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ORIGINAL RESEARCH

Ambient Particle Components and Newborn Blood Pressure in Project Viva

Antonella Zanobetti, PhD; Brent A. Coull, PhD; Heike Luttmann-Gibson, PhD; Lenie van Rossem, PhD; Sheryl L. Rifas-Shiman, MPH; Itai Kloog, PhD; Joel D. Schwartz, PhD; Emily Oken, MD, MPH; Jennifer F. Bobb, PhD; Petros Koutrakis, PhD; Diane R. Gold, MD, MPH

BACKGROUND: Both elemental metals and particulate air pollution have been reported to influence adult blood pressure (BP). The aim of this study is to examine which elemental components of particle mass with diameter ≤2.5 μm ($PM_{2.5}$) are responsible for previously reported associations between $PM_{2.5}$ and neonatal BP.

METHODS AND RESULTS: We studied 1131 mother-infant pairs in Project Viva, a Boston-area prebirth cohort. We measured systolic BP (SBP) and diastolic BP (DBP) at a mean age of 30 hours. We calculated average exposures during the 2 to 7 days before birth for the $PM_{2.5}$ components—aluminum, arsenic, bromine, sulfur, copper, iron, zinc, nickel, vanadium, titanium, magnesium, potassium, silicon, sodium, chlorine, calcium, and lead—measured at the Harvard supersite. Adjusting for covariates and $PM_{2.5}$, we applied regression models to examine associations between $PM_{2.5}$ components and median SBP and DBP, and used variable selection methods to select which components were more strongly associated with each BP outcome. We found consistent results with higher nickel associated with significantly higher SBP and DBP, and higher zinc associated with lower SBP and DBP. For an interquartile range increase in the log Z score (1.4) of nickel, we found a 1.78 mm Hg (95% CI, 0.72–2.84) increase in SBP and a 1.30 (95% CI, 0.54–2.06) increase in DBP. Increased zinc (interquartile range log Z score 1.2) was associated with decreased SBP (–1.29 mm Hg; 95% CI, –2.09 to –0.50) and DBP (–0.85 mm Hg; 95% CI: –1.42 to –0.29).

CONCLUSIONS: Our findings suggest that prenatal exposures to particulate matter components, and particularly nickel, may increase newborn BP.

Key Words: air pollution ■ child blood pressure ■ metals ■ pregnancy

Particle air pollution, known to increase the global burden of cardiovascular morbidity and mortality,[1-4] has been linked to acute increases in blood pressure (BP) that may partially mediate the relation of air pollution with adverse cardiovascular outcomes in adults.[5-8] Recent articles have found that particulate air matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$) may have a significant impact on systolic blood pressure (SBP) and diastolic blood pressure (DBP) not only in adults but also in children.[9-17] Longitudinal evidence is still sparse and to some extent inconsistent, but some studies of children suggest that early life or prenatal air pollution may influence not only short-term outcomes but also the long-term trajectory of BP,[9,11,13,15] and therefore the risk of elevated BP in later childhood and early adulthood.

It is not well understood which specific components of particle mass may explain its cardiovascular toxicity. Metals within PM have been considered both as markers of sources and also in terms of their potential to have direct vascular effects. Even in adults, studies on associations of metals and other elemental components of PM with BP are sparse, with inconsistent findings.[18,19] Similarly, a recent review of the few studies of prenatal or childhood metal exposures (mostly measured in human compartments and not as PM

Correspondence to: Antonella Zanobetti, PhD, Department of Environmental Health; Harvard T.H. Chan School of Public Health, 401 Park Drive, Landmark Center, Suite 415, P.O. Box 15698, Boston, MA 02215. E-mail: azanobet@hsph.harvard.edu

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CLINICAL PERSPECTIVE

What Is New?

- To the best of our knowledge, this is the first study to examine the short-term associations of elemental particle components with newborn systolic and diastolic blood pressure, and to apply variable selection methods to disentangle which particulate air matter with aerodynamic diameter <2.5 μm components, many of which have nontraffic sources, were associated with newborn blood pressure.
- Our findings suggest that prenatal exposures to particulate air matter with aerodynamic diameter <2.5 μm components, and particularly nickel, in the week before delivery, may increase neonatal systolic and diastolic blood pressure.

What Are the Clinical Implications?

- The pollution component–related changes in newborn blood pressure may reflect mechanisms through which maternal exposure to pollution influences newborn cardiovascular function, with as yet unknown long-term implications for long-term blood pressure in later childhood or adulthood.
- As higher later childhood blood pressure has been found to be a predictor of adult hypertension and cardiovascular disease in later life, particulate matter component-associated increases in newborn blood pressure could potentially contribute to increased cardiovascular health risks at older ages.
- Better understanding of the sources as well as the specificity of action of the responsible particulate matter constituents could lead to more targeted and effective regulations.

Nonstandard Abbreviations and Acronyms

BC	black carbon
BKMR	Bayesian kernel machine regression
DBP	diastolic blood pressure
LASSO	least absolute shrinkage and selection operator
PIAMA	Prevention and Incidence of Asthma and Mite Allergy birth cohort study
PM	particulate matter
$PM_{2.5}$	particle mass with diameter <2.5 μm
SBP	systolic blood pressure

components) presented inconsistent but suggestive evidence that arsenic, mercury, and lead may directly affect childhood BP.[14]

Disentangling associations of individual or mixtures of PM components with BP is a statistical challenge in that it involves handling multiple comparisons that are often dependent and sometimes related to pollution sources. In previous studies, models containing 2 pollutants at a time have been applied, but only few recent studies have used variable selection methods such as adaptive least absolute shrinkage and selection operator (LASSO) and Bayesian kernel machine regression (BKMR)[20,21] to simultaneously examine numerous exposures, and no study used these methods to quantify the effects of $PM_{2.5}$ mixtures on BP in children.

In a previous study in the Boston-area Project Viva cohort,[12] we showed that ambient prenatal exposures to $PM_{2.5}$ and black carbon (BC) averaged over 2 to 30 days before birth were positively associated with newborn SBP. In the present study in the same cohort, we investigated the associations between ambient levels of $PM_{2.5}$ elemental composition during the prenatal period with newborn SBP and DBP. We applied adaptive LASSO and BKMR to identify which components within the $PM_{2.5}$ mixture were associated with newborn BP.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Project Viva at emily_oken@harvardpilgrim.org.

Study Population

Study subjects were participants in Project Viva, a prospective prebirth cohort study of prenatal exposures, pregnancy outcomes, and child health. Between 1999 and 2002, we recruited women during their initial prenatal visit at the obstetrical offices of Atrius Harvard Vanguard Medical Associates, a multispecialty group practice located in eastern Massachusetts. The details of recruitment procedures and inclusion and exclusion criteria have been previously published.[22,23] The institutional review boards of participating institutions approved the study protocols, and all mothers provided written informed consent at enrollment and for their infants after birth.[23]

In the initial cohort of 2128 live singleton births, we performed in-person visits during the delivery hospital stay only during weekdays (n=1714, 81%), and we measured newborn BP (n=1131, 66%). Reasons for not obtaining a BP measurement were parents not giving consent for measurements (n=328), infant not available when staff was present (n=104), infant transferred to neonatal intensive care unit (n=78), measurements

could not be performed (infant too fussy; n=32), and other reasons (n=41).

