

## ORIGINAL ARTICLE

# Exploration of the composition and sources of urban fine particulate matter associated with same-day cardiovascular health effects in Dearborn, Michigan

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The objective was to explore associations of chemical components and source factors of ambient fine particulate matter (aerodynamic diameter  $\leq 2.5 \mu\text{m}$ ;  $\text{PM}_{2.5}$ ) with cardiovascular (CV) changes following same-day exposure to ambient  $\text{PM}_{2.5}$ . Twenty-five healthy adults living in rural Michigan were exposed to ambient air in an urban/industrial community for 4 to 5 h daily for five consecutive days. CV health outcomes were measured 1–2 h post exposure. Contributing emission sources were identified via positive matrix factorization. We examined associations between  $\text{PM}_{2.5}$  mass, composition and source factors, and same-day changes in CV outcomes using mixed-model analyses.  $\text{PM}_{2.5}$  mass ( $10.8 \pm 6.8 \mu\text{g}/\text{m}^3$ ), even at low ambient levels, was significantly associated with increased heart rate (HR). Trace elements as well as secondary aerosol, diesel/urban dust and iron/steel manufacturing factors potentially explained the HR changes. However, trace element analysis demonstrated additional associations with other CV responses including changes in blood pressure (BP), arterial compliance, autonomic balance and trends toward reductions in endothelial function. Two factors were related to BP changes (diesel/urban dust, motor vehicle) and trends toward impaired endothelial function (diesel/urban dust). This study indicates composition of  $\text{PM}_{2.5}$  and its sources may contribute to CV health effects independently of  $\text{PM}_{2.5}$  mass.

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## INTRODUCTION

Exposure to ambient fine particulate matter (aerodynamic diameter  $\leq 2.5 \mu\text{m}$ ;  $\text{PM}_{2.5}$ ) is a known risk factor for cardiovascular (CV) morbidity and mortality.<sup>1</sup> As the U.S. Environmental Protection Agency moves toward a multi-pollutant approach to quantify the health consequences of air pollution mixtures, identifying the most harmful emission sources will assist policy makers in developing better targeted air pollution regulations as compared with traditional mass-based PM standards.<sup>2</sup> However, parsing the relative contributions of specific sources to a complex mixture of ambient  $\text{PM}_{2.5}$  and its associated health effects remains challenging.

Only a handful of epidemiological studies have examined associations between source-apportioned  $\text{PM}_{2.5}$  and CV health outcomes. Studies that did include source apportionment data identified an association between CV morbidity and mortality, and exposure to combustion-derived PM including traffic and industrial sources.<sup>3–7</sup> However, most of the epidemiological studies that focused on short-term ambient PM exposure only examined the linkage between hospital records of population health data for clinically apparent outcomes (for example, mortality, myocardial infarction) and not for more subtle biological changes of potential pathophysiological relevance. Moreover, daily air pollution levels

were measured at fixed monitoring sites, often far from residences of exposed individuals. While these studies provide critical information on population exposure, given that daily pollution data from fixed monitoring sites do not necessarily represent the true exposure of any given subject, the exposure assessment findings in these studies may have limited applicability as compared with a controlled clinical human exposure study. Furthermore, measuring 24-hour averaged  $\text{PM}_{2.5}$  concentrations (and those of the underlying constituents) significantly attenuates temporal variability of exposure, obfuscating associations between emission sources/components and health effects.

The primary objective of this study was to examine associations of various  $\text{PM}_{2.5}$  chemical components and sources with same-day CV changes following acute exposure to ambient  $\text{PM}_{2.5}$  in an urban/industrial community. We specifically designed this study to discern the health impact of acute same-day exposures on outcomes of physiological relevance to the CV system, given that health effects of this duration and their associations with source-resolved  $\text{PM}_{2.5}$  have rarely been investigated. The primary “powered” outcomes of the study were blood pressure (BP), heart rate variability (HRV) and vascular diameter changes in response to alterations in  $\text{PM}_{2.5}$  mass. This paper presents pre-defined yet secondary analyses of these data, which by nature means the

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current findings represent exploratory observations that may be useful for designing future studies. By transporting healthy adults living in rural Michigan to an urban/industrial community for acute exposure, the study was able to isolate exposure periods (4–5 h) and accurately measure actual exposures in detail for each subject. As our recent animal toxicological study in Detroit showed that decreased HRV was most strongly associated with motor vehicle/diesel factor during summer months,<sup>8</sup> it was of particular interest to study how a complex urban air shed with multiple combustion sources would affect the CV health of human subjects.

## MATERIALS AND METHODS

### Site Description

An urban exposure site was chosen in Dearborn, Michigan with the highest PM<sub>2.5</sub> levels in the state.<sup>9</sup> Figure 1 shows maps of the Dearborn area and the study site and highlights some of the major PM<sub>2.5</sub> point sources in Wayne County.<sup>10</sup> Because of their proximity, nearby communities are impacted by emissions from heavy motor vehicle traffic and industrial activities including iron-steel manufacturing, refining, sewage sludge incineration and coal-fired utilities along the Detroit River. Figure 1 also includes a wind rose plot of average PM<sub>2.5</sub> concentrations at the study site.

