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Impact of personal and ambient-level exposures to nitrogen dioxide and particulate matter on cardiovascular function

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Abstract

This work explored the association between nitrogen dioxide (NO₂) and PM_{2.5} components with changes in cardiovascular function in an adult non-smoking cohort. The cohort consisted of 65 volunteers participating in the US EPA's Detroit Exposure and Aerosol Research Study (DEARS) and a University of Michigan cardiovascular sub-study. Systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), brachial artery diameter (BAD), brachial artery flow-mediated dilatation (FMD) and nitroglycerin-mediated arterial dilatation (NMD) were collected by in-home examinations. A maximum of 336 daily environmental and health effect observations were obtained. Daily potassium air concentrations were associated with significant decreases in DBP ($-0.0447 \text{ mmHg/ng/m}^3 \pm 0.0132$, $p = 0.0016$, lag day 0) among participants compliant with the personal monitoring protocol. Personal NO₂ exposures resulted in significant changes in BAD (e.g., $0.0041 \text{ mm/ppb} \pm 0.0019$, $p = 0.0353$, lag day 1) and FMD (0.0612 ± 0.0235 , $p = 0.0103$, lag day 0) among other findings.

Keywords

air pollutant concentrations; exposure assessment; particulate matter; epidemiology

Introduction

Numerous human exposure studies or assessments have investigated the variability of ambient and/or personal-based concentrations of NO₂ (nitrogen dioxide) across metropolitan or regional areas (Brauer et al. 1989; Romieu et al. 1996; Burnett et al. 1998; Sarnat et al. 2001, 2006; Schildcrout et al. 2006; Bell et al. 2007; US EPA 2008; Williams et al. 2009). Similar research has been reported for potential PM exposures in the US (Wallace et al. 1985; Evans et al. 2000; Williams et al. 2000a, 2000b, 2000c, 2000c, 2003a, 2003b; Wallace and Williams 2005; Wallace et al. 2006a, 2006b; US EPA 2009; Williams et al. 2009) and Europe (Koistinen et al. 1999; Lai et al. 2004; Neri et al. 2005).

Estimated human exposures to ambient concentrations of PM and NO₂ have been linked with multiple health effects (US EPA 2008, 2009). Recent epidemiological studies have established associations of short-term exposures within select susceptible or general

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Supplementary Material Online
Supplementary Tables S1 and S2.

subpopulations for PM_{2.5} (fine particulate matter) with changes in select cardiovascular (CV) endpoints (Auchincloss et al. 2008; Brook 2008; Schneider et al. 2008; Brook and Rajagopalan 2009, Brook et al. 2009a, 2009b, 2010a, 2010b; He et al. 2010). Little is known about potential NO₂ effects on human health beyond those associated with well established respiratory changes (Romieu et al. 1996; Burnett et al. 1998). The US EPA has recently reported that there is inadequate evidence to infer the presence or absence of a causal relationship between short-term human exposures to NO₂ and cardiovascular effects (US EPA 2008).

The US EPA's recent Detroit Exposure and Aerosol Research Study (DEARS) and the University of Michigan's CV sub-study were observational human exposure and epidemiological investigations into short-term (daily) changes in personal and ambient-based pollutant concentrations and their impact on select CV endpoints (Williams 2005; Williams et al. 2009; Brook et al. 2010a, 2010b). Our first analyses demonstrated that personal-level exposure to PM_{2.5} (i.e., mass concentration) on lag day 1 was associated with an increase in systolic blood pressure (SBP) of 1.4 mmHg (95% CI 0.76–2.06) per 10 µg/m³ among protocol-compliant subjects (Brook et al. 2010a). There were some additional associations of personal-level PM_{2.5} exposures with reductions in brachial artery diameter (BAD) on lag day 2 consistent with arterial vasoconstriction. Ambient PM_{2.5} mass concentration was not related to any CV outcome parameter measured in our cohort. The objective of the current work was to evaluate the effects of exposure to various PM_{2.5} inorganic and organic components and NO₂ on CV function and establish their risk estimates. We report findings on CV outcomes including SBP and diastolic blood pressure (DBP), heart rate (HR), BAD, brachial artery flow-mediated dilatation (FMD), and nitroglycerin-mediated arterial dilatation (NMD). While these health measures are not inclusive of all CV functions reported to be linked to various air pollutant exposures, they provided a low burden, non-invasive approach for investigating a variety of potential physiological mechanisms. The impact of ambient-based or personal-based exposure measurements were investigated relative to health outcomes. In addition, the degree to which the cohort was protocol compliant (wearing of the personal monitoring vest and environmental tobacco smoke [ETS] restrictions) on the resulting risk estimates were determined.

Materials and methods

Field study design and implementation

Detailed descriptions of the overall study design and field implementation of the DEARS and the linked health study have been reported previously (Williams 2005, Williams et al. 2009; Brook et al. 2010a, 2010b; Phillips et al. 2010; Rodes et al. 2010). The field panel study had a number of exposure study objectives associated with intensive personal, residential and community-based exposure monitoring comparisons involving a large number of pollutant species (PM, gases, semi-volatile organics). The US EPA (US EPA 2010) has made the study design of the DEARS and information pertaining to its integration with the CV sub-study available online (www.epa.gov/dears). This was a two-year effort (winter 2005 through winter 2007). Volunteers living in suburban neighborhoods believed to be impacted by various environmental sources (e.g., mobile emissions, industrial, mixed) were selected from various neighborhoods in Wayne County, Michigan, in a purposeful manner. Even so, the study population did not represent the general population as a whole. Participants had to be at least 18 years of age, non-smoking and live in a non-smoking household. There was no exclusion criteria associated with sex, occupation, or ethnicity. All participants had to either read or comprehend English or Spanish instruction. The only health exclusion for the cohort was their need to be ambulatory. Individuals living in the selected neighborhoods were contacted by study personnel and provided information about

both the exposure and cardiovascular studies. Individuals consenting to the DEARS exposure study then had the option of consenting to participate in the companion health study. Participants were monitored for a maximum of 5 days in the summer and then 5 days in the following winter.