At enrollment, mothers self-reported their age (years) and prepregnancy weight and height, which we used to calculate prepregnancy body mass index. Maternal third-trimester BP (millimeters of mercury) obtained from the medical record was calculated as the average BP between 28 and 32 weeks of gestation. Maternal prepregnancy serial urine and BP measurements (which we used to identify gestational hypertension or preeclampsia) were abstracted from outpatient and hospital medical records. Mother's self-reported race/ethnicity was categorized as Black, Hispanic, White, or other (including Asian, American Indian, more than 1 race/ethnicity, and other). Maternal smoking and physical activity were also self-reported. We obtained infant birth weight (kilograms), sex, and date of birth from the hospital record. We included socioeconomic status on an individual level estimated by maternal education reported at enrollment (college graduate versus less) and at the block group level as median household income derived from the Census 2000 (http://www.census.gov/prod/cen2000/doc/sf3.pdf).

Our outcomes were newborn SBP and DBP. We used a Dinamap Pro 100 automated oscillometric recorder (model 8100; Critikon Inc., GE Medical Services, Tampa, FL) according to a standardized protocol. We took 5 measurements 1 minute apart, and we recorded infant position (in bassinet or held), extremity used (left or right arm), cuff size, and infant state (quiet sleep, active sleep, quiet awake, active awake). We obtained 5 readings on 1092 infants, 4 readings on 15 infants, 3 readings on 7 infants, 2 readings on 7 infants, and 1 reading on 10 infants, for a total of 5565 readings on the 1131 participants. We then computed the median of the measurements in each child and used this as our outcome.

Environmental Data

Temporally Resolved Exposure Measures

Ambient concentrations of BC, $PM_{2.5}$ and $PM_{2.5}$ components were collected at the Harvard Supersite in Boston, Massachusetts, located on the roof of the Countway Library of the Harvard Medical School near downtown Boston[24] between 1999 and 2002, in close proximity to the hospitals where newborn BP measurement took place.

We measured BC concentrations using an Aethalometer (Magee Scientific Co., Model AE-16, Berkeley, CA). Daily integrated $PM_{2.5}$ samples were collected on Teflon filters using Harvard Impactors and were analyzed for elements by x-ray fluorescence at the Harvard T.H. Chan School of Public Health.

The $PM_{2.5}$ components that we examined were aluminum, arsenic, bromine, sulfur, copper, iron, zinc, nickel, vanadium, titanium, magnesium, potassium, silicon, sodium, chlorine, calcium, and lead. Other elements obtained as part of the speciation analysis of the filters were excluded either because the analytical measurement was judged to be unreliable or the element had a large proportion of the measurements below the method detection limit.

For $PM_{2.5}$ and each $PM_{2.5}$ component, we computed 2- to 7-day moving averages as the average of the measurements of the day of birth and additional previous days until the specified number of days were included; we then created *Z* scores of each log-transformed component. We a priori selected the 2- to 7-day moving averages because this averaging time is used to represent short-term exposure, which in our previous paper showed the strongest associations with newborn BP.

We obtained local meteorological data, including temperature and dew point temperature, measured at the Boston Logan airport station, from the National Oceanic and Atmospheric Administration.[25]

Spatially and Temporally Resolved $PM_{2.5}$ Predictions

As previously described,[12] we estimated daily $PM_{2.5}$ exposure at each mother's residential address. Mothers reported their home address at enrollment and updated it at each subsequent study visit, including at birth. We geocoded addresses using ArcGIS software StreetMap data (Environmental Systems Research Institute, Redlands, CA).

We generated daily predictions of $PM_{2.5}$ concentration levels across New England at a 1×1 km spatial resolution, using a hybrid satellite-based model incorporating daily satellite remote sensing data, monitored concentrations, meteorological variables, and land use regression variables. This model has been previously validated (mean "out-of-sample" R^2 was 0.88 for days with this information and 0.87 for days without), and full details of the modeling framework have been previously published.[26]

Statistical Analysis

To understand which PM components were associated with newborn systolic and diastolic BP, we applied several methods in subsequent steps. First, to assess the associations of $PM_{2.5}$ and its components with DBP and SBP, we used a linear regression model, adjusting for the same covariates we had included in our prior study of $PM_{2.5}$ and newborn BP,[12] namely, maternal age, third-trimester maternal BP, race/ethnicity (categorical: Black, Hispanic, other [incuding Asian, American Indian, more than 1 race/ethnicity,

and other], White), and educational level (categorical: college degree versus less); infant's postnatal age (in hours) and birth weight, infant state at BP (quiet sleep, active sleep, quiet awake, active awake), and median neighborhood income (continuous). The model also included same-day temperature, as well as sine and cosine terms of day of year to account for annual trends in BP as well as season of birth.

Second, we examined the associations of each PM component separately with newborn SBP and DBP, by fitting 2-pollutant models, with each model including $PM_{2.5}$ and 1 component.[27] Third, we examined the correlation of the components and then ran a multipollutant regression model with $PM_{2.5}$ and all the components together in the same model. Fourth, to understand which of these components were more important in their association with the outcomes within the $PM_{2.5}$ mixture, and to address multicollinearity, we applied 2 different methods for quantifying health risks associated with an environmental mixture and to check for consistency of results across different approaches: adaptive LASSO and Bayesian kernel machine regression (BKMR).

LASSO is a regression shrinkage and selection approach that can be used to select important predictors from a large list of correlated predictors. In the adaptive LASSO model, we forced the covariates that we adjusted for in the regression models outlined above to remain in the model and applied a penalty term to the $PM_{2.5}$ components in the models.

BKMR is a joint estimation and variable selection approach that flexibly identifies important components within a multipollutant mixture. In this approach, the outcome is regressed on a flexible function of the collection of components of interest. BKMR[28] uses a Gaussian kernel function, which allows for the estimation of potentially nonlinear and nonadditive exposure–response function for a set of correlated exposures. We selected the components on the basis of a posterior inclusion probability of 0.5 and above. Specific details of these methods are in Data S1.

Our final model included the most important components based among the ones selected with adaptive LASSO and BKMR, and from the results of the 2-pollutant and multipollutant models. We also included $PM_{2.5}$ in all models in addition to the selected components to adjust for potential confounding of associations with $PM_{2.5}$ components by total $PM_{2.5}$ mass.[27] In sensitivity analyses, we also adjusted for BC. To evaluate the potential of unmeasured confounding, we applied a negative control analysis; specifically, in the final models with the selected components, we included in addition to $PM_{2.5}$ and the elements, the corresponding exposures for the same average measured immediately after birth. The concept behind this negative control analysis is that if there is unmeasured temporal confounding, the exposures measured after birth would show associations with BP after controlling for prior exposure. We present the results as the change in BP in millimeters of mercury for each interquartile range (IQR) (25th–75th percentile) increment in each Z score of the log of the pollutant, reported with 95% CIs.

RESULTS

Table 1 shows the characteristics of the mother–infant pairs with neonatal BP measurements in Project Viva. Mean SBP was 72.5±9.0 mm Hg, and the mean DBP was 43.8±6.5 mm Hg. Among the 1131 mothers, 67% were college graduates, 68.7% were White, and 11.8% smoked during pregnancy. In Table 2, we present descriptive statistics for $PM_{2.5}$ and the 17 elements for the 2- and 7-day moving averages, while their correlations are in Tables S1 and S2.

The results were similar across all models that we applied. Figures 1 and 2 show the results from the multipollutant linear regression model with all components in the same model adjusting for $PM_{2.5}$, the 2-pollutant models including each component and $PM_{2.5}$, and BKMR, for those elements that were selected by adaptive LASSO and BKMR. Figures S1 through S4 present the results of the analyses for all components examined, applying the multipollutant and 2-pollutant models for both newborn SBP and DBP.