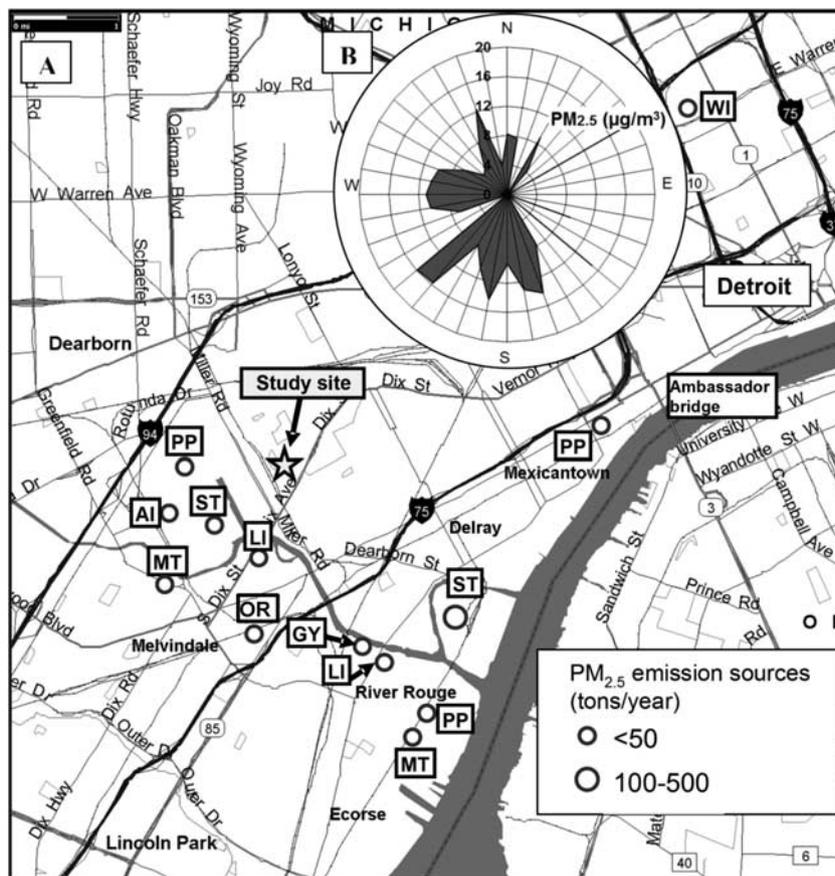
### Study Outline

With approval from the Institutional Review Board of the University of Michigan, we enrolled 25 healthy (age 18–50 years) non-smoking subjects from non-smoking households without known CV disease or risk factors (BP < 140/90 mm Hg; fasting glucose < 126 mg/dl; without diagnosis of or treatment for hyperlipidemia during screening visits). Subjects were not taking any known medications that could alter CV function.

Subjects lived in locations (near Dexter or Tecumseh, Michigan PM monitoring sites) that exhibited background levels of transported regional PM<sub>2.5</sub> typically 5–10 µg/m<sup>3</sup> lower than the exposure site.<sup>11</sup> Subjects were instructed to remain within the region of their residence throughout the study period and were driven to the exposure site by a research assistant for the five consecutive daily exposure periods (Monday to Friday). During the commute to and from the site (40 min, including 36 interstate highway miles), subjects wore a properly fitted N-95 mask (3M model 1860) to reduce exposure to traffic-related particles. A similar mask recently proved effective in removing almost all PM down to a few nanometers during exposure to diesel and traffic-related PM.<sup>12</sup> During each exposure, subjects rested comfortably in chairs at the same spot (under an open-air shelter from the direct sun and rain) for 4 to 5 h. Exposures began at 0900 or 1000 hours depending upon subject availability and ended at 1400 hours each day.

### Exposure Measurement

**Sampling methods.** At a location ~35 feet from the subjects, ambient PM<sub>2.5</sub> samples during each daily exposure period (totaling sixty-nine samples) were collected on 47-mm Teflon filters (Gelman Sciences) during two summers (22 June 2009 to 28 August 2009 and 14 June 2010 to 16 July 2010). A vacuum pump moved air through a Teflon-coated cyclone inlet (URG) at 16.7 l/min. The volume of air was determined using a calibrated dry test meter (Schlumberger). To provide enough statistical power for receptor models, a further 69 ambient PM<sub>2.5</sub> samples were collected over 8-hour periods using a dichotomous sampler equipped with a 2.5-µm size-selective inlet and were incorporated into the PMF analysis. These additional samples were collected over three 8-hour periods per day in August of 2009 (10 August 2009 to 20 August 2009) and July 2010 (7 July 2010 to 22 July 2010) (22% of these samples overlapped with the exposure periods). Ambient concentrations of organic carbon (OC) and elemental carbon (EC) were measured via a semi-continuous OC-EC field analyzer (Sunset laboratory) operated by the Michigan Department of



**Figure 1.** (A) A Dearborn area map showing the location of the sampling site and major industrial sources for PM<sub>2.5</sub> in Wayne and Monroe Counties, Michigan (USEPA-NEI, 2008 (AI: auto industries, GY: gypsum industries, LI: lime industries, OR: oil refineries, MT: metal processing; PP: coal-fired power plants, ST: iron/steel industries, WI: waste incinerator). (B) A wind rose plot of average PM<sub>2.5</sub> concentrations at the study site.

