outdoor-ambient PM_{2.5} levels during the prior week translated into clinically relevant elevations in systolic (range: 2.4–3.1 mm Hg) and diastolic (range: 1.6–4.6 mm Hg) levels in overweight adults. Besides body mass index, there were no other significant effect modifiers (age, sex, baseline BP) of the BP responses induced by PM_{2.5}.

In Michigan, there was no consistent effect of outdoor-ambient (Figure 3a) or prior 24-hour personal-level PM_{2.5} exposures (Figure 3b) on BP in the entire cohort or overweight adults. Regarding secondary outcomes, no consistent associations were observed between outdoor-ambient and personal-level PM_{2.5} concentrations and other mechanistic endpoints among all participants at either site (data not shown). Microvascular function (reactive hyperemia index) in Beijing and conduit endothelial function (FMD) in Michigan were not consistently impacted by PM_{2.5}. HRV metrics (SD of normal-to-normal intervals, low frequency/high frequency ratio) were also not significantly associated with exposures at either location.

DISCUSSION

This is the first study to simultaneously investigate in a coordinated fashion the hemodynamic actions of short-term exposures to ambient PM_{2.5} in healthy normotensive individuals at both the low and high extremes of global air pollution concentrations. In a heavily polluted city (Beijing), diastolic BP levels increased in relation to outdoor-ambient exposures. Overweight adults were more sensitive and showed clinically relevant increases in both systolic and diastolic BP in relation to real-world changes in outdoor-ambient as well as personal-level PM_{2.5} exposures. Conversely, where air pollutants remained low and within AQGs (Michigan), ambient PM_{2.5} was not linked to changes in BP. Our results support several conclusions. Foremost, even normotensive young adults are adversely impacted from a BP standpoint by the extremely high levels of PM_{2.5} routinely encountered in Beijing. Second, overweight adults appear to be more susceptible. Third, a lower concentration threshold may exist (given the lack of responses in Michigan) below which ambient PM_{2.5} poses no (or a reduced) risk for BP changes—at least among normotensive healthy people. Altogether our findings add further support for international efforts to improve air quality not only to prevent the adverse health effects of PM_{2.5}, but also to help in the global battle against high BP, the leading cause of morbidity and mortality worldwide.³

Fine particulate matter and BP

PM_{2.5} is major public health risk factor for myocardial infarctions, strokes, and heart failure.^{1,4,10} One plausible mechanistic explanation for this diverse array of cardiovascular events may be PM_{2.5}-induced elevations in BP.^{11–13} Several biological pathways may be responsible,^{11,18–23} including impaired endothelial-dependent vasodilatation and

Table 3. Environmental exposures in Beijing

Variable		Obs	Mean ± SD	Min	25 th Percentile	Median	75 th Percentile	Max
PM _{2.5} (µg/m ³)	Personal	253	52.4 ± 79.2	2.5	13.8	27.1	62.8	785.0
	Outdoor 7-day average	255	86.7 ± 52.1	30.6	46.8	69.8	117.0	236.2
Temp (°C)	Personal	–	–	–	–	–	–	–
	Outdoor 7-day average	255	10.4 ± 9.9	–1.8	0.6	7.4	19.7	27.7

Personal PM_{2.5} levels were averaged from all available 24-hour long period measurements performed on lag day 1. Personal temperature levels were not available due to a technical error. Outdoor PM_{2.5} and temperature levels were averaged over 4 separate 7-day long lag periods prior to all study visits.

Table 4. Environmental exposures in Michigan

Variable		Obs	Mean ± SD	Min	25 th Percentile	Median	75 th Percentile	Max
PM _{2.5} (µg/m ³)	Personal	95	12.2 ± 16.9	0.2	4.0	6.9	13.3	94.0
	Outdoor 7-day average	94	9.1 ± 1.8	5.5	7.7	9.1	10.7	12.4
Temp (°C)	Personal	98	22.0 ± 3.0	13.8	20.4	22.2	24.2	28.7
	Outdoor 7-day average	97	4.4 ± 9.8	–13.4	–3.9	2.9	12.7	23.2

Personal PM_{2.5} and temperature levels were averaged from all available 24-hour long period measurements performed on lag day 1 prior to visit 2 during both study blocks. Outdoor PM_{2.5} and temperature levels were averaged over 4 separate 7-day long lag periods prior to all study visits.