Each measurement day consisted of a 24 ± 2.5 hour period (~ 9 am to 9 am) from Tuesday through Sunday morning. Field staff were responsible for placing monitoring vests containing low burden exposure monitoring devices for NO_2 and $\text{PM}_{2.5}$ on the participants each day, recovering them the following day and collecting survey and other data associated with the study. Participants were asked to wear the vests except for periods of sleeping, bathing or the changing of clothes. Personal monitoring protocol compliance was associated with participants wearing the vest at least 60% of each 24-h period including times associated with sleep events. Ambient-based measurements from a central monitoring site were obtained simultaneously each day using the same monitoring protocols and on the same time schedule.

Field staff returned to the home between 16:00 and 20:00 h where the novel in-home clinical measures were then performed. Brook et al. (2010a, 2010b) have described this subpopulation and the means by which the afore-mentioned CV measures were obtained for the 65 participants. This cohort represented a population having a mean age of 44.6 y.o., 77% female, and predominantly African-American (54%). Participants were requested to maintain their non-study medication schedules. There was a wide range of baseline health characteristics with a substantial percentage of individuals having self-reported CV risk factors (hypertension, 34%; diabetes 16%; hyperlipidemia, 23%). However, few (< 6%) patients reported having any established CV disease (e.g., previous myocardial infarction, 4%). A total of 12% of the cohort took angiotensin converting enzyme/angiotensin receptor blockers, 6% used a diuretic, 8% used a beta blocker, and 13% used a calcium channel blocker. The remainder (61%) reported no use of CV medications. The mean initial screening BP was $126.6 \pm 18.2/75.5 \pm 10.8$ mm Hg and fewer than 15% of subjects reported taking blood pressure medications on a daily basis. Human participation in the studies was approved through institutional review boards at the University of Michigan, RTI International (a field support contractor to the US EPA), and the US EPA's Human Subject Research Office.

PM_{2.5} components

Filters associated with personal and ambient $\text{PM}_{2.5}$ data collections were analyzed by X-ray fluorescence (XRF) for the presence of select elements (Williams et al. 2009) by the US EPA's onsite XRF laboratory. Operating parameters for this laboratory, its quality assurance procedures and the comparability of data from this laboratory in relation to other elemental analysis techniques have been reported in depth (Kellogg 2007; Niu et al. 2010). Only values being ≥ 3 times the measurement uncertainty were used in the resulting epidemiological analyses. This screening value has been developed as a result of extensive laboratory examination of detection, precision and instrumental sensitivity. The DEARS study design defined the historical level of elemental limits of detection for this laboratory (US EPA 2010) and the general number of elements detected here was consistent with expectations for the analytical method utilized. Eventually, elemental data for iron (Fe), zinc (Zn), potassium (K), manganese (Mn), sulfur (S), and calcium (Ca) were determined to be of a sufficient population for analysis. Estimates of $\text{PM}_{2.5}$ sulfate concentrations (as ammonium sulfate) were developed using elemental sulfur values and its normal MW conversion factor ($\times 4.125$). Each of the filters analyzed for elemental analysis were pre-screened for the presence of an optical marker of environmental tobacco smoke (ETS). The procedures to do this and ETS impact as a whole upon the data used in the current analysis

have been reported (Lawless et al. 2004; Williams et al. 2009; Brook et al. 2010a; Rodes et al. 2010).

In addition to XRF analysis, ambient-based PM_{2.5} filters were analyzed for the presence of elemental carbon (EC) and organic carbon (OC). Williams et al. (2009) and Baxter et al. (2008) have previously described the analytical procedures used to collect these filters, the laboratory techniques used in data recovery, and general discussions about some of the carbon findings associated with the DEARS.

Ambient levels of particulate-bound ammonium nitrate were determined by use of an active sampling system containing a mini-denuder and a sodium carbonate coated glass fiber filter. The use of this device in the DEARS has been reported (Williams et al. 2009) as well as analyte retention and eventual laboratory recovery procedures (Demokritou et al. 2001). All of the PM_{2.5} component analysis data were blank corrected using statistical findings obtained from extensive use of field and laboratory blanks. The average contribution (percentage) of any individual PM component to the whole was established by a simple ratio of the observed component mass to that of the total PM_{2.5} filter mass.

Gaseous pollutant measurements

The DEARS study designed called for the collection of NO₂, ozone (O₃), and sulfur dioxide (SO₂) gaseous pollutant measurements. The procedures used to collect daily measures of personal and ambient measures of these pollutants using an Ogawa passive diffusion badge and the resulting laboratory analyses have been reported (Williams et al. 2009). This same report identified personal exposure concentrations of O₃ and SO₂ being routinely below the limit of detection during the study. A full reporting of gaseous pollutant measurements in the DEARS is being reported elsewhere that documents the low environmental concentrations encountered and the spatial/temporal relationships. Even though ambient concentrations for these two pollutants were typically measured successfully, it was recognized that the study participants had few personal exposure monitoring events of sufficient data quality to permit a successful integration with the full analysis. Likewise, personal monitoring indicated that ambient-based measurements, while of sufficient data quality for examination, had little relationship with the participant's true exposures. Therefore, any health findings associated with ambient measurements might be misleading. For this reason, only data from the NO₂ monitoring was utilized in the analysis. Passive monitoring for NO₂ has been widely used by the EPA and others with good success (Mukerjee et al. 2004; Yu et al. 2008). An environmental limit of detection of 5 ppb was established based upon field and laboratory blanks. All field samples were observed to be at or above the limit of detection following blank correction.

In-home cardiovascular measures

A detailed discussion about the instruments and procedures used to collect in-home measures of select CV observations and initial epidemiological findings associated with participant's exposures to various PM_{2.5} source categories have been reported in depth (Brook and Rajagopalan 2009; Brook et al. 2010a). In brief, SBP, DBP, HR, BAD, FMD and NMD were obtained on days coincidental to the exposure monitoring. Participants were asked to maintain their normal daily procedures with the exception that they were to fast and to refrain from heavy exercise and/or physical exertion for a period at least 4 h prior to the examination if at all possible. Participants lay supine for 10 min prior to automated SBP, DBP, and HR measurements. The SBP, DBP, and HR measures were obtained via an automated monitor (Omron 780; Omron, Kyoto, Japan). Measures were collected in triplicate with 1-min lapses between measures. The average of the 2nd and 3rd BP and heart rate was used for analyses. The arterial ultrasound measures (BAD, FMD, NMD) were

obtained using a portable ultrasound system (Terason, Burlington, MA, USA) employing a 10.0 MHz linear array transducer (Terason 2000 with ECG-gated image acquisition). A period of 5 min of upper arm occlusion followed by rapid cuff deflation was used in the FMD protocol. NMD was determined following a 3-min lapse of sublingual nitroglycerin administration by mouth. The procedures employed and the recognized guidelines used in collecting/validating data for the standard measures and the 0.4 mg sublingual nitroglycerin mediated parameter have been reported elsewhere (Brook et al. 2005, 2009, 2010a).