Environmental Quality (MIDEQ). However, this instrument was inoperable during parts of the study, resulting in 21% of the OC-EC dataset (29 out of 138 samples) being unavailable.

**Analytical methods.** Gravimetric determinations were made using a microbalance (MT-5 Mettler) in a temperature/humidity-controlled Class 100 clean laboratory and followed the Federal Reference Method.<sup>13</sup> PM samples collected on Teflon filters were wetted with ethanol and extracted in 10% nitric acid solution. Extracts were then analyzed for a suite of trace elements using inductively coupled plasma-mass spectrometry (ELEMENT2, Thermo Finnigan). This analysis method incorporated daily quality assurance and quality control measures including field blanks, Milli-Q blanks, replicate analyses and external standards (Online Supplementary Table 1).

**CV outcomes.** Health outcomes were measured at the University of Michigan Research Vascular Laboratory starting at 1500 hours on each day of exposure, with subjects fasting for 7 h before testing. The testing sequence was the same for each patient and all visits. Protocol details are provided elsewhere.<sup>14</sup>

After resting supine for 10 min, subject's BP and heart rate (HR) were measured (Omron 780) in triplicate on their right arm. Next, 6 min of supine resting HRV was recorded and later analyzed for time and frequency domain metrics (evo Holter monitor; Pathfinder software; Spacelabs). Afterward, right radial artery tonometry was performed and pulse wave analyses were used to calculate aortic hemodynamic profiles. Carotid-to-femoral arterial pulse wave velocity measurements for arterial compliance were next performed (SphygmoCor; AtCor Medical). Microvascular endothelial function and nitroglycerin-mediated dilatation were the final outcomes performed on the right hand using the EndoPAT2000 system (Itamar Medical). Details of these CV measurements are included in Supplementary Material.

**Data analysis.** Models for determining associations between PM<sub>2.5</sub> exposure as well as specific chemical components with each temporally corresponding health outcome were developed using mixed-model approaches. Mixed-models with random parameters were implemented to account for within-subject correlation due to having repeated measures of the same subjects across 5 days. Bayesian Information Criteria were used to assess model fit and to select the best correlation structure for the random parameters. Statistical results present parameter estimates showing the magnitudes of associations and *P*-values demonstrating the strengths of associations in the trends of the exploratory observations.

Major emission sources contributing to ambient PM<sub>2.5</sub> levels in Dearborn were determined via EPA Positive Matrix Factorization (PMF) 3.0. Receptor modeling including PMF has been widely used in source apportionment studies to assess source contributions.<sup>15–18</sup> The sum of the analytical and sampling uncertainty and method detection limit (MDL) were used to calculate the uncertainty (U) assigned to each measured concentration data point as follows:

$$U = \sqrt{(\sqrt{(SC)^2 + (AM)^2} \times (\text{concentration}))^2 + (MDL)^2}$$

(where SC = the uncertainty of sample collection, AM = the uncertainty of analytical measurement). SubMDL values were replaced by half of MDL for the measured data. On the basis of EPA's PMF guidelines<sup>19</sup> and Paatero and Hopke (2003), signal-to-noise ratios were used to determine species categorization. The optimal solution was determined by multiple model runs to examine the effect of the number of factors assigned and via a bootstrapping technique on the range of physically reasonable results where the objective function Q-value does not change substantially.

## RESULTS

Table 1 presents mean health outcomes for all subjects over the entire study period. Fourteen and eleven subjects were enrolled during 2009 and 2010, respectively, and the combined 25 subjects (17 females) had a mean age of  $38 \pm 12$  years. The average exposure duration each day at the study site was  $240 \pm 2$  and  $300 \pm 0.3$  min for summers 1 and 2, respectively.

### Source Characterization During Exposure Periods

The average ambient PM<sub>2.5</sub> concentration across all exposure periods was  $10.8 \pm 6.8 \mu\text{g}/\text{m}^3$ ; averages for individual exposure

**Table 1.** Mean health outcome values (*n* = 25).

|  | Mean ± SD <sup>a</sup> | σ(IQR) <sup>b</sup> |
|--|------------------------|---------------------|
| <i>Microvascular function</i>                |                        |                     |
| RHI  | 2.19 ± 0.38            | 0.4 (0.3–0.5)       |
| Nitroglycerin index                          | 1.69 ± 0.64            | 0.4 (0.1–0.6)       |
| <i>Arterial compliance and hemodynamics</i>  |                        |                     |
| Systolic BP (mm Hg)                          | 117 ± 14               | 5.2 (2.5–6.7)       |
| Diastolic BP (mm Hg)                         | 75 ± 9                 | 3.7 (2.2–4.4)       |
| HR (beats/min)                               | 68 ± 10                | 4.0 (2.9–4.7)       |
| Augmentation Index at HR of 75 beats/min (%) | 15.4 ± 11.9            | 5.5 (2.5–6.6)       |
| Pulse wave velocity (m/s)                    | 6.9 ± 1.3              | 0.6 (0.4–0.8)       |
| <i>Heart rate variability</i>                |                        |                     |
| SD of normal-to-normal beats (ms)            | 63.2 ± 27.6            | 12.4 (7.5–15.9)     |
| High frequency peak (ms <sup>2</sup> )       | 1231 ± 1721            | 586 (181–1021)      |
| Low frequency peak (ms <sup>2</sup> )        | 1194 ± 1287            | 753 (117–766)       |
| Ratio low to high frequency peaks (LF/HF)    | 2.1 ± 1.7              | 1.2 (0.6–1.7)       |