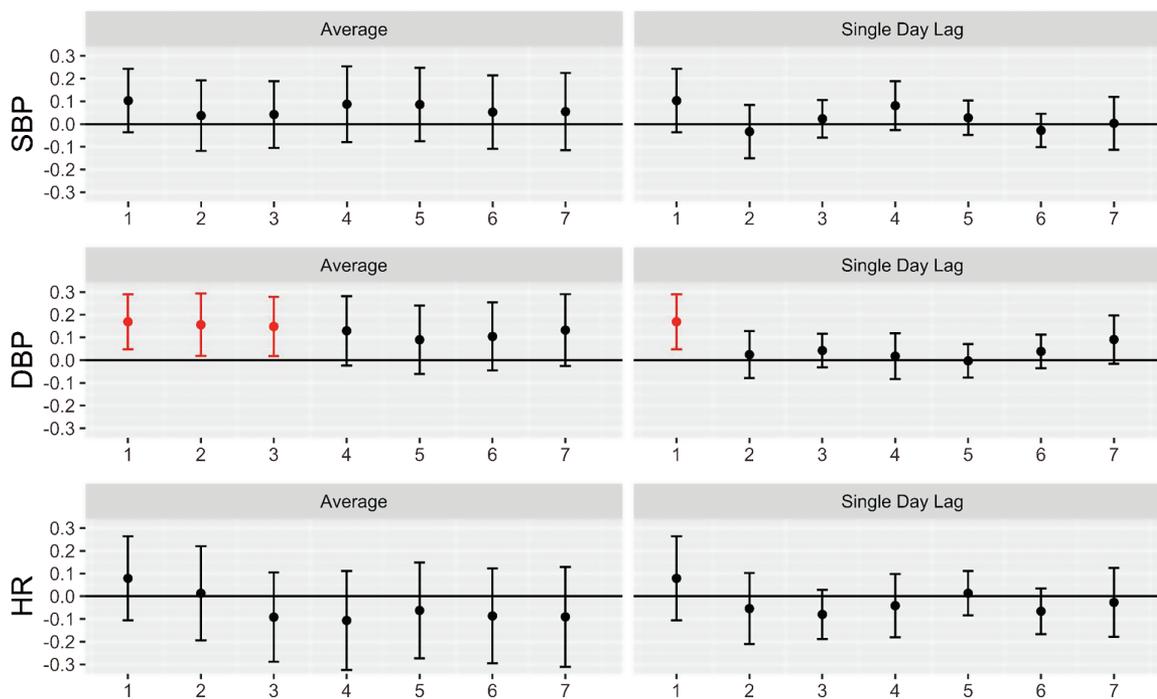


Figure 1. Associations of ambient outdoor fine particulate matter concentrations with blood pressure and heart rate among all patients in Beijing. Average, associations (beta coefficients and 95% confidence intervals) of rolling mean fine particulate matter levels (per 10 µg/m³ increase) averaged over all exposure days up through lag day(s) 1–7 with blood pressure levels and heart rate. Single day lag, associations (beta coefficients and 95% confidence intervals) of individual lag day fine particulate matter levels (per 10 µg/m³ increase) with blood pressure levels and heart rate. Models adjusted for dichotomized body mass index (≥ 25 kg/m²), sex, age, study visit (1–4), same-day ambient outdoor temperature. No effect modification by body mass index in this model. Abbreviations: DBP, diastolic blood pressure (mm Hg); HR, heart rate (beats/min); SBP, systolic blood pressure (mm Hg).

autonomic imbalance. In this current study, we were not able to identify the precise mechanism underlying the BP elevations in Beijing. Perhaps due to a lack of statistical power for these secondary outcomes, neither microvascular function

nor HRV metrics were consistently associated with PM_{2.5}. An alternative explanation may be that differing pathways are responsible for increasing BP at varying time courses of exposure. Hyperacute responses over a few minutes-to-hours