Statistical analyses

Repeated CV responses within each subject can induce a correlation structure on the observations due to variation in the responses between subjects. The more variation between subjects the more correlation between the repeated responses within subjects. We accounted for this correlation structure by using a linear mixed model. It was assumed that the association between each of the CV health outcomes and personal- or ambient-level PM_{2.5} components was linear with an intercept varying at random over individuals and a common slope, representing the linear relationship, for all subjects. Several predictors of the response were included in the base model as fixed effects: age (A), gender (G), race (R), body mass index (BMI), same-day community-level temperature (T), season (S) and an indicator for the use/non-use of medication (I). The base model is summarized in Equation (1) for subject i at study day j ($j = 1, \dots, 5$),

$$Y_{ij} = \beta_0 + \beta_1 \text{Comp}_{ij}(k) + \beta_2 A_i + \beta_3 G_i + \beta_4 R_i + \beta_5 \text{BMI}_i + \beta_6 T_{ij} + \beta_7 S_{ij} + \beta_8 I_i + \alpha_i + \varepsilon_{ij} \quad (1)$$

where Y_{ij} is a CV health outcome and $\text{Comp}_{ij}(k)$, the k -lag day personal- or ambient level component prior to the health outcome measurement day. Note that up to 2-day lagged component was considered ($k = 0, 1$, or 2). The random effects by subject, α_i , were assumed to be independently distributed with a normal distribution $\alpha_i \sim N(0, \sigma^2)$ and the within-subjects errors, ε_{ij} , were assumed to be distributed $\varepsilon_{ij} \sim N(0, \sigma^2 R_i)$, where R_i was the correlation matrix for the residuals. It was also assumed α_i and ε_{ij} were independent of each other. The first-order autoregressive structure, denoted by AR(1), was explored for the correlation R_i in the analysis, which implies observations closer to each other in time exhibit higher correlation than observations farther apart in time. The likelihood ratio test showed the AR(1) correlation structure did not improve the fit in all models considered.

Data validation was conducted by examining unusual values. A few extreme values were detected in personal level components such as NO₂ (> 100 ppb), iron (> 600 ng/m³), zinc (> 600 ng/m³), potassium (> 500 ng/m³), and calcium (> 1000 ng/m³), while none in ambient components displayed extreme values. We conducted a sensitivity analysis to these extreme values by removing them from the dataset and comparing the component coefficients and their standard errors to those derived by models which included all the data. We concluded that the component effects were not sensitive to these extreme values for all cases examined except for NO₂ on FMD. Since those extreme personal measurements were believed to be real, they were all included in the analyses. We conducted another sensitivity analysis associated with medication use among the participants to account for these effects by adding an indicator variable for each medication at a time to the base model (1). Overall, the individual medication usage resulted in negligible changes of the risk coefficients and significances from the base model.

We categorized the data into four groups by two factors, vest compliance rate (more or less than 60%) and ETS (more or less than personal-level of 1.5 µg/m³): “All subjects” for total subject population, “Vest” for a subgroup who met the protocol compliant, “Low ETS” for a

subgroup who had low ETS exposures, and “Vest_Low ETS” for a subgroup who had both protocol compliant and low ETS exposures. ETS represents a highly complex aerosol with component concentrations far exceeding those normally observed in ambient air. We had also previously established in this study cohort that ETS exposures could impact SBP. Therefore, data stratification by ETS exposures provided the means to effectively reduce exposure misclassification of health risk associated with the ambient environment. We report in Rodes et al. (2010) the means for establishing ETS exposures and the rationale for the selection of the aforementioned screening value. Tables 1 and 2 report the summary statistics of personal- or ambient-level components for each group. The base model was applied to the entire population and to each group separately.

Results

The full details of the patients’ characteristics and health conditions have previously been reported in Brook et al. (2010a). Descriptive statistics for the respective exposure variables are presented in Tables 1 and 2. Most notable in Table 1 is the modest ambient mass concentrations observed for the various pollutants. With the exception of one day where there was very high NO₂ (100 ppb), concentrations for this pollutant were typically well below the annual NAAQS limit of 53 ppb (median = 23.0 ppb). The maximum value of 100 ppb is equal to the existing 1-hour NAAQS. This airshed had an average PM_{2.5} mass concentration of 15.4 µg/m³ during the study (Brook et al. 2010a). Mass contribution of the PM_{2.5} components was observed to vary (data not shown). NO₃ contributed only a modest amount to the PM_{2.5} overall average mass concentration (~ 10%). Sulfate and OC were estimated to contribute significantly more on average (39.6% and 40.3%, respectively). Fe, Zn, Ca, K, Mn, and Pb collectively contributed less than 2.5% to the total average daily ambient PM mass concentration. Pb values are reported only here and in Table 2 due to the total lack of significance to any observed health outcome.

Personal versus ambient Spearman correlations among the protocol compliant subgroups were consistently higher than among all subjects (Supplementary Table S1, available online). Even so, both were similar (e.g., sulfate 0.898 vs. 0.882; NO₂ 0.140 vs. 0.105 for protocol-compliant vs. all subjects, respectively). Significant ambient vs. personal elemental concentration relationships for Fe, Zn, and Ca, were also obtained but with poorer agreement ($r < 0.33$). Ongoing work to be reported elsewhere for this subject population indicates that use of residential gas appliances in the participant’s home significantly impacted their overall NO₂ exposures and is the probable cause of the poor ambient-personal relationship mentioned above. One such example is the NO₂ concentration of 191 ppb reported here. Even so, the daily average personal exposure to this pollutant was only 3.6 ppb higher than that observed in the ambient. Residential air exchange in the home, as well as activities like cooking, cleaning and grooming among others often impact the relationship between personal measures and those obtained from a central community monitor. Efforts to identify the factors that influenced PM_{2.5} personal exposures in the DEARS are ongoing and not yet available for inclusion here.