Abbreviations: BP, blood pressure; HR, heart rate; RHI, reactive hyperemia index.  
<sup>a</sup>Values are the mean and SD of the health measures for all subjects determined over all 5 days of the exposure period.  
<sup>b</sup>Values are σ, the average of within-subject SD and interquartile range for all subjects over 5 days of the exposure period.

periods ranged from 0.9 to 29.0  $\mu\text{g}/\text{m}^3$ . Concentrations of major components and trace elements measured during daily exposure periods are shown in Table 2. Although the average mass concentration during this study was about half of our previous summer study in Detroit ( $23 \pm 14 \mu\text{g}/\text{m}^3$ ), many elements measured during the exposure study in Dearborn were comparable (e.g., Pb, Ti, Mn) or even higher (e.g., Ce, Cu, Cd, Mg, Ca, Ba).<sup>20</sup>

For the first attempt, five factors were extracted from the 69 exposure study period samples (Online Supplementary Table 2). However, one factor was loaded with elements that appeared to be associated with both diesel-powered and gasoline-powered vehicle factors. As described in the methods section, additional samples were pooled to boost the total number of samples to 138 in an attempt to separate the two factors. With 138 samples, PMF then was able to extract six source factors including two separate vehicle factors (Figure 2; Online Supplementary Table 2). Six factors were determined to be optimal based on the distribution of residuals and prediction of total mass ( $R^2 = 0.80$ ). The FPEAK value was set at zero, where the value of robust Q reaches a global minimum.

The first factor had statistically significant loadings of EC, Ba, Mg, Al, P, Ca, Mn, Fe, Zn, K, Pb and Ti. This factor had trace element components indicating a major diesel vehicle contribution. Ba, Fe and Mn are present in brake wear dust, and Zn is present in tire wear dust and in tailpipe emissions due to its use in motor oil.<sup>21,22</sup> High loadings of crustal elements including Ca, Al, Mg and K suggest that this factor included vehicle exhaust and entrained road/urban dust. The closest major interstate is about one mile from the site, and several active trucking terminals are within one mile north of the site, with several hundred trucks loading and unloading everyday. Thus, it is not surprising that the impact from the trucking terminals presents as a mixture of vehicle exhaust and high levels of urban dust. In addition, the OC/EC ratio for diesel engines is higher when idling than when under heavy load.<sup>23</sup> This is likely why our OC/EC ratio is higher than values from other diesel emission studies. Finally, sulfur was not included in this factor, possibly due to the ultra-low sulfur diesel fuel mandated for on-road vehicles in 2007.

**Table 2.** Ambient PM<sub>2.5</sub> and elemental concentrations of during exposure periods.

|                   | Mean ± SD (μg/m <sup>3</sup> ) |
|-------------------|--------------------------------|
| PM <sub>2.5</sub> | 10.8 ± 6.79                    |
| Organic carbon    | 5.42 ± 1.54                    |
| Elemental carbon  | 0.488 ± 0.265                  |
| Elements          | Mean ± SD (ng/m <sup>3</sup> ) |
| Na                | 220 ± 72.6                     |
| Mg                | 51.2 ± 32.7                    |
| Al                | 85.5 ± 30.4                    |
| P                 | 24.2 ± 6.22                    |
| S                 | 957 ± 806                      |
| K                 | 124 ± 82.8                     |
| Ca                | 332 ± 121.8                    |
| Ti                | 1.830 ± 0.794                  |
| V                 | 0.810 ± 1.103                  |
| Cr                | 15.52 ± 6.06                   |
| Mn                | 7.61 ± 6.89                    |
| Fe                | 199.3 ± 149.6                  |
| Co                | 0.1043 ± 0.0519                |
| Ni                | 2.23 ± 2.32                    |
| Cu                | 15.55 ± 25.6                   |
| Zn                | 42.0 ± 39.0                    |
| As                | 0.630 ± 0.515                  |
| Se                | 0.932 ± 0.981                  |
| Rb                | 0.385 ± 0.450                  |
| Sr                | 1.384 ± 1.105                  |
| Mo                | 0.696 ± 0.407                  |
| Ag                | 0.370 ± 0.812                  |
| Cd                | 1.017 ± 0.613                  |
| Sb                | 0.728 ± 0.613                  |
| Ba                | 8.92 ± 2.65                    |
| La                | 0.205 ± 0.453                  |
| Ce                | 0.1269 ± 0.0833                |
| Pb                | 9.83 ± 6.95                    |