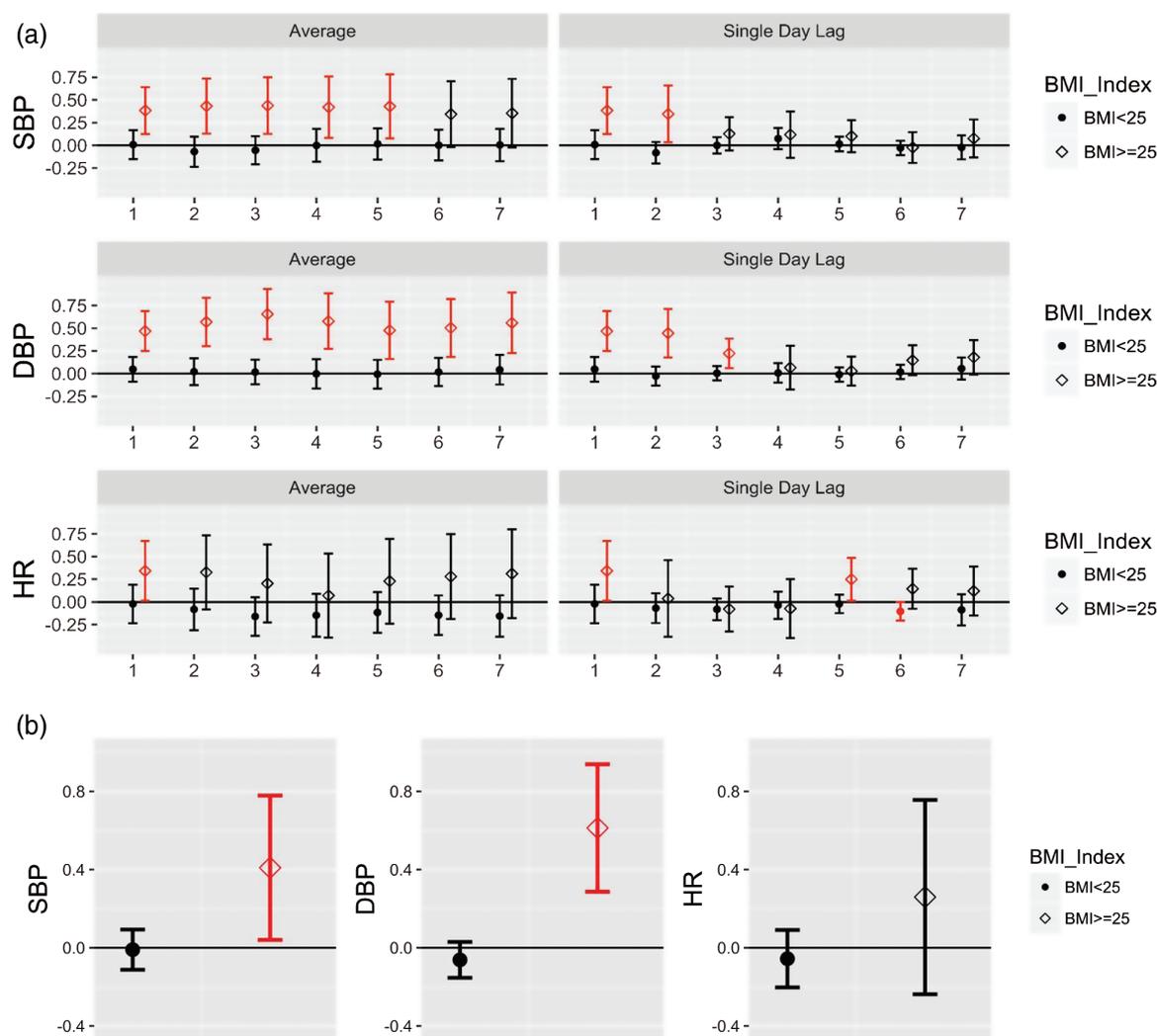


Figure 2. Fine particulate matter and blood pressure responses in Beijing. **(a)** Associations of ambient outdoor fine particulate matter concentrations with blood pressure and heart rate among overweight and lean patients in Beijing. Average associations (beta coefficients and 95% confidence intervals) of rolling mean fine particulate matter levels (per $10 \mu\text{g}/\text{m}^3$ increase) averaged over all exposure days up through lag day(s) 1–7 with blood pressure levels and heart rate. Single day lag, associations (beta coefficients and 95% confidence intervals) of individual lag day fine particulate matter levels (per $10 \mu\text{g}/\text{m}^3$ increase) with blood pressure levels and heart rate. Models adjusted for dichotomized body mass index, sex, age, study visit (1–4), same-day ambient outdoor temperature, and [body mass index $\geq 25 \text{ kg}/\text{m}^2$ ($n = 62$) * fine particulate matter] (interaction effect). **(b)** Associations of personal fine particulate matter exposures with blood pressure levels and heart rate among overweight and lean patients in Beijing. Associations (beta coefficients and 95% confidence intervals) of prior 24-hour fine particulate matter exposures (per $10 \mu\text{g}/\text{m}^3$ increase) with blood pressure levels and heart rate. Models adjusted for dichotomized body mass index, sex, age, study visit (1–4), and [body mass index $\geq 25 \text{ kg}/\text{m}^2$ ($n = 62$) * fine particulate matter] (interaction effect). Abbreviations: DBP, diastolic blood pressure (mm Hg); HR, heart rate (beats/min); SBP, systolic blood pressure (mm Hg).