Table 1. Characteristics of 1131 Mother–Infant Pairs in Project Viva

Characteristics	N (%)	Mean±SD
Maternal age, y		32.0±5.3
Maternal college graduate	752 (67.0)	
Mother's race/ethnicity	193 (17.2)	
Black		
Hispanic	70 (6.2)	
White	771 (68.7)	
Other (including Asian, American Indian, more than 1 race/ethnicity, and other)	89 (7.9)	
Maternal smoking during pregnancy		
Never	778 (69.2)	
Former	213 (19.0)	
Smoker	133 (11.8)	
Gestational age, wk		39.7±1.4
Child birth weight, kg		3.52±0.50
Newborn systolic blood pressure, mm Hg		72.5±9.0
Newborn diastolic blood pressure, mm Hg		43.8±6.5

Table 2. Summary of the 2- and 7-Day Moving Averages of $PM_{2.5}$ Mass and Its Components During the Study Period

Pollutant	Unit	2-d Average			7-d Average		
		Mean	SD	IQR	Mean	SD	IQR
$PM_{2.5}$	$\mu g/m^3$	11.61	5.29	6.49	11.48	3.52	4.22
BC	ng/m^3	0.70	0.39	0.46	0.69	0.30	0.38
Aluminum	ng/m^3	56.63	36.33	30.17	57.61	31.36	20.84
Silicon	ng/m^3	85.60	66.48	51.75	87.77	59.24	37.68
Potassium	ng/m^3	40.27	20.25	23.02	40.09	13.54	16.85
Calcium	ng/m^3	33.33	18.41	18.10	34.31	13.94	11.47
Titanium	ng/m^3	3.91	2.16	2.17	3.93	1.51	1.34
Iron	ng/m^3	73.40	33.51	36.04	74.77	23.90	22.76
Magnesium	ng/m^3	58.09	22.91	26.62	58.32	15.05	17.40
Sulfur	ng/m^3	1213.00	800.11	857.44	1199.00	569.95	526.73
Arsenic	ng/m^3	0.62	0.54	0.86	0.62	0.30	0.42
Copper	ng/m^3	3.69	1.74	2.23	3.70	1.02	1.44
Zinc	ng/m^3	13.78	14.09	7.44	13.89	7.66	6.31
Bromine	ng/m^3	0.63	1.35	1.53	0.60	0.75	0.98
Lead	ng/m^3	6.55	4.12	3.72	6.60	2.67	2.31
Vanadium	ng/m^3	4.71	3.35	3.52	4.79	2.28	2.88
Nickel	ng/m^3	4.26	3.76	3.44	4.42	2.98	3.37
Sodium	ng/m^3	208.34	111.18	142.87	209.36	76.19	99.81
Chlorine	ng/m^3	8.80	27.21	3.13	9.11	20.82	3.84

BC indicates black carbon; IQR interquartile range; and PM2.5, particle mass with diameter <2.5 μm.

For SBP, the elements selected by the adaptive LASSO were sulfur, nickel, zinc, and chlorine consistently across the 4- to 7-day moving averages. Using BKMR, we found that the components have a linear dose-response relationship with the outcome. BKMR identified nickel and zinc with the highest posterior inclusion probability across all averaging times. We found that all 3 models indicate that nickel and sulfur were associated with higher SBP, while zinc and chlorine were associated with lower SBP, with effect sizes increasing with increasing averaging times. As shown in Figure 1, while nickel and zinc were significantly associated with BP, the associations for sulfur and chlorine were only suggestive.

The results for DBP are presented in Figure 2. Adaptive LASSO selected nickel, zinc, sulfur, silicon, arsenic, copper, and lead, while BKMR identified nickel and zinc with the highest posterior inclusion probability. All models showed increasing effect sizes with increasing moving averages, with the nickel effects being significantly positive and the zinc association being significantly negative. We also found suggestive positive associations between DBP and sulfur and arsenic, and suggestive negative associations between DBP and each of copper, lead, and silicon.

Based on the previous results, our final model included the 7-day moving average for nickel, zinc, and $PM_{2.5}$. Table 3 presents the results from this final model with $PM_{2.5}$, nickel, and zinc, and the results of the sensitivity analysis adding BC to the model, while including exposure after birth as a negative control. We found significantly higher SBP and DBP in association with increases in $PM_{2.5}$; for an IQR increase (IQR, 4.2 mg/m^3) in the 7-day moving average $PM_{2.5}$, we found a 0.69 mm Hg (95% CI, 0.003–1.38) increase in SBP, and a 0.71 mm Hg (95% CI, 0.22–1.21) increase in DBP.

We found a significant positive association between nickel and both SBP and DBP with a 1.78 mm Hg (95% CI, 0.72–2.84) increase in SBP and a 1.30 (95% CI, 0.54–2.06) increase in DBP, for an IQR increase (IQR log Z score 1.4) in nickel. We found lower SPB (–1.29 mm Hg; 95% CI, –2.09 to –0.50) and DBP (–0.85 mm Hg; 95% CI, –1.42 to –0.29) in association with an IQR (IQR log Z score 1.2) increase in zinc.

When we included BC in the models, the association between nickel and zinc and both SBP and DBP were similar, while the magnitude of the association of $PM_{2.5}$ was decreased. As a control, when we included PM_{25}, nickel, and zinc 7-day averages after birth, we found that the effects of these exposures were nonsignificant and almost null, while the main exposures measured before birth were fundamentally unchanged. These analyses support that the associations that we found were specific to the exposure time windows of interest, and not biased because of unmeasured temporal confounding.[29]