The second factor had the highest loadings of S and Se and moderate loadings of OC and EC. Among all chemical components, S and Se had the two highest correlations with PM<sub>2.5</sub> mass (0.81 and 0.65, respectively; Online Supplementary Table 3). This factor likely includes emissions from regional (rather than local) coal-fired utility boilers as they have been associated with the highest contributions to sulfur particles and SO<sub>2</sub> in the Midwestern region.<sup>18,24</sup> However, because coal combustion is believed to be a minor contributor to the OC fraction of ambient PM<sub>2.5</sub>,<sup>25</sup> this factor may include secondary sulfate and OC particles from other sources and was identified as a secondary aerosol.

The third factor appears to be associated with refinery emissions with high loadings of La and Ce. Rare-earth elements including La and Ce are used extensively in oil refinery processes for catalytic cracking reactions.<sup>26</sup> A large oil refinery is located one mile from the study site.

The fourth factor had the highest OC, Ba, Al, P and K concentrations and elevated levels of EC, S, Ca and Zn, and appears to represent gasoline-powered vehicles or traffic-related particles.<sup>21</sup> As discussed for the diesel-powered vehicle factor, moderate/high loadings of crustal elements including Al, K and Ca suggest that this factor also is likely to include entrained road/urban dust. Furthermore, Ba and Zn are present in tire and brake wear dust as well as in tailpipe emissions due to its use in motor oil.<sup>21,22</sup>

The fifth factor, iron/steel manufacturing, was associated with the highest Fe, Mn and Zn concentrations and elevated concentrations of Pb. The EPA has reported that several large iron/steel manufacturing facilities in SW Detroit are major sources of ambient PM<sub>2.5</sub> in Wayne County.<sup>9</sup>

Finally, the sixth factor was characterized as incinerators and metal processing facilities due to the highest loadings of Pb and Cd, which are regarded as signatures for incineration.<sup>27</sup> However, this factor is also associated with medium loadings of Mo, Al and Fe. Mo is often used as an alloying agent,<sup>28</sup> and these metals along with Pb and Cd are likely associated with several metal processing and auto-industries around the site (Figure 1).

Figure 3 shows average major source factor contributions to ambient PM<sub>2.5</sub> during the exposure periods. The contribution from the secondary aerosol factor was the highest, followed by gasoline and diesel vehicles.

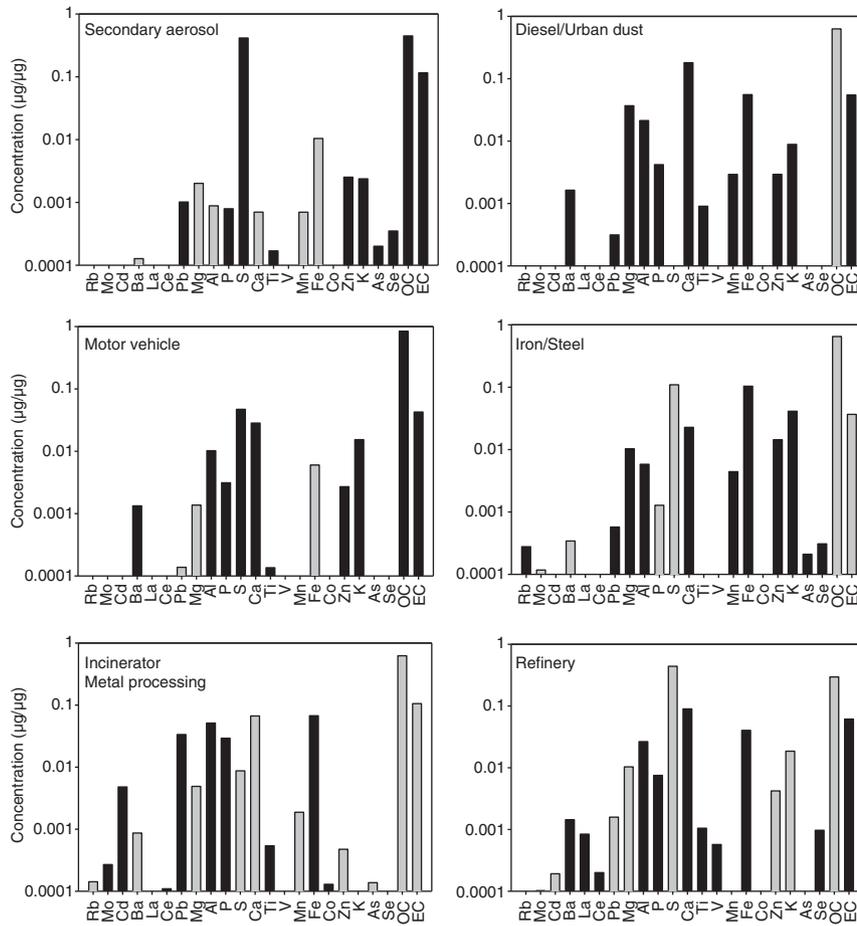
Associations Between PM<sub>2.5</sub> Mass/Components and CV Outcomes  
PM<sub>2.5</sub> mass concentration was significantly associated with increased HR as shown in Table 3. To identify PM<sub>2.5</sub> components potentially responsible for the HR increase, we evaluated its relationship with specific components. Indeed, increased HR was positively associated with several individual elements (Table 4). While PM<sub>2.5</sub> mass alone was not associated with other health outcomes, we further explored the possibility that they might be altered by specific underlying PM<sub>2.5</sub> components. Two elements (Mg and Fe) showed trends toward associations with decreased reactive hyperemia index (RHI), a metric of impaired microvascular endothelial-dependent vasodilation (Table 4). We also observed other significant associations between specific elements and other health outcome changes not associated with PM<sub>2.5</sub> mass alone (Online Supplementary Table 4). Overall, we did not observe significant associations with any health outcome and either EC or OC.