are likely primarily mediated by relative increases in sympathetic nervous system activity, as shown by controlled experiments.¹⁸ $\text{PM}_{2.5}$ inhalation can trigger autonomic reflex arcs by activating airway receptors (e.g., transient receptor potential).^{19,21} In support of this pathway, air pollutants increased the low frequency/high frequency ratio within a few hours in our prior studies in Beijing; however, continued HRV changes were not observed 1–7 days later despite the fact that BP levels remained persistently elevated.^{16,24} It is possible that baroreflex changes attenuated the ability to observe alterations in HRV after the first day. It is equally plausible that other biological pathways sustained the BP elevations after 24-hours and over more prolonged time periods such as in this current study.¹¹

The interaction of pro-oxidative particulate components (e.g., organic species) with lung-based cells (e.g., macrophages) can instigate inflammatory responses that spill-over into the systemic circulation.¹ A wide array of mediators (e.g., cytokines, endothelin, oxidized lipids), as well as particulate constituents (e.g., metals), have been implicated in prompting vasoconstriction and/or impairing vasorelaxation which could thereafter result in an increase in BP.^{20,22,23} The lack of concomitant endothelial dysfunction in our current study does not rule out this pathway but makes it a less compelling explanation.

Recently, a study in heavily polluted Shanghai has shed some new light on the possible mechanistic underpinning that could explain persistent elevations in BP following

