Differences in Blood Pressure and Vascular Responses Associated with Ambient Fine Particulate Matter Exposures Measured at the Personal versus Community Level

Robert D. Brook[1], Robert L. Bard[1], Richard T. Burnett[2], Hwashin H. Shin[2], Alan Vette[3], Carry Croghan[3], Michael Phillips[4], Charles Rodes[4], Jonathan Thornburg[4], Ron Williams[3]

[1] *Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI, 48106, USA*

[2] *Biostatistics and Epidemiology Division, Health Canada, Ottawa, Ontario, Canada*

[3] *U.S. Environmental Protection Agency, Research Triangle Park, NC, 27711, USA*

[4] *RTI International, Research Triangle Park, NC, 27709, USA*

Correspondences:

Robert D. Brook, MD
24 Frank Lloyd Wright Dr PO Box 322
Ann Arbor, MI. 48106
robdbrok@umich.edu
(734) 998-5627
(fax) (734) 232-2292

Main body word count: 4,499

List of Abbreviations

BAD, brachial artery diameter

BP, Blood pressure

CI, confidence interval

CV, cardiovascular

DEARS, Detroit Exposure Aerosol Research Study

EPA, Environmental Protection Agency

FMD, flow mediated dilatation

NMD, nitroglycerin mediated dilatation

PEAO, personal $PM_{2.5}$ exposure of ambient origin

PEM, Personal Environmental Monitor

PENAO, personal $PM_{2.5}$ of non-ambient origin

PM, particulate matter

$PM_{2.5}$, fine particulate matter < 2.5 μm

SHS, secondhand smoke

TPE, total personal-level $PM_{2.5}$ exposure

Background: Higher ambient fine particulate matter ($PM_{2.5}$) levels can be associated with increased blood pressure (BP) and vascular dysfunction. Whether particles encountered at the personal-level elicit differing responses from those of background community $PM_{2.5}$ remains unknown.

Objectives: We aimed to determine the differential effects on BP and vascular function of daily changes in community ambient- versus personal-level $PM_{2.5}$ measurements having minimal exposure misclassification bias and confounding.

Methods: CV outcomes included vascular tone and function (brachial artery diameter (BAD) and flow-mediated dilatation (FMD), respectively) and BP measured in the residences of 65 non-smoking subjects. $PM_{2.5}$ exposure metrics included 24-hour integrated personal- (by vest monitors) and community-based ambient levels measured for up to 5 consecutive days during a summer and/or winter period (total of 357 observations). The associations between community and personal-level $PM_{2.5}$ exposures with alterations in the CV outcomes were assessed by linear mixed models.

Results: Mean daily personal and community measures of $PM_{2.5}$ were 21.9 ± 24.8 $\mu g/m^3$ and 15.4 ± 7.5 $\mu g/m^3$, respectively. Community $PM_{2.5}$ levels were not associated with CV outcomes. On the other hand, a 10 $\mu g/m^3$ increase in total personal-level $PM_{2.5}$ exposure (TPE) was associated with a systolic BP elevation (+1.41 mm Hg; lag day 1, $p<0.001$) and trends toward vasoconstriction in sub-sets of individuals (e.g. decreased brachial artery diameter (BAD)) by 0.08 mm; lag day 2 among subjects with low secondhand smoke (SHS) exposure, $p=0.07$). Both TPE and SHS were associated with an elevated systolic BP on lag day 1. FMD was not associated with any exposure.

Conclusions: Higher $PM_{2.5}$ levels monitored with low-bias and minimally-confounded personal monitors at the personal-level during routine daily activity were associated with modest increases in systolic BP and trends toward arterial vasoconstriction in some scenarios. Comparable elevations in community $PM_{2.5}$ levels were not related to these outcomes, suggesting that the specific components within personal and background ambient $PM_{2.5}$ may elicit differing CV responses of possible adverse health consequences.