#### Associations Between PM<sub>2.5</sub> Source Factors and CV Outcomes

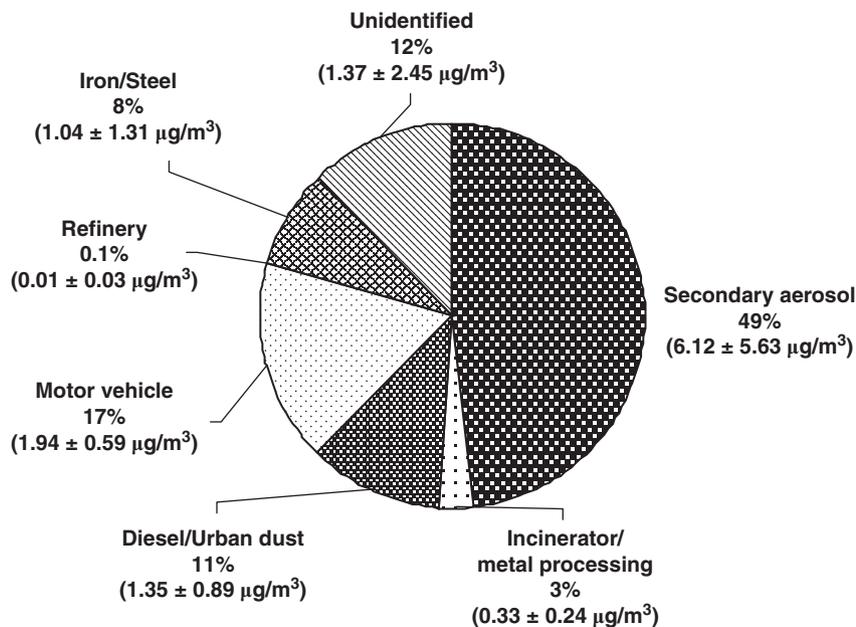
To evaluate sources potentially responsible for changing health outcomes in a more comprehensive and cogent manner beyond analyzing the numerous associations with the individual PM components, we evaluated changes in health outcomes with concentrations of factors determined by source apportionment methods (Table 5). Of the six factors extracted from PMF, secondary aerosol, diesel/urban dust and iron/steel manufacturing source factors were also positively associated with HR changes. However, we uncovered additional associations not observed in previous analyses. Diesel/urban dust and motor vehicle factors were each related to BP changes (in an opposite manner), while the diesel/urban dust factor was additionally related to trends toward impaired microvascular endothelial function (decreased RHI).

## DISCUSSION

Although source apportionment and epidemiology have been combined to investigate PM health effects at a population level, to our knowledge this is the first study to evaluate associations between subdaily (4–5 h) ambient urban pollution exposures including both chemical components and sources — as measured for each individual subject — and surrogate CV outcomes of pathophysiological relevance. Exposure to higher PM<sub>2.5</sub> mass concentrations was associated with increased HR during the same day, as we have previously shown in the Detroit area using personal monitoring.<sup>29</sup> However, this study provides additional unique insights. We demonstrated several further associations between specific chemical components and not only increased HR, but also alterations in other health outcomes. We also observed associations between certain source factors and changes in other health outcomes not related to simple PM<sub>2.5</sub> mass levels. The findings underscore the importance of evaluating specific components and sources of PM<sub>2.5</sub> in health outcome studies, as extant pollution-related adverse effects may be obfuscated when exposure assessment relies solely upon PM<sub>2.5</sub> mass.



**Figure 2.** Factor profiles resolved for the ambient PM<sub>2.5</sub> sources. Factor profiles resolved from the positive matrix factorization (PMF) analysis of 138 ambient filter samples collected during the summers of 2009 and 2010 (Black bars: significant based on the fifth percentile of the bootstrap uncertainty distribution analysis. Gray bars: not significant/high uncertainty).



**Figure 3.** Average factor contributions to ambient PM<sub>2.5</sub> during the summers of 2009 and 2010.

The average PM<sub>2.5</sub> mass concentration during the exposure periods was unexpectedly lower ( $10.8 \pm 6.8 \mu\text{g}/\text{m}^3$ ) than what we recorded for previous summer exposure studies. This was partly due to the timing of the exposure periods, which started between 0900 and 1000 hours and ended between 1300 and 1400 hours each day. These exposure periods typically exhibit lower concentrations than early in the morning, when elevated rush-hour vehicle emissions and local fossil-fuel combustion emissions are often confined and concentrated within a shallow boundary layer.