The average personal exposure to various PM_{2.5} elemental constituents (Table 2) was often higher than those observed for the ambient monitoring (Table 1). One such example is that of K (75.1 ng/m³ vs. 50.9 ng/m³, respectively) for the protocol compliant subgroup. Such increases at the personal level would be expected due to the known influence of indoor residential sources of elemental pollutants from household products and residential PM_{2.5} infiltration and resuspension activities (Landis et al. 2001; Conner and Williams 2004).

Correlations among the various pollutants at the ambient and personal levels are reported in Tables 3 and 4, respectively. Spearman correlations for the ambient measures indicate that

NO₂ was more highly associated with Fe than with any other pollutant ($r = 0.354$, $p = 0.004$). It was also significantly associated with NO₃, OC and EC in the ambient setting. All of the elemental species (Fe, Zn, Ca, K, and Mn) were collinear to some degree. The greatest degree of linear association was that of K and Zn ($r = 0.823$, $p = 0.000$). The Vest-compliant subgroup correlations in Table 4 indicate a modest agreement between NO₂ and sulfate personal exposures ($r = 0.278$, $p = 0.000$). With rare exception (K vs. Zn), significant collinearity between the elemental species was observed for the personal setting. Fe exposures were highly associated with Zn, Ca, and Mn in particular ($0.57 < r < 0.66$).

Observed associations significant at the 5% level (i.e., $p \leq 0.05$) between exposure to various pollutants and CV end points are presented in Table 5. We highlight data findings associated with ambient pollutants without categorization by subgroup (e.g., ETS exposures). In contrast, we will report findings from the exposure compliant subgroup (Vest) where personal monitoring is of importance. ETS impacts on personal monitoring findings will not be directly reported but will be incorporated into the overall discussion. A reporting of select risk estimates of at least $p \leq 0.1$ by pollutant, health outcome, and personal monitoring subgroup are available in the material located in Supplementary Table S2 (available online). Screening of significance at the $p = 0.05$ instead of the $p = 0.1$ level and our focus on only the total subjects and protocol compliant subgroups significantly reduced the total number of risk estimates we are reporting from 105–21, with a majority of the former being associated with PM_{2.5} components. Some of the PM_{2.5} components were observed to significantly impact health outcomes only among specific subcategories (e.g., ambient nitrate versus the protocol compliant, low ETS subgroup for the DBP health outcome – see Supplementary Table S2, available online) and are worthy of further consideration elsewhere.

BP associations

Personal-level concentrations of Fe were highly associated with an increase in SBP and DBP risk coefficients (0.0128 mm Hg, 0.0084 mm Hg, per ng/m³ respectively) on lag day 0 among all subjects. Similar positive increases in DBP related to personal Fe exposure on lag day 0 were also found for vest-compliant subjects with $p = 0.09$ (Supplementary Table S2, online). Personal exposure levels of K were observed to negatively influence both SBP and DBP at various lag times. The strongest of these associations was for the subgroup meeting full protocol compliance (-0.0447 mm Hg DBP per ng/m³).

HR associations

Ambient concentrations of EC, Fe and Zn were observed to impact participants' heart rates. Results indicated significant associations (i.e., reductions) ranging from -0.0163 bpm per ng/m³ (Zn) to as high as -3.2289 bpm per $\mu\text{g}/\text{m}^3$ (EC). EC is derived from fossil fuel combustion and is primarily associated with diesel vehicles. A strong association between ambient NO₂ levels and reduced HR were similarly observed (-0.0982 bpm per ppb). As an example, individuals experiencing 24 ppb daily average concentrations of NO₂ (Table 1) would be expected to have a resulting decrease in HR of about 2 bpm.

BAD associations

Ambient K concentrations were associated with positive (i.e., an increase consistent with vasodilatation) changes in BAD (risk coefficient = 0.0037 mm per ng/m³). This is consistent with the significant decreases in both SBP and DBP observed at lag 0 for personal exposures to K. Conversely, personal K concentrations indicated a much weaker but negative risk change in BAD estimate (risk coefficient = -0.0007 mm per ng/m³). Likely of more interest for this health measure was the impact of personal NO₂ concentrations on BAD. For both the "All subject" population and the protocol vest-compliant subgroups, significant risk

coefficients were observed. The results were somewhat contradictory in that the sign of the risk changed for the protocol compliant group by lag structure (day 1 = 0.0041, day 2 = -0.0067). The “All subjects” personal monitoring group identified a negative risk (-0.0049 mm per ppb) on lag day 2 similar to that obtained for the protocol compliant group. Ambient NO₂ was not associated with changes in BAD.

FMD and NMD associations

The most consistent finding and perhaps most compelling observation presented in Table 5 is that personal NO₂ concentrations were associated with positive changes in FMD. The findings were consistent across days and vest compliance status. The strongest of these risk coefficients was for the personal monitoring subgroup who were protocol compliant (risk coefficient = 0.0720 mm per ppb, lag 1). Even so, little overall risk estimate differences were observed between the “All subjects” and the protocol-compliant subgroup regardless of lag structure.

NMD was not observed to be a particularly strong health outcome in any of the analyses. Only ambient concentrations of OC were significant for this outcome and these were contraindicating by lag structure (lag 0 = -0.5866, lag 2 = 1.0661) for the “All subject” population. NMD findings we have reported in other investigations of this same cohort have shown similar non-effects for this health outcome and it would appear to be poorly associated with effects associated with PM_{2.5} mass or its elemental components (Brook et al. 2010a).