Key Words: Blood vessels, endothelial function, hypertension, air pollution

What this paper adds:

- The method of assessing an individual's exposure to $PM_{2.5}$ (personal vest monitoring versus ambient community-level exposure metrics) influences the observed relationships with BP and vascular function.
- Higher TPE levels during the previous day after accounting for vest compliance and SHS exposures are associated with modest increases in systolic blood pressure (BP), but not with changes in vascular function.
- The lack of an association between community ambient $PM_{2.5}$ levels and systolic BP suggests that fine particles encountered at the personal-level may elicit differing responses than background ambient levels.
- These findings add to the evidence that personal-level exposures to present-day ambient concentrations of $PM_{2.5}$ encountered during routine daily activity may be capable of eliciting adverse biological reactions known to promote CV events in susceptible individuals.

Fine particulate matter (PM) < 2.5 μm ($PM_{2.5}$) air pollution is associated with increased cardiovascular (CV) morbidity. Among potential mechanisms, $PM_{2.5}$-mediated vasoconstriction, endothelial dysfunction, and raised blood pressure (BP) may play important roles.[1] Indeed, higher ambient $PM_{2.5}$ levels have been associated with impaired brachial flow-mediated dilatation (FMD) and elevated BP.[2-6] However, the responsible particle constituents and sources remain uncertain.

Changes in health outcomes are typically linked to community-level ambient $PM_{2.5}$, which consists of the relatively homogenous background particle concentrations from regional sources (e.g., power generation, secondary aerosols). In these studies it is implicitly assumed that subjects are equally exposed to the ambient $PM_{2.5}$ within a region at any given time. However, actual total personal-level $PM_{2.5}$ exposure (TPE) is determined by multiple factors unique to each individual, including exposure to particles of both ambient and non-ambient origin.[7-10] Personal $PM_{2.5}$ exposure of ambient origin (PEAO) is derived from background community ambient particles; however, several additional factors also influence the levels (e.g. time spent outdoors). On the other hand, personal $PM_{2.5}$ of non-ambient origin (PENAO) is derived from sources encountered within micro-environments that affect TPE separate from community levels and PEAO.[8,10] These may include particles derived from indoor (e.g. cooking, cleaning) and outdoor (e.g. traffic) sources along with secondhand smoke (SHS). The extent to which these personal-level exposures, along with the differing particle sources/constituents that comprise them, elicit differing CV responses than background community-level $PM_{2.5}$ remains largely unknown.

Few studies have investigated the CV responses to air pollution exposure measured at a personal level.[3,5,7,8] No study has compared the differential effects of personal-level versus community-level ambient $PM_{2.5}$ concentrations on both vascular function and BP, and utilized robust personal-level metrics minimizing biases from unworn monitors and confounding from SHS. Thus, we designed a CV sub-study of the Detroit Exposure and Aerosol Research Study (DEARS) using enhanced personal monitoring to elucidate the specific air pollution components, sources, and time frames of exposure responsible. In this first report, we provide the initial results that compare the associations of changes in CV outcomes elicited by alterations in daily personal-level versus community ambient $PM_{2.5}$ exposures.

Materials and Methods

The study was approved by Institutional Review Boards of the University of Michigan and RTI International as well as the Human Subjects Approving Official of the Environmental Protection Agency (EPA).

Design

This project represents a CV sub-study of the main DEARS involving community, residential, and personal-based measurements of air pollutants targeting 120 participants randomly chosen to reflect the characteristics of the local population. The detailed methodology is described elsewhere.[11-12] Field sampling was conducted during 2 periods per year (winter and summer seasons) over 3 years (6 seasons) and completed during the spring of 2007 using a common protocol for direct comparisons between pollutant concentrations, constituents, and sources at the various spatial settings.[13-15] Pollution monitoring was conducted in 6 neighborhoods within Wayne County, Michigan along with one community site. One volunteer from each randomly selected household also underwent personal-level pollution monitoring for 5 consecutive days during winter and summer periods. All participants were non-smokers living in a non-smoking household and at least 18 years of age. There were no other exclusion criteria, including by race, occupation, sex, or health status. New volunteers were recruited on an ongoing basis each monitoring year. A variety of surveys were utilized to fully capture human and environmental factor data (www.epa.gov/dears) needed to determine potential environmental source contributions to personal exposures.[16] A randomized recruitment strategy was successful in enrolling nearly 140 participants in the main DEARS cohort. This approach involved establishing computer generated stratified systematic samples (clusters) selected from an address list which had been previously sorted using data from the 2000 Census block group profiles. A total of 1702 contacts were subsequently made with potential households ultimately resulting in a 19% recruitment response rate during the life of the study. A full description of the recruitment strategy will be described elsewhere. All DEARS participants were invited to participate in the in the CV sub-study during seasons 2-6. These participants had another visit for written informed consent. The average of the 2nd and 3rd of 3 seated BP measurements was determined and a fasting lipid profile with glucose was obtained (Cholestech Corp).