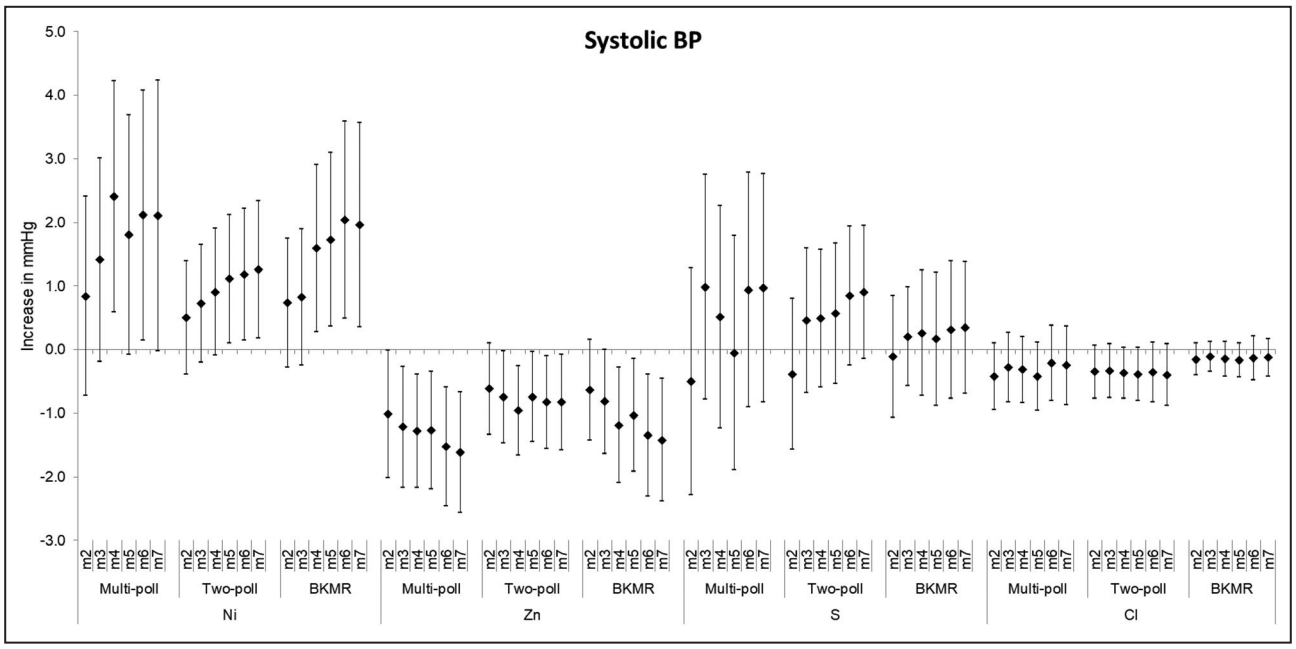

Figure 1. Changes in millimeters of mercury and 95% CI in newborn systolic blood pressure for an IQR increase in the log Z score of the 2- to 7-day average of each selected $PM_{2.5}$ mass components.
The results are reported for the components selected with LASSO and BKMR, and presented for the multipollutant model with all components in the same model (Multi-poll), the 2-pollutant model including each individual $PM_{2.5}$ component and $PM_{2.5}$ (Two-poll), and BKMR. All models adjusted for maternal age, third-trimester BP, race/ethnicity, education, and income, infant age and state at BP, sine, cosine, temperature, birth weight, and $PM_{2.5}$. BKMR indicates Bayesian kernel machine regression; BP, blood pressure; IQR, interquartile range; LASSO, least absolute shrinkage and selection operator; and PM2.5, particle mass with diameter <2.5 μm.

DISCUSSION

To the best of our knowledge, this is the first study to examine the short-term effects of particle metal components on newborn BP. In Project Viva, a Boston-area prebirth cohort, we found that higher exposures to $PM_{2.5}$ and to $PM_{2.5}$ components in the 2 to 7 days before birth may influence newborn SBP and DBP. Specifically, we found that nickel was significantly associated with higher newborn SBP and

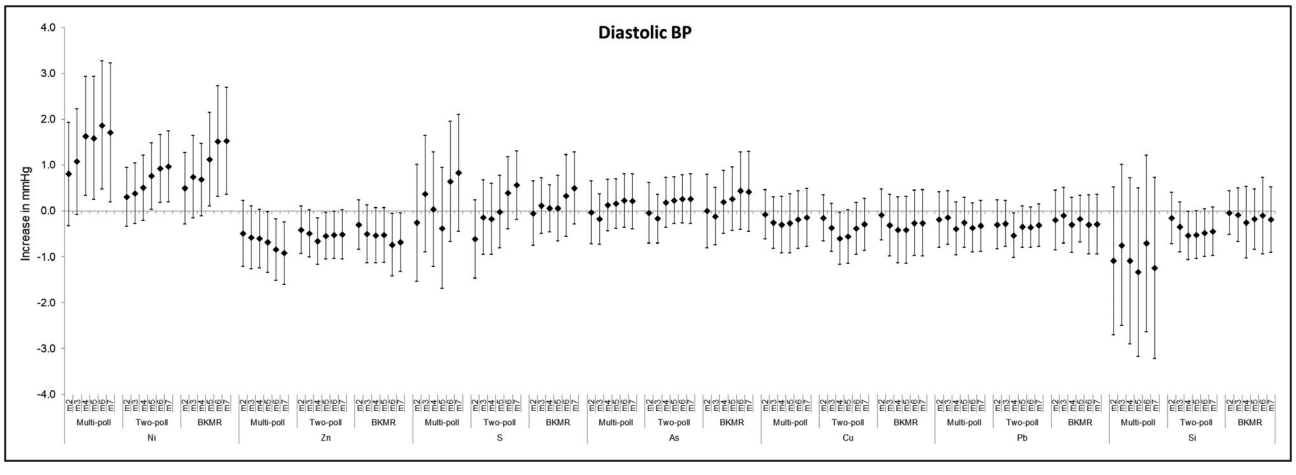

Figure 2. Changes in millimeters of mercury and 95% CI in newborn diastolic blood pressure for an IQR increase in the log Z score of the 2- to 7-day average of each selected $PM_{2.5}$ mass components.
The results are reported for the components selected with LASSO and BKMR, and presented for the multipollutant model with all components in the same model (Multi-poll), the 2-pollutant model including each individual $PM_{2.5}$ component and $PM_{2.5}$ (Two-poll), and BKMR. All models adjusted for maternal age, third-trimester BP, race/ethnicity, education, and income, infant age and state at BP, sine, cosine, temperature, birth weight, and $PM_{2.5}$. BKMR indicates Bayesian kernel machine regression; BP, blood pressure; IQR, interquartile range; LASSO, least absolute shrinkage and selection operator; and PM2.5, particle mass with diameter <2.5 μm.

Table 3. Changes in Millimeters of Mercury and 95% CI in Newborn Systolic and Diastolic Blood Pressure for an IQR Increase in the 7-Day Average of $PM_{2.5}$, Nickel, Zinc, and BC

Exposure	Systolic BP		Diastolic BP	
	Change	95% CI	Change	95% CI
Main model				
$PM_{2.5}$	0.69	0.003 to 1.38	0.71	0.22 to 1.21
Nickel	1.78	0.72 to 2.84	1.30	0.54 to 2.06
Zinc	−1.29	−2.09 to −0.50	−0.85	−1.42 to −0.29
Main model+BC				
$PM_{2.5}$	0.46	−0.28 to 1.21	0.50	−0.03 to 1.04
BC	0.72	−0.17 to 1.61	0.66	0.02 to 1.29
Nickel	1.67	0.60 to 2.74	1.19	0.43 to 1.96
Zinc	−1.34	−2.14 to −0.55	−0.90	−1.46 to −0.33
Main model+exposure after birth				
$PM_{2.5}$	0.55	−0.22 to 1.32	0.60	0.04 to 1.15
Nickel	2.03	0.85 to 3.22	1.49	0.63 to 2.34
Zinc	−1.37	−2.25 to −0.49	−0.87	−1.50 to −0.23
$PM_{2.5}$ after birth	0.12	−0.69 to 0.93	0.10	−0.48 to 0.69
Nickel after birth	0.32	−0.78 to 1.43	0.04	−0.76 to 0.84
Zinc after birth	−0.97	−1.99 to 0.05	−0.29	−1.03 to 0.45

Results for main model, and sensitivity analysis including BC, and exposure after birth. BC indicates black carbon; BP, blood pressure; IQR, interquartile range; and $PM_{2.5}$, particle mass with diameter <2.5 μm.

DPB, and that zinc was associated with lower SBP and DBP.