Despite the observed low PM<sub>2.5</sub> mass concentrations, there were several important associations between PM<sub>2.5</sub> components, sources and CV health outcomes. First, in addition to PM<sub>2.5</sub> mass concentration, increased HR was also associated with multiple elemental components and secondary aerosol, iron/steel

manufacturing and diesel/urban dust factors. That the secondary factor and PM<sub>2.5</sub> mass concentration were both associated with increased HR is not surprising, given that secondary aerosol comprises a major mass fraction of PM<sub>2.5</sub> and that previous studies have shown that elevated levels of sulfate particles may adversely affect CV health including autonomic function.<sup>30</sup> The observed associations between diesel/urban dust and increased HR/decreased RHI are consistent with other studies, which confirm that ambient PM can impair vascular function, particularly after exposure to traffic-related PM and combustion-derived PM.<sup>4,31,32</sup> The impact from the iron/steel manufacturing factor was somewhat expected, given the proximity of the nearest source to our study site (Figure 1). However, in contrast with previous small panel studies such as in Boston<sup>33</sup> or Mexico City,<sup>34</sup> there were no statistically significant associations between HRV and PM<sub>2.5</sub> components or sources. This may be due to differences in the specific study design including the studied subjects and the number of repeated measures, or simply the lower pollution levels observed during our study.

Most of the elemental species that were correlated with increased HR and/or decreased RHI were also highly loaded in specific source categories, supporting their selection as source tracers. For example, of those elements that were significantly associated with the health outcomes, S, Se, As and Ti were significant elements in the secondary aerosol factor profile based on the bootstrap uncertainty distribution analysis (Figure 2). However, the associations among individual chemical components, sources and CV health outcomes were not always consistent. For example, despite the statistically significant associations between the diesel/urban dust factor and increased HR and decreased RHI, EC — a signature component for diesel factor — was not associated with increased HR. This may be partly due to the missing OC-EC data as described in the Methods section. Therefore, caution is warranted in interpreting these associations between source factors and PM components, and health outcomes.

Of the six sources examined, the diesel/urban dust factor was most consistently associated with changes in RHI, Systolic BP and HR. While it is difficult to infer whether the diesel/urban dust factor is most important for the overall PM<sub>2.5</sub> association with the observed CV outcomes in Dearborn, many of our results are consistent with other recent studies that concluded that combustion-related PM is more harmful to health than non-combustion-related PM. For example, in a recent review<sup>35</sup> the authors concluded that there was sufficient evidence to support a causal

**Table 3.** Associations between cardiovascular outcomes and same-day PM<sub>2.5</sub> exposure at Dearborn.

| Outcome variable                                | $\beta$ -estimate <sup>a</sup> | P-value |
|---|--------------------------------|---------|
| <i>Microvascular function</i>                   |                                |         |
| RHI   | -0.12                          | 0.09    |
| Nitroglycerin index                             | -0.11                          | 0.31    |
| <i>Arterial compliance and hemodynamics</i>     |                                |         |
| Systolic BP (mm Hg)                             | -0.46                          | 0.73    |
| Diastolic BP (mm Hg)                            | 0.59                           | 0.42    |
| HR (beats/min)                                  | 2.1                            | 0.005   |
| Augmentation index at HR of 75 beats/min (%)    | 0.67                           | 0.61    |
| Pulse wave velocity (m/s)                       | 0.11                           | 0.36    |
| <i>Heart rate variability</i>                   |                                |         |
| SD of normal-to-normal beats (ms)               | -1.16                          | 0.53    |
| High frequency peak power (ms <sup>2</sup> )    | 209.7                          | 0.38    |
| Low frequency peak power (ms <sup>2</sup> )     | 103.1                          | 0.44    |
| Ratio low to high frequency peaks power (LF/HF) | 17.1                           | 0.63    |

Abbreviations: BP, blood pressure; HR, heart rate; RHI, reactive hyperemia index.  
<sup>a</sup>Mixed model association of outcome change per 10  $\mu\text{g}/\text{m}^3$  increase in PM<sub>2.5</sub> level during the same-day exposure period.