Discussion

It should be recognized that the analyses performed here did not examine combinations of pollutants and no *a priori* effects were tested. Therefore, this is an exploratory analysis of the data collected and could be considered hypothesis-generating. There is the possibility that statistically significant risk associations observed for any of the pollutants reported here might represent surrogates or confounders for one or more other pollutants. An example of such consideration is that of gaseous copollutants and PM_{2.5} where surrogate relationships were determined to be far more likely (Sarnat et al. 2001; Brown et al. 2009). We observed significant collinearity between ambient-based measurements of NO₂ with EC and Fe as well as personal-based collinearity between NO₂ and a number of PM constituents (sulfate, Fe, Zn, Ca). Both personal ozone and sulfur dioxide measurements were performed in the DEARS but a large fraction of those were determined to be below detection limits and therefore unavailable for inclusion in this effort as discussed earlier. Mean personal ozone and sulfur dioxide were 2.1 and 0.5 ppb, respectively (Williams et al. 2009) and far below national air quality standards. Even so, exposures to one or both of these gases might have had some unknown impact on the resulting health outcomes. The lack of sufficient data beyond the current study associating these specific outcomes with various PM_{2.5} constituents from personal measurements and various health outcomes also cautions such determinations at this time. Even so, others have agreed that there is a need for enhanced exposure characterization if we are to fully understand this issue (Grahame 2009).

Detectable levels of personal NO₂ exposures have been shown to exist across a wide range of geographical locations and subpopulations (Brauer et al. 1989; Kousa et al. 2001, Sarnat et al. 2001; Harrison et al. 2002; Lai et al. 2004; Brown et al. 2009). While adverse CV responses to NO₂ are often reported in epidemiological studies (Brook 2008), typically it has been presumed that NO₂ was not likely directly responsible but rather serving a marker for exposure to harmful traffic-related pollutants or combustion sources of particulate matter. Indeed, among the few studies that have evaluated the CV responses to NO₂, most have indicated this pollutant has little direct association with adverse CV changes in humans or

animals (Gong et al. 2005; US EPA 2008; Campen et al. 2010; Langrish et al. 2010). Importantly, Langrish et al. (2010) demonstrated experimentally that high concentration exposure to NO₂ (4 ppm) did not directly affect similar outcomes to our study including vascular function, blood pressure, or fibrinolytic function, albeit over only a few hour period. On the other hand, we surprisingly observed consistently strong associations between various exposure measurements with changes in HR, BAD, and FMD. Though it remains possible that NO₂ could still be a proxy for another “responsible” combustion pollutant in our study (i.e., recent traffic exposure), these results suggest that there may be some direct CV effects of this gaseous pollutant. Further studies are clearly warranted to explore the direct causal association between NO₂, and other gases (e.g., O₃) and CV disease.

The most consistent and probably most interesting response related to NO₂ in our study is the observed pro-vasodilatory properties associated with a positive increase in FMD. It is possible that inhaled NO₂ (which may be highly collinear with other NO_x, including NO or even nitrate) could have a systemic effect that promotes vasodilatation by enhancing vascular NO bioavailability. Indeed, inhaled NO (albeit at higher doses) is known to be transported throughout the circulation by several processes (e.g., nitrosothiols, conversion to nitrite, binding to hemoglobin) and to have distal “endocrine” effects that augment endogenous NO bioavailability within remote vascular sites (Cannon et al. 2001; Lundberg and Weitzberg 2005). While this is clearly speculation, it is plausible that exposure to sources of NO_x may itself augment systemic levels of CV NO that could in theory result in physiological changes (e.g., vasodilatation, reduced platelet aggregation). Clearly, more direct investigations into these effects are warranted.

In addition to the NO₂-related health responses, we observed several changes associated with exposures. Regarding BP, personal-level Fe was associated with an increased systolic level on day lag 0. This might suggest that exposure to Fe rapidly triggers oxidative stress within the vasculature instigating vasomotor imbalance favoring vasoconstriction. On the other hand, personal-level K was associated with a lower BP. We are not aware of any physiological rationale for why changes in K exposures would be related to a lowering of blood pressure. Even so, the effect appears consistent as it was present for the “All subjects” category and is stronger when personal exposure data with protocol compliance subpopulation (Vest) were used. Since atmospheric levels of K were low (Table 1), K might simply have been acting as a surrogate for other environmental pollutants the participants encountered that were correlated with K. Potassium (K) is a known component of biomass combustion emissions, which contain a large number of other copollutants, and is often used as a tracer of this pollution source. EPA Chemical Mass Balance (CMB) analysis of samples with both the organic biomass marker levoglucosan and the elemental biomass marker K (data to be reported elsewhere), showed that the K could not be explained using source profiles which included motor vehicle exhaust, wood smoke, mixed industrial, steel, and crustal. K is a component of both soil and biomass combustion-derived particulate matter but the CMB results show an excess of K that may be from local industrial sources in Detroit. Organic and inorganic speciation data will be examined in future US EPA source apportionment investigations to understand potential sources of the excess K.

In regards to HR, the reasons underlying the associations between ambient levels of several pollutants and reductions in HR are unclear. The underlying physiology responsible and health relevance of these observed reductions in HR related to these pollutants are not known. Given that the autonomic nervous system is responsible for controlling HR, it is possible that exposure to these pollutants is responsible for altering HR control via impacting sympathetic and/or vagal activity (Brook 2008). Regarding BAD changes, an explanation for the time-varying changes related to ambient and personal-level K are not

readily apparent; it may reflect differing biological responses at earlier versus later time points or a rapid vasoconstrictive response with a reflex compensatory vasodilatory response on the following day. The BAD responses related to NO₂ exposure were previously discussed. Finally, the major FMD changes were related to NO₂ as well. The observations suggest that personal-level exposures to ambient levels of NO₂ are associated with enhancement of systemic vascular endothelial-dependent vasodilatation. The potential meaning of this finding was previously discussed.

A number of environmental studies have examined PM_{2.5} sulfate, nitrate and carbon exposures among panel subjects (Brauer et al. 1989; Wallace and Williams 2005), but few have simultaneously investigated specific PM_{2.5} elemental components. Although not a panel study, Niu et al. (2010) have examined in detail the elemental PM_{2.5} composition of air samples from the Windsor, Canada area. They report elemental concentrations similar to those from the Detroit area associated with this current effort. The ambient pollutant concentrations observed here were consistent with the general range of those reported for typical US urban settings (Landis et al. 2001; US EPA 2008, 2009). Therefore, the health outcomes reported in the current effort would appear to be applicable to other locations with respect to concentration thresholds. Neri et al. (2005) have reported personal PM_{2.5} constituent concentrations associated with the European Genotox'ER study using a different analytical detection system. They consistently observed detectable levels of nickel and copper which we did not observe. Janssen et al. (2005) have reported personal PM_{2.5} constituent exposure levels in another European CV cohort and rarely observed detectable concentrations of manganese, nickel or vanadium. Riediker (2007) have indicated that personal exposure to PM_{2.5} copper might play an important role in certain CV impairments. Niu et al. (2010) have reported that the XRF instrumentation used to support the DEARS elemental analysis was not as sensitive as inductively coupled plasma-mass spectroscopy (ICP-MS). It did however provide the means to analyze thousands of PM samples efficiently and with good sensitivity for many of the elements.