Epidemiologic Evidence for Associations of Nickel or Zinc Components of PM With BP Changes in Adults and Children

Associations of pollution-related nickel and zinc with cardiovascular physiologic outcomes have been reported in some adult cohort studies. In a study of Chinese university students,[30] short-term (preceding day) $PM_{2.5}$ components including lead, nickel, zinc, magnesium, strontium, and arsenic, were associated (though for zinc, not significantly) with higher SBP and DBP. Nickel as a component of $PM_{2.5}$ was also associated with higher SBP in a panel study of elderly people in Belgium.[18] Among elderly men in the Massachusetts-based Veterans Affairs Normative Aging Study, using adaptive LASSO, Dai et al[21] found that exposure to a 7-day moving average of nickel was associated with increased SBP and DBP. Higher nickel levels in PM has also been associated with cardiovascular mortality and morbidity,[1,31-36] as has higher PM-associated zinc in a California mortality study.[37]

Epidemiologic studies of BP effects of nickel or zinc components of PM are far fewer. In the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort study,[16] investigators examined the long-term (annual) effects of $PM_{2.5}$ and particulate air matter with aerodynamic diameter <10 μm components on blood pressure in children aged 12 years and found a positive but nonsignificant association of SBP with vanadium (like nickel, correlated with oil combustion). DBP was higher with higher iron, silicon, and potassium in particulate air matter with aerodynamic diameter <10 μm, but no associations were found with nickel or zinc.

Potential Biologic Mechanisms for BP Associations With Nickel or Zinc PM Component Exposures

In adults, biological mechanisms through which relatively short-term inhalation of PM pollution can adversely affect intermediate cardiovascular outcomes include oxidative stress,[38] autonomic dysfunction,[39-42] systemic inflammation,[43] and downstream vascular endothelial dysfunction.[8,44-47] Associations of particle mass exposures with intermediate outcomes representing these mechanisms have been reproducibly demonstrated, but whether specific PM components like nickel and zinc are partially responsible for these responses is less well understood.

Zinc and copper are essential trace biometals that regulate cardiovascular homeostasis,[48] and zinc deficiency may play a role in high BP,[49-51] though vascular responses to zinc inhaled as a particle component may be quite distinct from effects of zinc as a nutrient. Animal studies have reported cardiovascular

toxicity of PM metal components including zinc and nickel.[52,53]

In a mouse model, exposure to nickel from concentrated New York particles was associated with acute changes in heart rate and variability.[33] Earlier toxicologic animal model studies have suggested that nickel is involved in signaling pathways relevant to cardiovascular responses.[33,54] Nickel may activate hypoxia-inducible factor 1 (an important factor in regulating cellular oxygen concentration) and the transcription factor nuclear factor κB (a family of proteins that regulates DNA transcription in cellular responses such as immune response, inflammatory response, and apoptosis), with subsequent upregulation of the intercellular adhesion molecule 1, vascular cell adhesion protein 1.[55,56] Nickel exposure may also play a key role in leukocyte recruitment in the vasculature, leading to vascular inflammation and dysfunction.[57]

Potential Mechanisms for Newborn BP Responses to PM-Associated Metals

For newborns, the pollution component–related changes in BP that we found might reflect mechanisms through which maternal exposure to pollution influences newborn cardiovascular function, with as yet unknown long-term implications for long-term BP in later childhood or adulthood.[13] As the nickel responses are to relatively short-term exposures, it is unlikely that they reflect structural cardiac or placental vascular changes, which may be influenced by PM exposures in pregnancy that occur earlier in pregnancy -or for longer periods of time.[22] It is more likely that the responses to nickel reflect functional perturbation of newborn cardiac output, autonomic or endothelial vascular responses. Relatively recent studies have shown that particle pollution reaches the fetal side of the human placenta.[58] These newborn functional responses may be downstream of placental vascular responses to the nickel component itself or to maternal systemic inflammatory responses specifically to nickel and other PM pollution.[58]

Direct Effects of PM Metal Components

One question that arises in any observational study is whether the components themselves are affecting BP, or whether they are serving as surrogates/markers for other pollutants or pollution sources. Metals in PM components come from oil combustion (eg, nickel, vanadium), traffic emission (eg, zinc, selenium, lead, copper, and BC), wood burning (eg, potassium), and sea salt (eg, chlorine and sodium), road dust (eg, calcium, aluminum, silicon, iron, and titanium), while sulfur and arsenic are regional pollutants.

In our previous study, we showed that multiple markers of traffic pollution ($PM_{2.5}$, BC, NO_2) were associated with BP. In this analysis, we found that also nickel, nontraffic pollution, is associated with BP. In our study, the sensitivity analysis showed that the results were stable when including BC in the model, a marker of traffic pollution, as well as when we include a negative control defined as exposure after birth. This suggests that not only traffic-related pollution but also nickel, a marker of oil combustion, may be having a direct effect on BP.

Our analyses also suggested that sulfur may be associated with higher SBP, while chloride was associated with lower newborn SBP, though these results were not statistically significant. The results for DBP point also to higher DBP in association with sulfur and arsenic and lower DBP in association with copper, lead, and silicon, even though the estimates were not statistically significant.

This is one of the few studies that has dealt with multiple correlated PM component exposures and health outcomes by applying variable selection methods such as adaptive LASSO and BKMR. We found that both methods identified important elements but with some differences. BKMR selected fewer components than adaptive LASSO, even though these components were included in the adaptive LASSO selection. BKMR has the ability to fit flexible functions of the exposures via the Gaussian kernel, allowing for nonlinear relationship between the exposures and the outcome. Notably, BKMR showed no deviation from linearity. The use of these multiple approaches to isolating the specific components associated with BP gives us increased confidence in our findings.

In addition to the study strengths and weakness previously discussed in our van Rossem paper,[12] we had additional challenges related to our use of central site measures of PM elemental exposures. While a strength of our study is improved spatial resolution of estimation of PM exposure, a limitation of our study is the use of temporally and not spatially variable measures of elemental particle exposures. Our underlying assumption is that the temporal variation of the central site monitor reflects the temporal variation at all subject locations. The van Rossem study[12] showed similar PM-related changes in BP regardless of whether we used central site temporally variable or spatiotemporally variable exposure estimates. However, it is possible that our effect estimates for PM-associated elemental exposures with BP would have been more precise, if we had less exposure misclassification. In addition, given that there are known differences in the intraurban spatial variation of $PM_{2.5}$ components,[59] assuming spatially homogeneous temporal variation of the PM components might be more appropriate for some components than others. This scenario would result in exposure error that varies across components, which would bias results toward the null in most realistic scenarios.[60]

A limitation of our study is that our cohort is predominantly composed of White and educated mothers, and it is not possible to examine whether a more racially/ethnically and socioeconomically diverse population yield different results. A Boston study[13,15] of a more socioeconomically disadvantaged and racially/ethnically diverse population found that maternal pollution exposures were associated with higher BP in later childhood; they did not assess PM component associations, nor did they have neonatal BP measures. Our potential to test for effect modification in this cohort of predominantly White and educated mothers was limited. It would be valuable, in future birth cohort studies, to assess whether either exposures or BP responses differed for neonates and children from disadvantaged neighborhoods.

Another limitation of the study is the investigation of multiple lags for multiple pollutants, which could present a multiple testing concern. We were not interested in the formal significance of the associations but on the overall pattern of the associations and the precision of the effect estimates. In addition, we used variable selection methods to reduce the impact of multiple testing.

A great strength of this paper and our statistical approach is that we overcame the challenges of simultaneous consideration of effects of multiple elements and demonstrated the robustness of our nickel and zinc associations with BP, regardless of statistical method. In addition, we addressed the potential for unmeasured temporal confounding by using the negative control method.

To the best of our knowledge, this is the first study to examine the short-term effects of particle components on newborn SBP and DBP, and to apply variable selection methods to choose which $PM_{2.5}$ components were associated with newborn SBP and DBP. Our results suggest that prenatal exposures to PM components, and particularly nickel, may increase newborn SBP and DBP.