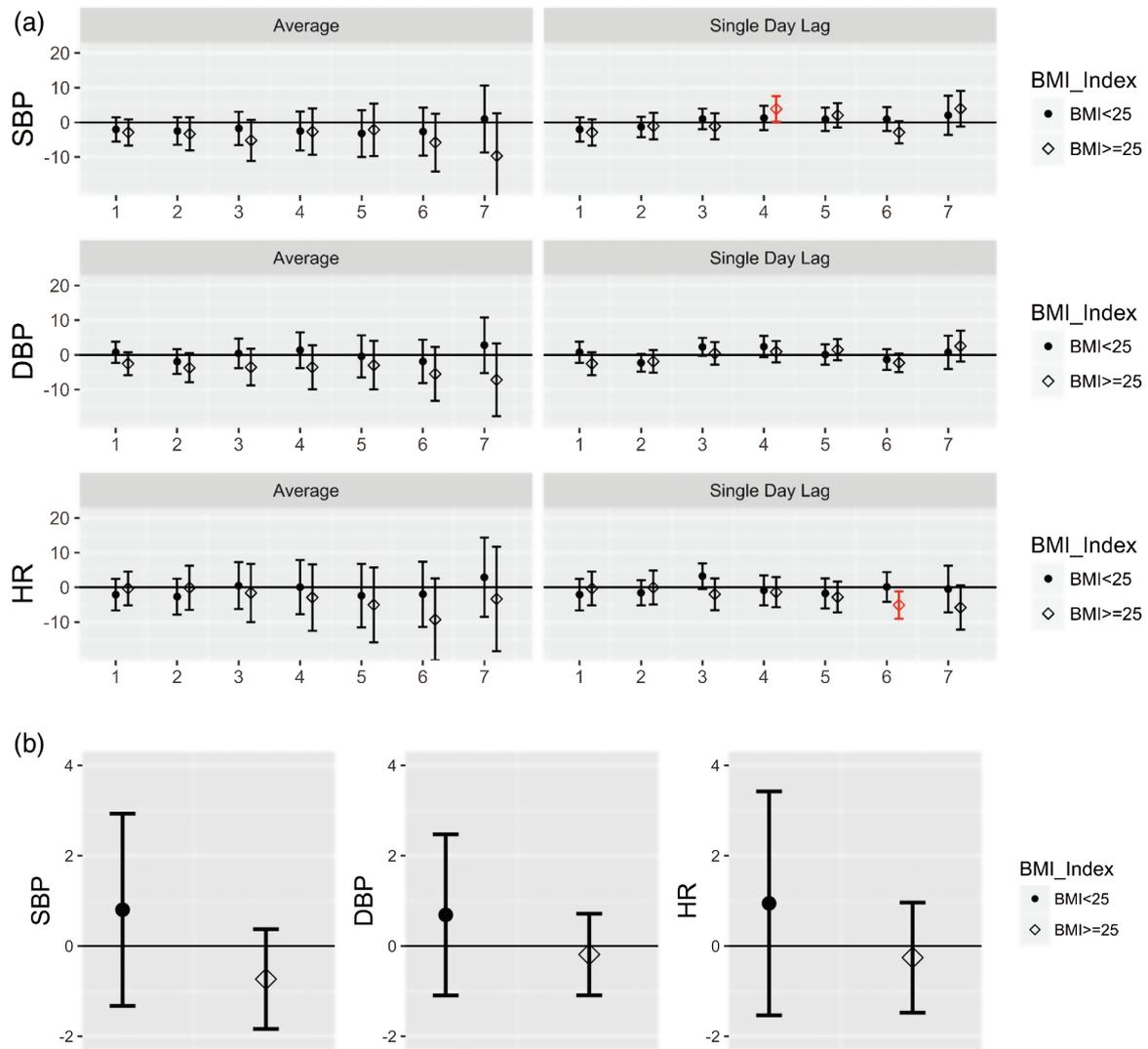


Figure 3. Fine particulate matter and blood pressure responses in Michigan. (a) Associations of ambient outdoor fine particulate matter concentrations and blood pressure levels and heart rate among overweight and lean patients in Michigan. Average, associations (beta coefficients and 95% confidence intervals) of rolling mean fine particulate matter levels (per 10 $\mu\text{g}/\text{m}^3$ increase) averaged over all exposure days up through lag day(s) 1–7 with blood pressure levels and heart rate. Single day lag, associations (beta coefficients and 95% confidence intervals) of individual lag day fine particulate matter levels (per 10 $\mu\text{g}/\text{m}^3$ increase) with blood pressure levels and heart rate. Models adjusted for dichotomized body mass index, sex, age, study block (1–2), same-day ambient outdoor temperature, and [body mass index ≥ 25 kg/m² ($n = 100$) * fine particulate matter] (interaction effect). (b) Associations of personal fine particulate matter exposures and blood pressure levels among overweight and lean patients in Michigan. Associations (beta coefficients and 95% confidence intervals) of prior 24-hour fine particulate matter exposures (per 10 $\mu\text{g}/\text{m}^3$ increase) with blood pressure levels and heart rate. Models adjusted for dichotomized body mass index, sex, age, study block (1–2), same-day personal-level temperature, and [body mass index ≥ 25 kg/m² ($n = 100$) * fine particulate matter] (interaction effect). Abbreviations: SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg); HR, heart rate (beats/min).