It would appear that ETS exposures might influence select CV functions. As an example, the greatest risk coefficient obtained for SBP was that associated with ambient pollutant concentrations in the subgroup having little to no ETS exposures (risk coefficient = -0.7785 mm Hg per $\mu\text{g}/\text{m}^3$ of OC (data not shown in Supplementary Table S2, available online). Therefore, exposure to ETS might make it more difficult to link SBP changes with ambient based measures of OC. ETS is comprised almost entirely of organic compounds so the observed confounding is not too surprising. Other such examples of ETS impact or near impact on the resulting risk coefficients are available in the supplemental material (Supplementary Table S2 online) for examination.

While personal exposure monitoring was not needed to examine the impact of ambient measures upon the health effects, such monitoring was needed to ensure the lowest degree of exposure measurement uncertainty. Brook et al. (2010a) and Rodes et al. (2010) have examined the impact of participant protocol compliance in the DEARS for both PM_{2.5} mass concentration and resulting health effects. They report that ensuring protocol compliance is critical to obtaining valid exposure data to support epidemiological analyses. Even so, Rodes et al. (2010) indicate that a personal monitoring compliance percentage as low as 40% in comparison to the 60% applied here might be acceptable in some situations. Such findings should suggest that the overall health outcomes observed here for the personal exposure analyses are even stronger considering the data inclusion restrictions on protocol compliance employed here and the subsequent reduction in overall statistical power.

The value of personal exposure monitoring (over ambient monitoring alone) in reducing exposure risk estimates or exposure misclassification in studies of this nature is clearly

demonstrated here. While personal and ambient mass concentrations were often in the same range for any given pollutant, the former often provided significantly improved exposure inputs for the analyses. Median personal exposure to Fe, in the protocol compliant subgroup, was only 61% of that associated with matched ambient monitoring as one example. Of the 21 significant exposure-CV associations reported in Table 5, 62% of these involve personal exposure findings. Only personal exposures were associated with any blood pressure changes, and with the majority of BAD and FMD outcomes. HR was the only CV function where no association with a personal measurement was established.

Few studies exist that will allow for a robust comparison between findings for this subject matter. This is because there is a lack of information concerning personal exposures to PM_{2.5} constituents or assurance that the personal monitoring performed was compliant (reduced exposure misclassification). In addition, all of the health measures obtained in this study were collected in the home rather than in a clinical setting involving the transportation of the subject to such a location. We believe home-based measurements ensured the highest data quality (Brook et al. 2010a). Home data collections helped to ensure a high degree of data collection completeness and minimize participant burden over the lifetime of the study. Minimizing burden was performed to the greatest extent possible. As an example, our selection of a 4-h fasting period instead of one of greater duration (e.g., 24-h) was made on negative feedback received from local citizens prior to the study as to their willingness to comply with a more burdensome study protocol.

It is useful to compare current study findings with earlier DEARS PM_{2.5} investigations concerning where individual components were not examined (Brook et al. 2010a, 2010b). Previously we demonstrated that personal-level PM_{2.5} was associated with an increase in SBP on lag day 1 (Brook et al. 2010a) and with reductions in BAD on lag day 2. This present analysis explored the specific PM constituents potentially responsible for these, among potentially additional, health responses. Unfortunately, the findings presented in the results and Table 5 do not easily explain the PM constituent that could be responsible for the increase in SBP on lag day 1. The closest association we observed was that personal-level exposure to Fe (or a surrogate) was related to elevations in SBP and DBP on lag day 0, a shorter time period. Given the ability of Fe to generate redox reactions, potentially in the vasculature, this may explain pro-vasoconstrictive responses (e.g., by reduction in bioavailable endogenous NO) (Brook 2008). This effect will be counter-balanced by the blood pressure lowering responses induced by K (or the responsible co-pollutant/surrogate). Regarding the reduction in BAD previously observed on lag day 2 related to PM_{2.5}, our findings suggest that NO₂ may be responsible for this delayed vasoconstrictive response. We speculate that perhaps the vasodilating affects directly attributable to NO₂ (e.g., NO_x or NO) inhalation, as described earlier, predominate shortly after exposure (i.e., increase in BAD on lag day 1) while the vasoconstrictive actions of the co-pollutants predominate later (i.e., decrease in BAD on lag day 2). These complicated and divergent responses are difficult to fully explain given the numerous pollutants investigated at different time periods and also recognizing that some responses may occur more rapidly, while other changes observed might even represent physiological counter-regulatory adaptations to earlier insults. Overall, however, there is some suggestion from our findings that the redox active element Fe may participate in rapid pro-hypertensive responses and K (or co-pollutants) counter this response by lowering BP. In addition, our findings support that NO₂ (or gaseous NO_x species) may directly augment endothelial function (i.e., FMD) and rapidly promote vasodilatation (i.e., increased BAD on lag day 1).

PM_{2.5} exposure has been previously linked with SBP, DBP and HR changes (Lin et al. 2009) where they did not examine specific PM_{2.5} constituents. Urch et al. (2004) observed changes in BAD associated with both EC and OC exposures in a controlled chamber

exposure among young, non-smoking, healthy adults. Our primary observation here for BAD is related to personal NO₂ exposures and one PM_{2.5} constituent (K). Exposures to PM_{2.5} emissions associated with bus stops have been shown to negatively impact FMD. The same study found no association with NO₂ exposures and FMD (Dales et al. 2007). Our only observation linking ambient EC with an effect involved HR. Mordukhovich et al. (2009) have reported that exposure to black carbon, an exposure measure based on reflectance that is a good proxy for EC, resulted in an increase in both SBP and DBP. By comparison, our closest observation involved a change of -1.9676 mm Hg DBP per $\mu\text{g}/\text{m}^3$ of ambient EC (DBP, lag 0, All subjects, $p = 0.0988$) as reported in Supplementary Table S2 (available online). Rats exposed to concentrated ambient air particulate from one of the same neighborhoods and collection periods as in the DEARS have been reported to have significant associations between EC and decreased heart rate and heart rate variability indicators (Rohr et al. 2010). Valenti et al. (2010) have reported health outcomes involving heart rate control of blood pressure in hypertensive rats following sidestream cigarette smoke exposure.