As childhood hypertension has been found to be strong predictor of adult hypertension and cardiovascular disease, in later life, PM component–associated increases in newborn BP could potentially contribute to an increase health risks at older ages.[61-63] Better understanding of the sources as well as the specificity of action of the responsible PM constituents could lead to more targeted and effective regulations.

ARTICLE INFORMATION

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Affiliations

From the Department of Environmental Health (A.Z., H.L.-G., J.D.S., P.K., D.R.G.) and Department of Biostatistics (B.A.C.), Harvard School of Public Health, Boston, MA; Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (L.v.R.); Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA (S.L.R.-S., E.O.); Department of Geography and Environmental Development, Ben-Gurion University of the Negev, Beer Sheva, Israel (I.K.); Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (J.D.S., D.R.G.); Biostatistics Unit, Kaiser Permanente Washington Health Research Institute, Seattle, WA (J.F.B.); and Department of Biostatistics, University of Washington, Seattle, WA (J.F.B.).

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Disclosures

None.

Supplementary Material

Data S1
Tables S1–S2
Figure S1–S4

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Additional information on LASSO and BKMR are provided below.

Least absolute shrinkage and selection operator (LASSO)

We applied the adaptive *least absolute shrinkage and selection operator* (LASSO) method to select important components from the $PM_{2.5}$ elemental components that were associated with our outcome. The LASSO is a regression shrinkage and selection approach that can be used to select important predictors from a large list of correlated predictors.

The method applies a penalty to the regression coefficients by minimizing the sum of squared errors subject to the sum of the absolute values of the coefficients being less than a constant [30]. The adaptive LASSO is an extension of the LASSO that uses weights for penalizing different coefficients in the penalty to achieve asymptotical normality and consistent selection.[31,32]

In the adaptive LASSO model we included the fixed covariates that we adjusted for in the ordinary regression models outlined above. We applied the above penalty term to the $PM_{2.5}$ components in the models, but not the adjustment variables. We selected the model with the minimum cross validation error, which yields a model result in which some coefficients are shrunk exactly to zero and some are non-zero. We then selected the components with non-zero coefficients. For this analysis we used the glmnet package in R version 3.5.3.

Bayesian kernel machine regression (BKMR).

Bayesian kernel machine regression (BKMR) is a joint estimation and variable selection approach that flexibly identifies important components within a multi-pollutant mixture. This method has been previously applied to assess the joint effect of in utero exposure to arsenic, manganese, and lead on children's neurodevelopmental outcomes[22] and in a toxicology study of air pollution mixtures and hemodynamics [33]

In this approach, the health outcome is regressed on a flexible function of the collection of components of interest. The form of the function is modeled via the use of a kernel, which is a matrix of pair-wise distances between each observation in the exposure space. BKMR[33] uses a Gaussian kernel function, which allows for the estimation of potentially nonlinear and non-additive exposure–response function for a set of correlated exposures. Taking a Bayesian approach to model fitting, the approach also incorporates a variable selection feature, which yields importance scores for each exposure defined as the posterior probability that an exposure should be included in the model. The resulting Bayesian credible intervals account for the uncertainty associated with both the selection of exposures in the model and estimation of the exposure-response function. In situations when mixture components are highly correlated, the data may not be able to distinguish among these correlated components, and one can apply a hierarchical variable selection approach, which incorporates information on the structure of the mixture into the model (grouped variable selection). From the fitted model, one can estimate a variety of summary statistics such as the posterior inclusion probability (PIP) for each of the components, as well as visualizations of different cross-sections of the exposure-response surface. This method is implemented in the BKMR R package (https://jenfb.github.io/BKMR/overview.html)[34].

The BKMR model is: $Y_i = h(X_i) + \beta_T Z_i + e_i$

where Z_i is the matrix of the fixed adjustment variables as defined in our main model, and X_i is the matrix of the components. The function h is an exposure–response function that allows for nonlinearity and/or interaction among the mixture components.

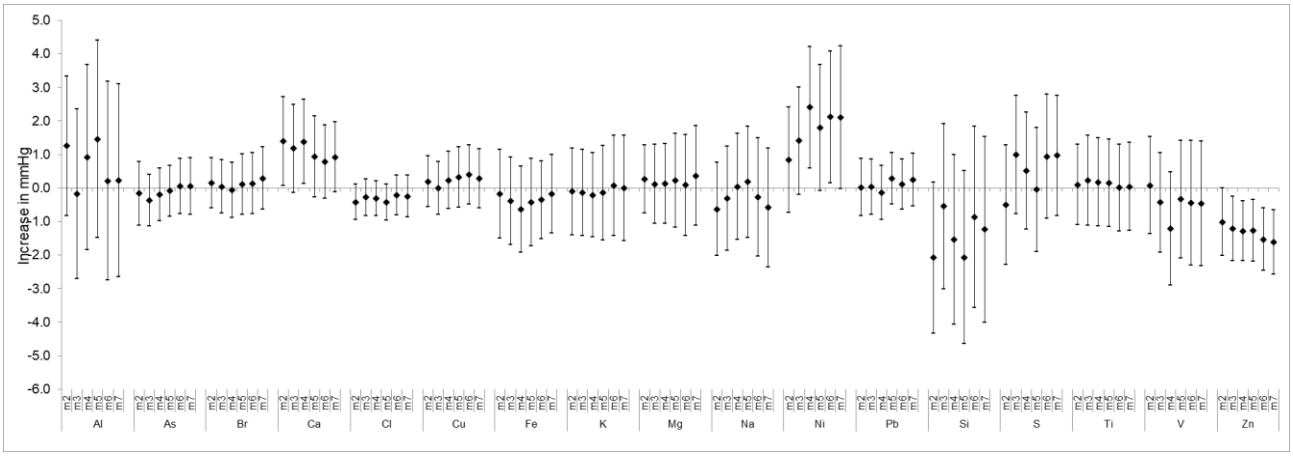
Table S1. Correlations between the PM2.5 components for the two days moving average.