exposure to higher ambient PM_{2.5} levels.^{25,26} In a randomized double-blind cross-over study, Li *et al.* corroborated that PM_{2.5} indeed raises BP over a few days. However, the investigators further demonstrated that an increase in circulating stress hormones (e.g., catecholamines, cortisol) and a host of metabolic derangements concomitantly occurred. Air purification was effective in lowering both stress hormones as well as BP. The findings strongly support that PM_{2.5} induces an activation of the hypothalamic-pituitary-adrenal axis which may be responsible for eliciting a number of adverse cardio-metabolic responses, including elevations in BP, over subacute time periods²⁶. The fact that overweight adults were

more susceptible in Beijing suggests that they may be more primed for PM-induced activation by these stress pathways. However, this must remain a speculation while we await the results of future analyses of stored blood samples from this current study.

Clinical implications

The magnitude of BP elevations induced by real-world levels of PM_{2.5} in Beijing accord with prior meta-analyses (2–4 mm Hg).^{12,13} Our current findings are important because they illustrate that the prohypertensive actions

of PM_{2.5} adversely impact even healthy young normotensive adults living in heavily polluted cities. This has critical public health implications as hundreds of millions of individuals are at risk. Most prior studies, along with our own reports in Beijing,¹⁶ typically involved diverse populations (e.g., including the elderly) or patients with pre-existing diseases (e.g., the metabolic syndrome). Given that air pollution levels are continuing to increase worldwide,^{3,5} billions of people will face unhealthy PM_{2.5} concentrations for decades to come. While a 2–4 mm Hg increase in BP may pose a modest risk to any single individual, the enormous size of the population affected means that PM_{2.5} exposure translates into a major threat to global public health.^{3,27} Indeed, short-term elevations in ambient air pollutants have been linked to emergency department visits for hypertension.^{28,29} Longer-term exposures have even been associated with the development of overt hypertension.^{13,15,17} Our findings add to the body of evidence that ambient PM_{2.5} is an important environmental risk factor promoting higher levels of BP at a population level.

Conversely, the very low levels of air pollution encountered in Michigan were not linked to changes in BP. This stands in contrast to several of our own prior studies in this area.^{8,9,14} One explanation may be that PM_{2.5} levels were even lower (by 40%) in this current (9.1 µg/m³) compared to our prior reports (~15 µg/m³). While large epidemiological studies show that no lower threshold exists below which PM_{2.5} is “safe” (even when <10 µg/m³) from a cardiovascular risk standpoint,⁴ our findings suggest that this may not hold true for its risk to BP. The air pollution levels in almost all prior studies investigating the impact on BP have been higher than those encountered in our current study.^{11–13} It is thus possible that short-term exposure to PM_{2.5} levels averaging below 10 µg/m³ pose less discernable risk for raising BP over a few days (at least among healthy young normotensive individuals). An alternative explanation may be that very high concentrations of PM_{2.5} (such as in Beijing and during controlled exposures¹⁸) are capable of raising BP in both healthy as well as mixed populations of individuals, whereas very low levels can only elicit adverse responses among susceptible adults. Indeed, several prior studies have suggested that at-risk patients may suffer more robust BP elevations (e.g., 5–10 mm Hg) following short-term PM_{2.5} exposures.^{8,12,14} In this current study, overweight adults also had larger elevations in BP (at least in Beijing). Susceptible populations (e.g., elderly, hypertensives) may be less able to physiologically counter the BP-raising actions of PM_{2.5} inhalation.¹¹ However, we were not able to test this conjecture in this study as we deliberately enrolled younger healthier patients compared to our previous studies in both Beijing^{16,24} and Michigan.^{8,9,14} Finally, it is possible that our study lacked the power to observe small BP changes among healthy normotensive individuals despite the fact that it was of similar size to our prior studies involving mixed populations.