Exposure Assessments and $PM_{2.5}$ Measurement

Personal $PM_{2.5}$ data collections were performed using Personal Environmental Monitors (PEMs) designed by RTI International (Research Triangle Park, NC 27709) as previously reported by Williams et al.[12] and elsewhere.[9,17-19] PEM sampling was initiated each monitoring day (Tuesday through Saturday) at a consistent time (9 am ± 2.5 hr). Each monitoring session represented a continuous 24 hr period of air collection (~2.9 m^3). Personal monitors were deployed using a lightweight nylon monitoring vest[19] with the inlet of the PEM sampler positioned in the breathing zone. Study participants were instructed to perform routine daily activities and to wear the vest at all times except for periods of sleeping, bathing, or the changing of clothes (exclusion scenarios) when it was to be kept as close as possible to the subject (e.g. side of bed). The vest contained sensors[12] that provided information as to how compliant the participant was relative to wearing the vest during all times except the exclusion scenarios. Data from these sensors and surveys provided the means to establish a percentage of time per day when the vest was worn in compliance. Only results from subjects meeting a pre-specified compliance rate of ≥60% were analyzed in this study including 65% of all participants, with the rationale described elsewhere that this should yield the most accurate and robust estimation of the health-exposure association.[12]

Community PM monitoring was conducted at a nearby State of Michigan air quality monitoring site (Allen Park). The distance to this site from the neighborhoods was 2.5-18 miles. This site was selected because of its proximity to many of the neighborhoods and the fact that it is classified as a residential neighborhood monitor with respect to local PM attainment issues. The specifics of this monitoring have been previously described.[12]

Air samples collected on Teflon filters were returned to the EPA laboratory for analysis. This included determining the amount of loaded $PM_{2.5}$ mass.[17,20] as well as the elemental composition of the mass. X-ray fluorescence (XRF)[19,21,22] was used to establish the sulfur component of the loaded mass on each filter as a potential marker of PM of ambient origin. The use of sulfur as a regional PM trace marker has been reported by ourselves and others.[23-25] Few indoor sources of sulfur exist. Therefore, its determination often provides insight as to the extent that PM of ambient origin impacts the personal breathing zone of an individual. The ratio of elemental sulfur found on the personal filter as compared to that from a date matched community-based sample provides the means to establish the personal exposure factor to PM of ambient origin (F_{pex}). Knowing this factor allows for the capacity to categorize TPE into sub-categories:

of ambient (i.e. PEAO) and non-ambient (i.e. PENAO) origins.[10] Some of the indoor and personal sources impacting PENAO would be expected to be those from cooking, cleaning, and grooming activities.[26] This categorization of PM exposure sources is important because PM regulations are established on community concentrations and the vast majority of all PM epidemiological studies have utilized community measures as their surrogate for personal exposure.[12]

While DEARS participants reported to be non-smokers living in non-smoking households, compliance with this requirement and the participant's exposure to SHS was determined. Personal exposure filter samples were optically analyzed for SHS using a technique previously described by Lawless et al.[27] and Williams et al.[12] Data from this effort provided a mass-based estimate ($\mu g/m^3$) of SHS impact upon all personal exposure measurements. While this optical measure was not specific to just SHS-absorbing constituents, it did provide a rapid means of determining potential SHS compliance issues during the field monitoring. In addition, it provided the means of establishing a semi-quantitative method to identify participants that might have been impacted by SHS. Personal monitoring samples having SHS concentrations $\geq 1.5\ \mu g/m^3$ were a priori defined for the purposes of this study as being impacted. This value was previously established based upon the fact that such concentrations would typically represent approximately 5-10% of the total sample mass associated with personal monitoring.[12]