	Two days moving averages																	
	$PM_{2.5}$	**Al**	**Si**	**K**	**Ca**	**Ti**	**Fe**	**Mg**	**S**	**As**	**Cu**	**Zn**	**Br**	**Pb**	**V**	**Ni**	**Na**	**Cl**
$PM_{2.5}$	1	0.34	0.16	0.60	0.22	0.31	0.33	0.46	0.78	0.17	0.17	0.14	0.37	0.21	0.27	0.16	0.48	-0.06
Al	0.34	1	0.93	0.58	0.57	0.73	0.61	0.51	0.43	0.09	0.13	0.02	0.14	0.22	0.05	-0.03	0.37	-0.05
Si	0.16	0.93	1	0.48	0.61	0.72	0.59	0.43	0.19	0.02	0.11	0.03	0.07	0.19	0.02	-0.05	0.22	-0.04
K	0.60	0.58	0.48	1	0.36	0.52	0.54	0.42	0.49	0.15	0.22	0.19	0.46	0.32	0.29	0.26	0.43	0.04
Ca	0.22	0.57	0.61	0.36	1	0.53	0.59	0.31	0.19	-0.01	0.20	0.16	0.14	0.21	0.24	0.12	0.26	0.10
Ti	0.31	0.73	0.72	0.52	0.53	1	0.66	0.40	0.31	0.06	0.22	0.15	0.23	0.19	0.12	0.06	0.23	-0.07
Fe	0.33	0.61	0.59	0.54	0.59	0.66	1	0.31	0.32	0.05	0.32	0.26	0.30	0.24	0.34	0.31	0.24	-0.05
Mg	0.46	0.51	0.43	0.42	0.31	0.40	0.31	1	0.57	0.15	0.08	0.06	0.29	0.24	0.18	0.07	0.71	0.16
S	0.78	0.43	0.19	0.49	0.19	0.31	0.32	0.57	1	0.24	0.13	0.10	0.35	0.19	0.22	0.11	0.65	-0.08
As	0.17	0.09	0.02	0.15	-0.01	0.06	0.05	0.15	0.24	1	0.04	-0.01	0.04	0.18	0.04	0.00	0.25	0.01
Cu	0.17	0.13	0.11	0.22	0.20	0.22	0.32	0.08	0.13	0.04	1	0.19	0.24	0.18	0.19	0.18	0.06	0.00
Zn	0.14	0.02	0.03	0.19	0.16	0.15	0.26	0.06	0.10	-0.01	0.19	1	0.26	0.29	0.26	0.29	0.06	0.05
Br	0.37	0.14	0.07	0.46	0.14	0.23	0.30	0.29	0.35	0.04	0.24	0.26	1	0.20	0.35	0.34	0.36	0.15
Pb	0.21	0.22	0.19	0.32	0.21	0.19	0.24	0.24	0.19	0.18	0.18	0.29	0.20	1	0.18	0.17	0.26	0.18
V	0.27	0.05	0.02	0.29	0.24	0.12	0.34	0.18	0.22	0.04	0.19	0.26	0.35	0.18	1	0.84	0.31	0.09
Ni	0.16	-0.03	-0.05	0.26	0.12	0.06	0.31	0.07	0.11	0.00	0.18	0.29	0.34	0.17	0.84	1	0.18	0.06
Na	0.48	0.37	0.22	0.43	0.26	0.23	0.24	0.71	0.65	0.25	0.06	0.06	0.36	0.26	0.31	0.18	1	0.37
Cl	-0.06	-0.05	-0.04	0.04	0.10	-0.07	-0.05	0.16	-0.08	0.01	0.00	0.05	0.15	0.18	0.09	0.06	0.37	1

Table S2. Correlations between the PM2.5 components for the seven days moving average.

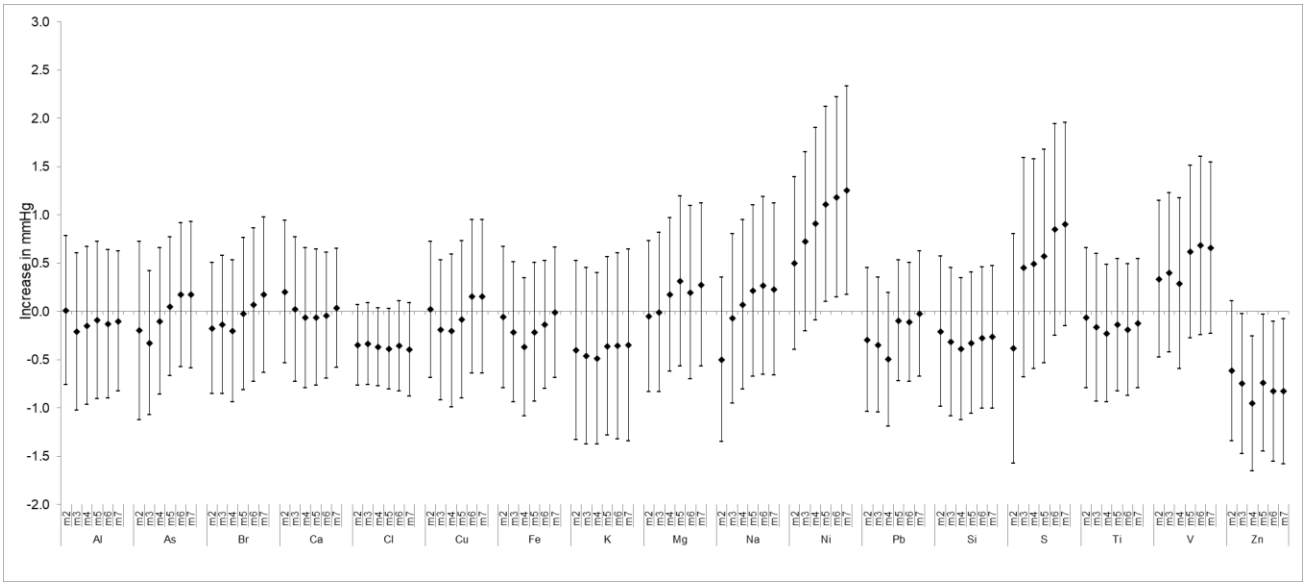
	Seven days moving averages																	
	$PM_{2.5}$	**Al**	**Si**	**K**	**Ca**	**Ti**	**Fe**	**Mg**	**S**	**As**	**Cu**	**Zn**	**Br**	**Pb**	**V**	**Ni**	**Na**	**Cl**
$PM_{2.5}$	1	0.26	0.11	0.48	0.21	0.29	0.29	0.48	0.80	0.15	0.12	0.16	0.33	0.18	0.23	0.08	0.48	-0.02
Al	0.26	1	0.97	0.62	0.60	0.88	0.61	0.65	0.35	0.04	0.01	-0.07	0.08	0.20	0.00	-0.09	0.38	0.04
Si	0.11	0.97	1	0.58	0.63	0.86	0.61	0.56	0.15	-0.03	0.02	-0.09	0.02	0.16	-0.01	-0.08	0.26	0.05
K	0.48	0.62	0.58	1	0.44	0.63	0.57	0.49	0.34	0.12	0.16	0.27	0.47	0.35	0.30	0.30	0.44	0.12
Ca	0.21	0.60	0.63	0.44	1	0.62	0.56	0.36	0.15	-0.05	0.16	0.06	0.06	0.14	0.22	0.03	0.29	0.21
Ti	0.29	0.88	0.86	0.63	0.62	1	0.69	0.58	0.31	0.02	0.10	0.03	0.18	0.17	0.09	-0.01	0.30	0.03
Fe	0.29	0.61	0.61	0.57	0.56	0.69	1	0.37	0.25	0.03	0.27	0.18	0.20	0.21	0.31	0.29	0.24	0.07
Mg	0.48	0.65	0.56	0.49	0.36	0.58	0.37	1	0.64	0.17	0.06	-0.01	0.26	0.33	0.10	-0.01	0.77	0.14
S	0.80	0.35	0.15	0.34	0.15	0.31	0.25	0.64	1	0.23	0.03	0.04	0.32	0.19	0.14	-0.02	0.65	-0.07
As	0.15	0.04	-0.03	0.12	-0.05	0.02	0.03	0.17	0.23	1	0.14	0.08	0.03	0.31	0.01	0.07	0.27	0.10
Cu	0.12	0.01	0.02	0.16	0.16	0.10	0.27	0.06	0.03	0.14	1	0.30	0.17	0.22	0.24	0.29	0.09	0.14
Zn	0.16	-0.07	-0.09	0.27	0.06	0.03	0.18	-0.01	0.04	0.08	0.30	1	0.21	0.32	0.36	0.38	0.04	0.06
Br	0.33	0.08	0.02	0.47	0.06	0.18	0.20	0.26	0.32	0.03	0.17	0.21	1	0.11	0.27	0.29	0.38	0.11
Pb	0.18	0.20	0.16	0.35	0.14	0.17	0.21	0.33	0.19	0.31	0.22	0.32	0.11	1	0.14	0.13	0.33	0.17
V	0.23	0.00	-0.01	0.30	0.22	0.09	0.31	0.10	0.14	0.01	0.24	0.36	0.27	0.14	1	0.84	0.31	0.12
Ni	0.08	-0.09	-0.08	0.30	0.03	-0.01	0.29	-0.01	-0.02	0.07	0.29	0.38	0.29	0.13	0.84	1	0.16	0.07
Na	0.48	0.38	0.26	0.44	0.29	0.30	0.24	0.77	0.65	0.27	0.09	0.04	0.38	0.33	0.31	0.16	1	0.37
Cl	-0.02	0.04	0.05	0.12	0.21	0.03	0.07	0.14	-0.07	0.10	0.14	0.06	0.11	0.17	0.12	0.07	0.37	1

Figure S1. Changes in mmHg and 95% CI in newborn systolic blood pressure for an IQR increase in the two to seven-days average of each PM2.5 mass components.