**Table 4.** Associations between chemical components and same-day changes in HR and endothelial function.

| Element | HR (beats/min)                 |                                |         | RHI                            |                                |         |
|---------|--------------------------------|--------------------------------|---------|--------------------------------|--------------------------------|---------|
|         | $\beta$ -estimate <sup>a</sup> | $\beta$ -estimate <sup>b</sup> | P-value | $\beta$ -estimate <sup>a</sup> | $\beta$ -estimate <sup>b</sup> | P-value |
| As      | 2.16                           | 1.14                           | 0.009   |                                |                                |         |
| Ca      | 0.0088                         | 1.12                           | 0.010   |                                |                                |         |
| Ce      | 12.12                          | 0.85                           | 0.049   |                                |                                |         |
| Fe      | 0.0069                         | 1.14                           | 0.008   | -0.00048                       | -0.079                         | 0.061   |
| Mg      | 0.037                          | 1.26                           | 0.006   | -0.0023                        | -0.079                         | 0.076   |
| Mn      | 0.12                           | 0.87                           | 0.043   |                                |                                |         |
| P       | 0.21                           | 0.98                           | 0.043   |                                |                                |         |
| Rb      | 1.87                           | 0.81                           | 0.060   |                                |                                |         |
| S       | 0.0018                         | 1.46                           | 0.008   |                                |                                |         |
| Se      | 1.12                           | 1.12                           | 0.009   |                                |                                |         |
| Ti      | 1.2826                         | 1.06                           | 0.012   |                                |                                |         |

Abbreviations: BP, blood pressure; HR, heart rate; RHI, reactive hyperemia index.

<sup>a</sup>Mixed-model association of outcome change (HR, RHI) per 1 ng/m<sup>3</sup> increase in metal concentration during the same-day exposure period. Only results with P-values < 0.1 are shown.

<sup>b</sup>Results shown per SD increase in metal concentration.

**Table 5.** Associations between PM<sub>2.5</sub> levels by source identification and same-day changes in health outcomes.

| Source            | RHI<br>β-estimate <sup>a</sup><br>β-estimate <sup>b</sup> | P-value | Systolic BP<br>β-estimate <sup>a</sup><br>β-estimate <sup>b</sup> | P-value | Heart rate<br>β-estimate <sup>a</sup><br>β-estimate <sup>b</sup> | P-value |
|-------------------|---|---------|---|---------|--|---------|
| Secondary aerosol |   |         |   |         | 0.25 <sup>a</sup><br>1.4 <sup>b</sup>                            | 0.007   |
| Diesel/urban dust | -0.086 <sup>a</sup><br>-0.076 <sup>b</sup>                | 0.072   | -1.58 <sup>a</sup><br>-1.40 <sup>b</sup>                          | 0.018   | 1.3 <sup>a</sup><br>1.2 <sup>b</sup>                             | 0.006   |
| Motor vehicle     |   |         | 2.12 <sup>a</sup><br>1.25 <sup>b</sup>                            | 0.048   |  |         |
| Iron/steel        |   |         |   |         | 0.59 <sup>a</sup><br>0.79 <sup>b</sup>                           | 0.072   |

Abbreviations: BP, blood pressure; HR, heart rate; RHI, reactive hyperemia index.

<sup>a</sup>Mixed-model association of outcome change per 1 μg/m<sup>3</sup> increase in PM<sub>2.5</sub> by source identification during the same-day exposure period. Only results with P-values <0.1 are shown.

<sup>b</sup>Results shown per SD increase in PM<sub>2.5</sub> by source identification.

relationship between exposure to traffic-related air pollution and CV mortality and morbidity. In addition, another recent review by Grahame *et al.*<sup>31</sup> reported growing observations that mobile and diesel sources or elemental carbon sources may be responsible for acute CV outcomes in multiple locations including Los Angeles, Boston and New York.

Given the exploratory nature of this study, we are careful not to over interpret its potential health relevance. In general, these observations support that exposures to ambient air pollution from various sources can differentially impact CV physiology. Changes in CV health effects were small, as would be expected given the small study, healthy nature of the subjects and low levels of ambient pollutant concentrations in Michigan. Nonetheless, changes in HR and BP may represent pollutant-mediated alterations in autonomic balance favoring sympathetic activity. These small perturbations will be inconsequential for healthy people, but might help explain linkages between PM and CV events in large epidemiological studies, and if they occur population-wide and to highly susceptible individuals, autonomic imbalance and increased HR (or BP) are established markers of increased CV risk.<sup>1</sup> The immediate impact of the changes in RHI is less certain. However, the pollutants associated with reduced microvascular endothelial function might impair coronary flow reserve among people with established coronary artery disease, thus promoting cardiac ischemia.

It is important to recognize a few limitations. As this was a secondary analysis of a previous study,<sup>14</sup> we performed multiple comparisons, which may produce spurious associations. However, we explicitly acknowledge that this study was exploratory and therefore we chose not to statistically correct for the multiple comparisons. Rather, we provide these findings so that future studies can build on them by designing trials with *a priori* defined hypotheses regarding health effects of different PM<sub>2.5</sub> constituents and sources. We also were unable to explore for potential health effects induced during longer lag-periods, such as the possibility for differential responses occurring the day following exposures. Also, the potential impact of gaseous pollutants or temporally co-varying environmental factors (e.g., noise, meteorological parameters) was not fully accounted for in our models. Finally, this was not a mechanistic study, but an exploration of potential surrogate markers of CV risk that might differ among exposure metrics. In this context, we deliberately will not speculate why certain particulate sources or constituents may cause differing health effects. The broad pathways whereby particles can mediate remote CV responses have been described in detail previously.<sup>1</sup> Given our findings, future studies in animal models, toxicological settings and/or controlled human exposures can further explore the potential biological mechanisms underlying the differing CV responses reported in this novel analysis.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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