The results reported here were associated with novel, yet high quality exposure and health data collected as part of paired human exposure and epidemiological field studies in the Detroit area over an extended study period and involving a large number of participants. While the results are similar to a number of findings from other studies, the fact that personal level NO₂ and K were so strongly associated with a number of health outcomes is noteworthy. Likewise, the lack of association with sulfate, and the weaker or limited associations with nitrate and carbon (EC and OC) components with many of the health outcomes here and which are often reported in large, ambient-based epidemiological studies, might be indicative of the lesser effect of these components. This might be an indication that enhanced exposure characterization, such as that performed here, results in an increased ability to detect previously unreported effects. The Detroit airshed is not dominated by PM_{2.5} sulfate mass as are many eastern US cities. The general lack of health associations here for this component cannot be explained at this time. Future work will examine the potential impact of various exposure source categories on these health outcomes and the time-activity patterns of the participants and will consider the comprehensive suite of organics measured in the DEARS. It is also a limitation that this study was not designed to explore patient-level susceptibility (e.g., pre-existing diabetes or hypertension) to air pollution exposures regarding the health outcomes. Future studies may be able to address this issue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Ambient NO₂ and PM_{2.5} constituent descriptive exposure statistics.

Variable ¹	N	Mean	SD	CV	Min	Q1 ²	Median	Q3 ³	Max
NO ₂	357	24.0	11.4	47.5	0.0	18.0	23.0	28.0	100.0
NO ₃	357	2.8	2.8	100.0	<0.1	1.0	1.6	3.8	14.0
OC	357	6.2	2.2	35.5	2.4	4.8	6.0	7.1	15.2
EC	357	0.7	0.3	42.9	<0.1	0.5	0.7	0.9	1.7
Sulfate	296	6.1	5.3	86.9	0.80	2.4	4.4	7.4	28.0
Fe	296	161.0	66.0	41.0	31.0	115.0	157.0	218	374.0
Zn	211	31.6	36.4	115.2	3.1	15.0	22.4	30.5	210.2
Ca	296	129.0	68.6	53.2	24.0	81.8	114.4	157.9	381.0
K	177	50.9	20.0	39.3	17.3	36.9	45.2	63.8	110.0
Mn	236	6.3	2.5	39.7	2.8	4.4	6.2	7.8	17.7
Pb	32	8.0	1.4	17.5	5.2	6.9	7.9	9.2	10.8

¹ NO₂ data reported in units of ppb; NO₃, OC, EC and sulfate reported in µg/m³; Fe, Zn, Ca, K, Mn, and Pb reported in units of ng/m³.

² Q1, 25th percentile;

³ Q3, 75th percentile.

Table 2

Personal NO₂ and PM_{2.5} constituent descriptive exposure statistics.

Variable ^f	N	Mean	SD	CV	Min	Q1 ²	Median	Q3 ³	Max
NO₂									
All	326	27.6	19.5	70.7	0.0	17.0	24.0	32.0	191.0
Vest	228	27.0	18.6	68.9	5.0	17.0	24.0	31.0	191.0
Low ETS	137	24.8	10.6	42.7	5.0	18.0	23.0	31.0	62.0
Sulfate									
All	261	4.6	4.9	106.5	0.3	1.5	2.7	5.4	26.8
Vest	173	4.9	5.2	106.1	0.5	1.6	2.8	5.6	26.8
Low ETS	135	5.5	5.6	101.8	0.5	1.7	3.5	7.0	26.8
Fe									
All	254	132.5	121.2	91.5	17.8	58.0	97.6	148.9	820.8
Vest	169	140.0	137.1	97.9	17.8	59.5	96.5	151.5	820.8
Low ETS	131	146.4	140.5	96.0	17.8	63.3	104.0	156.2	820.8
Zn									
All	172	55.4	135.3	244.2	5.7	15.8	23.1	41.0	1198.9
Vest	122	54.4	119.0	218.8	5.7	16.0	14.9	41.5	1198.9
Low ETS	93	58.7	132.5	225.7	5.7	16.6	25.2	47.8	1198.9
Ca									
All	261	124.0	222.8	179.7	17.0	56.9	84.7	130.1	2584.7
Vest	173	142.1	265.5	185.4	17.0	65.2	93.4	144.0	2584.7
Low ETS	135	133.6	210.8	157.8	17.0	63.3	94.9	143.5	2396.2
K									
All	120	101.5	151.0	148.8	27.7	40.0	54.4	84.4	1049.4
Vest	68	75.1	64.1	85.3	28.3	40.5	52.6	80.5	378.4
Low ETS	47	59.0	43.1	73.1	28.3	38.6	47.2	67.2	315.1
Mn									

Variable ¹	N	Mean	SD	CV	Min	Q1 ²	Median	Q3 ³	Max
All	89	8.7	3.4	39.1	5.4	6.4	7.6	9.9	21.7
Vest	59	9.3	3.7	39.8	5.4	6.6	8.3	11.1	21.7
Low ETS	48	9.3	3.9	41.9	5.4	6.4	8.2	11.1	21.7
Pb									
All	11	22.7	23.6	104.0	11.3	14.3	15.0	18.0	93.2
Vest	6	28.4	31.8	112.0	12.4	14.3	15.5	18.7	93.2
Low ETS	3	14.4	2.1	14.6	12.4	13.4	14.3	15.5	16.6

¹ NO₂ data reported in units of ppb; Sulfate reported in µg/m³; Fe, Zn, Ca, K, Mn, and Pb reported in units of ng/m³. “All” refers to All subject population; “Vest” refers to protocol compliant subjects, “Low ETS” refers to compliant subjects with low ETS exposures.

² Q1, 25th percentile.

³ Q3, 75th percentile.