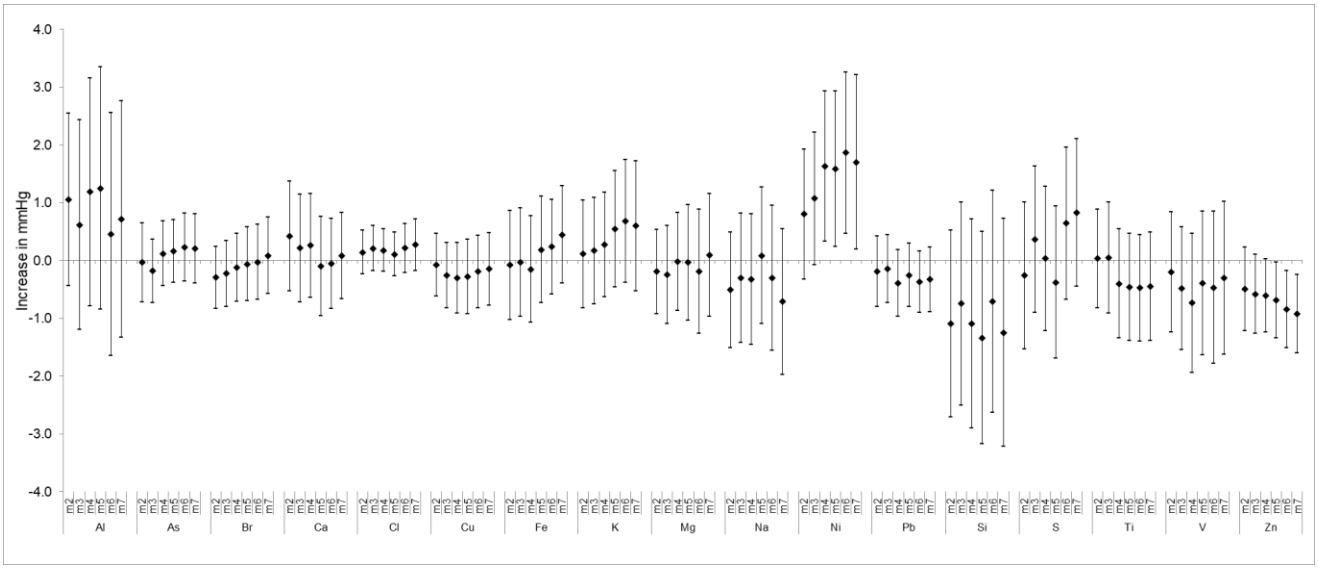
Results from the multi-pollutant model with all components in the same model. All models adjusted for maternal age, 3rd trimester BP, race/ethnicity, education, and income, infant age and state at BP, sine, cosine, temperature, birthweight and $PM_{2.5}$.

Figure S2. Changes in mmHg and 95% CI in newborn systolic blood pressure for an IQR increase in the two to seven-days average of each $PM_{2.5}$ mass components.



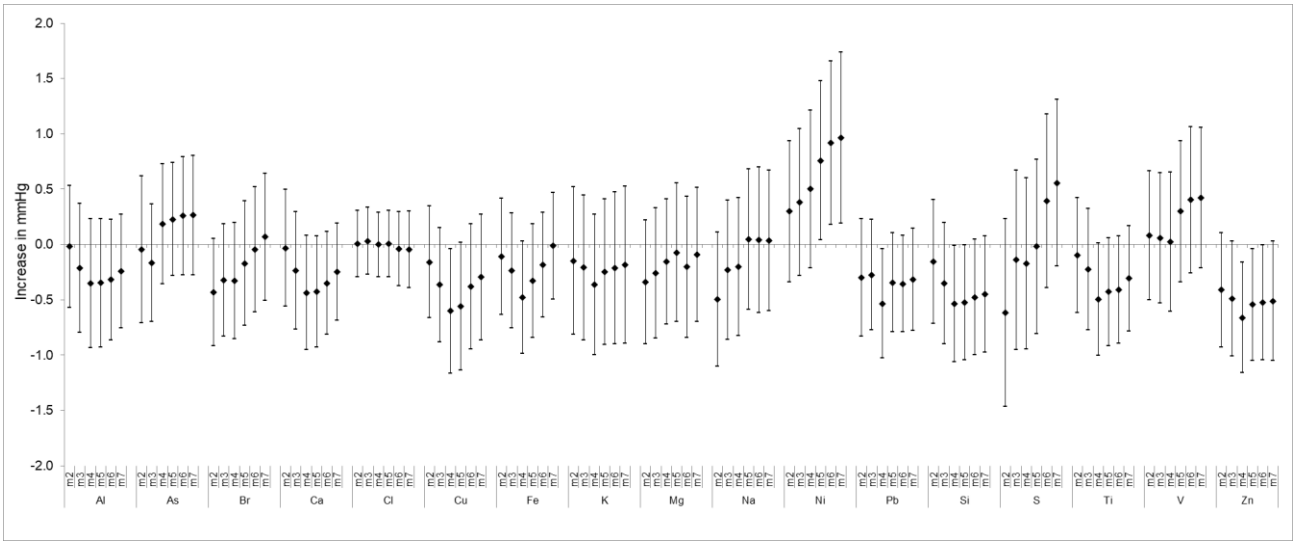
Results for the two-pollutant model including each individual $PM_{2.5}$ component and $PM_{2.5}$. All models adjusted for maternal age, 3rd trimester BP, race/ethnicity, education, and income, infant age and state at BP, sine, cosine, temperature, birthweight and $PM_{2.5}$.

Figure S3. Changes in mmHg and 95% CI in newborn diastolic blood pressure for an IQR increase in the two to seven-days average of each $PM_{2.5}$ mass components.



Results from the multi-pollutant model with all components in the same model. All models adjusted for maternal age, 3rd trimester BP, race/ethnicity, education, and income, infant age and state at BP, sine, cosine, temperature, birthweight and $PM_{2.5}$.

Figure S4. Changes in mmHg and 95% CI in newborn diastolic blood pressure for an IQR increase in the two to seven-days average of each $PM_{2.5}$ mass components.



Results for the two-pollutant model including each individual $PM_{2.5}$ component and $PM_{2.5}$. All models adjusted for maternal age, 3rd trimester BP, race/ethnicity, education, and income, infant age and state at BP, sine, cosine, temperature, birthweight and $PM_{2.5}$.