Our findings support that health care providers and patients living in regions with air pollution above AQGs (which is 90% of the global population) should be aware of the potential for short-term changes in PM_{2.5} leading to an increase in BP or worsening hypertension control. The good

news is that we show here that low levels of PM_{2.5} < 10 µg/m³ might not elevate BP. Recent short-term trials also illustrate that usage of air purifiers and wearing of N95 respirators can not only reduce exposure to PM_{2.5} but also provide discernable health benefits (including a decrease in BP)^{25,26}. These findings support worldwide efforts to improve air quality as an integral part of the global fight against hypertension. As outlined previously,^{26,30} we believe that taken together these findings also strongly support launching large-scale outcome trials to formally test whether personal-level interventions (e.g., N95 respirator masks) can reduce clinical cardiovascular events in at-risk populations living in heavily polluted areas. Such definitive clinical trials would help provide the evidence-base needed to guide health care providers across the globe on how to counsel their patients to best take personal action to avoid the adverse health effects of PM_{2.5} when living in regions above current AQGs.

Limitations

Our studies were “harmonized” as much as possible; nevertheless, some design variations (e.g., racial composition, number of exposures, endothelial function, and HRV protocols) occurred due to feasibility reasons. Some of these variations could underlie the discordant BP responses between sites. However, we believe it is far more likely that the large differences in PM_{2.5} levels were responsible. It was difficult to statistically assess for the responsible factor because of strong colinearity among race, study site, and PM_{2.5} concentration. Genetic differences in susceptibility could be involved and thus require future study.

While BP was measured slightly differently in Michigan versus Beijing, we used a validated automated monitor along with methods that accord with BP guidelines at both sites. Though it cannot be ruled out, it is doubtful that this slight difference was responsible for our results. For example, BP has been determined by a large variety of methods (and likely with a varying degree of accuracy and “reactivity” during measurement) in many prior studies,^{11–18} yet numerous previous experiments (as well as their meta-analyses) have still shown positive associations with acute BP changes and PM_{2.5} levels. Thus, the minor difference in how we measured BP between sites is very unlikely to be a reason (i.e., be a true confounder) for differences in the associations with PM_{2.5} levels. Moreover, core experimental aspects were similar at both locations which allowed us to investigate the primary objective to characterize the BP responses to ambient PM_{2.5} among healthy adults living in both a heavily polluted as well as a clean environment.

Outdoor-ambient levels at nearby monitors may suffer from exposure misclassification; however, we substantiated as best as possible with available technologies our study findings by also including personal-level exposure monitors. As with all panel study designs, we were only able to evaluate for the acute health effects of short-term changes in air pollution levels. The impact of long-term exposures on chronic BP levels requires a cohort study design which is beyond the scope of this study. However, despite the fact that individuals living in Beijing are without a doubt chronically exposed to

higher PM_{2.5} levels over years, they were still susceptible to acute changes in that they showed alterations in BP in association with changes in ambient levels during the prior week. Follow-up studies will assess the impact of other co-pollutants (e.g., ozone, NO_x) and particle constituents in altering BP; however, any unobserved impacts are likely independent from (i.e., not a confounder of)^{1,10} those induced by PM_{2.5}. Lack of associations in Michigan may also have been due to inadequate statistical power (i.e., too small of a sample size as there were fewer participants than in Beijing) given the low PM_{2.5} levels and small interday variability. Our study was powered ($n = 50$) with the primary outcome being BP; however, PM_{2.5} levels were lower than anticipated, particularly as compared to our prior studies in the same area. Even if this is the case, it still supports our main contention that there is thus a blunted impact of air pollution on BP at these lower levels (even if a larger study would have been able to detect smaller associations than we were powered to find in this study based upon prior positive studies in Michigan at higher air pollution levels).

CONCLUSIONS

Short-term elevations in ambient PM_{2.5} levels may trigger an acute increase in BP even among healthy young normotensive adults who live in highly polluted regions. No adverse hemodynamic responses were observed in a clean location. This adds further support for the key public health importance of worldwide efforts to improve air quality as an integral part of the global public health battle against hypertension.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

The authors declared no conflict of interest.

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