Table 3Spearman correlations of ambient NO₂ and PM_{2.5} components.

Variable	NO ₃	OC	EC	Sulfate	Fe	Zn	Ca	K	Mn
NO ₂	0.244 (<i>p</i> =0.000)	0.124 (<i>p</i> =0.019)	0.337 (<i>p</i> =0.000)	-0.014 (<i>p</i> =0.813)	0.354 (<i>p</i> =0.004)	0.095 (<i>p</i> =0.170)	0.236 (<i>p</i> =0.693)	0.030 (<i>p</i> =0.693)	0.103 (<i>p</i> =0.115)
NO ₃		-0.076 (<i>p</i> =0.152)	-0.283 (<i>p</i> =0.000)	0.198 (<i>p</i> =0.001)	-0.119 (<i>p</i> =0.040)	0.202 (<i>p</i> =0.003)	-0.004 (<i>p</i> =0.943)	0.317 (<i>p</i> =0.000)	-0.046 (<i>p</i> =0.479)
OC			0.520 (<i>p</i> =0.000)	0.383 (<i>p</i> =0.000)	0.347 (<i>p</i> =0.000)	0.427 (<i>p</i> =0.000)	0.302 (<i>p</i> =0.000)	0.481 (<i>p</i> =0.000)	0.273 (<i>p</i> =0.000)
EC				0.381 (<i>p</i> =0.000)	0.463 (<i>p</i> =0.000)	0.358 (<i>p</i> =0.000)	0.216 (<i>p</i> =0.000)	0.303 (<i>p</i> =0.000)	0.140 (<i>p</i> =0.032)
Sulfate					0.073 (<i>p</i> =0.212)	0.416 (<i>p</i> =0.000)	0.025 (<i>p</i> =0.671)	0.387 (<i>p</i> =0.000)	0.198 (<i>p</i> =0.002)
Fe						0.560 (<i>p</i> =0.000)	0.703 (<i>p</i> =0.000)	0.501 (<i>p</i> =0.000)	0.680 (<i>p</i> =0.000)
Zn							0.253 (<i>p</i> =0.000)	0.823 (<i>p</i> =0.000)	0.568 (<i>p</i> =0.000)
Ca								0.426 (<i>p</i> =0.000)	0.423 (<i>p</i> =0.000)
K									0.583 (<i>p</i> =0.000)

Table 4

Spearman correlations of personal NO₂ and PM_{2.5} components for the vest-compliant subgroup.

Variable	Sulfate	Fe	Zn	Ca	K	Mn
NO ₂	0.278 (<i>p</i> =0.000)	0.262 (<i>p</i> =0.001)	0.285 (<i>p</i> =0.002)	0.356 (<i>p</i> =0.000)	0.029 (<i>p</i> =0.817)	0.030 (<i>p</i> =0.824)
Sulfate		0.506 (<i>p</i> =0.000)	0.460 (<i>p</i> =0.000)	0.411 (<i>p</i> =0.000)	0.207 (<i>p</i> =0.090)	0.215 (<i>p</i> =0.102)
Fe			0.653 (<i>p</i> =0.000)	0.621 (<i>p</i> =0.000)	0.243 (<i>p</i> =0.049)	0.574 (<i>p</i> =0.000)
Zn				0.494 (<i>p</i> =0.000)	-0.085 (<i>p</i> =0.648)	0.343 (<i>p</i> =0.027)
Ca					0.450 (<i>p</i> =0.000)	0.545 (<i>p</i> =0.000)
K						0.468 (<i>p</i> =0.019)

Table 5

Select pollutant and cardiovascular effect risks by cardiovascular function (results with p values < 0.05).

Exposure ¹	Outcome	Lag	Group ²	Risk	Unit	SE	P-value	Obs
P Fe	SBP	0	All subjects	0.0128	mmHg/ng/m ³	0.0054	0.0183	240
P K	SBP	2	All subjects	-0.0237	mmHg/ng/m ³	0.0108	0.0403	43
P Fe	DBP	0	All subjects	0.0084	mmHg/ng/m ³	0.0036	0.0188	240
P K	DBP	0	All subjects	-0.0124	mmHg/ng/m ³	0.0056	0.0305	114
P K³	DBP	0	Vest	-0.0447	mmHg/ng/m ³	0.0132	0.0016	62
A NO ₂	HR	0	All subjects	-0.0982	bpm/ppb	0.0319	0.0023	336
A EC	HR	0	All subjects	-3.2289	bpm/μg/m ³	1.4203	0.0238	336
A Fe	HR	0	All subjects	-0.0163	bpm/ng/m ³	0.0065	0.0126	276
A Zn	HR	0	All subjects	-0.0296	bpm/ng/m ³	0.0145	0.0429	197
P NO ₂	BAD	2	All subjects	-0.0049	mm/ppb	0.0023	0.0366	114
P NO₂	BAD	1	Vest	0.0041	mm/ppb	0.0019	0.0353	122
P NO₂	BAD	2	Vest	-0.0067	mm/ppb	0.0029	0.0256	77
P K	BAD	0	All subjects	-0.0007	mm/ng/m ³	0.0003	0.0442	106
A K	BAD	1	All subjects	0.0037	mm/ng/m ³	0.0017	0.0380	93
P NO ₂	FMD	0	All subjects	0.0468	mm/ppb	0.0174	0.0079	253
P NO ₂	FMD	1	All subjects	0.0648	mm/ppb	0.0273	0.0196	164
P NO₂	FMD	0	Vest	0.0612	mm/ppb	0.0235	0.0103	172
P NO₂	FMD	1	Vest	0.0720	mm/ppb	0.0328	0.0316	110
A Mn	FMD	0	All subjects	-0.2551	mm/ng/m ³	0.1275	0.0475	190
A OC	NMD	0	All subjects	-0.5866	mm/μg/m ³	0.2941	0.0487	156
A OC	NMD	2	All subjects	1.0661	mm/μg/m ³	0.4539	0.0274	54

¹Models starting with "P" are associated with personal exposure measurements. Models starting with "A" relate to ambient measures. Risk refers to effect per exposure unit identified in text.

²Bold results represent personal monitoring findings of main interest because the significant results ($p < 0.05$) were found among the "Vest"-compliant subgroup.