Cardiovascular Endpoint Protocols

All study visits were performed at the participant's residence for up to 5 consecutive evenings, Tuesday through Saturday, between the hours of 4 and 8 PM. These CV visits took place on concurrent days with pollution vest monitoring, as per design of the main DEARS. There were 4 CV outcomes for which this study was a priori designed and powered. These include changes in: systolic and diastolic BP, brachial artery diameter (BAD) and FMD. Participants were instructed to maintain their daily routine, including taking all medications, but to fast for at least 4 hours prior to the scheduled visits and to avoid unusual physical activity. At each visit, subjects lied supine for 10 minutes prior to automated BP (Omron 780 monitor) and heart rate measurement that was obtained in triplicate with a one minute lapses between measures. The average of the 2nd and 3rd BP and heart rate was used for analyses.

Brachial images were obtained with a portable Terason2000 ultrasound system with a 10.0 mHz linear array transducer with ECG-gated image acquisition (http://www.terason.com/; Teratech, Corp.). Five minutes of upper arm occlusion using a rapidly deflating arm cuff was performed in order to determine FMD, which was defined as the mean percent increase in BAD above baseline diameter from between 50-70 seconds after cuff deflation. Images were analyzed using semi-automated edge detection software (Vascular Research Tools, Medical Imaging Applications; http://www.mia-llc.com/). NMD was next determined as the percent dilatation of the BAD 3 minutes following 0.4 mg of sublingual nitroglycerin. Detailed descriptions of the methods have been previously described and accord with guidelines,[28] while the reproducibility of our testing is reported elsewhere.[29]

Statistical Assumptions and Models

The mean 24-hour integrated $PM_{2.5}$ exposure assessed by community ambient $PM_{2.5}$, and personal-level exposures meeting (60% compliant were each associated with the biological responses measured 1 and 2 days later (lags 1 and 2). Due to the fact that the CV outcomes were obtained between 4-8 PM on study days, the $PM_{2.5}$ mass levels of exposure (personal and community mean daily levels) occurred from approximately 7-11 to 31-35 hours (lag 1) and from 31-5 to 55-9 hours (lag 2) prior to the measured CV outcome. There is a brief period during the same morning of each day prior to obtaining CV outcomes when the exposure to $PM_{2.5}$ was not characterized, which will be done in subsequent analysis by data from continuous nephelometry. Only the CV outcomes measured on Wed-Sat could be matched with the corresponding lag TPE measurement period (Tues-Fri), thus reducing the number of personal PM-CV outcome associations available compared to the associations with community ambient levels. In addition, because some subjects performed less than 3 consecutive days of CV outcomes, fewer results were available for lag 2 day personal monitoring associations and we did not look at longer lag periods > 2 days or moving averages of duration greater than 1 day as the number of observations was substantially reduced. Two subjects who had only 1 day of CV measurements were not included in the analyses because data from the required 1 previous days' personal monitoring could not be matched up to their CV outcomes. Missing days of CV outcome measurements were due to inabilities to schedule a visit at the subjects' home at the required time on every day of PM monitoring among all subjects; however, this did not disqualify them from

initial enrolment into the sub-study. Eight extreme outliers (>2 standard deviations from means of BAD, FMD and NMD) were believed to result from errors in ultrasound measurements upon evaluation of the data and by pre-specified quality control measures.[28] We pre-determined that these erroneous measurement results be excluded. Using mixed models, we assessed the associations between each of the CV responses and exposure metrics to $PM_{2.5}$ with other available predictors included as fixed effects (age, gender, race, body mass index and ambient temperature). Full details of the model are provided in the supplement. The analysis was preformed by function "lme (linear mixed-effects model)" in R (version 2.8.1) with significance defined as a p value of <0.05 or <0.1.

Results

Tables 1 and 2 demonstrate the characteristics of the 65 subjects enrolled in the CV sub-study. Eighteen subjects participated in 2 separate consecutive seasons; thus, there were a total of 83 subject-observation periods. Two subjects had 2, ten subjects had 3, twenty-four subjects had 4, and forty-five subjects had 5 days of CV observations per study season. Supplement Table 1 demonstrates enrollment timing and acquired CV outcome observations. Participants reported on average that they were engaged in an occupational setting 36% of their time while they spent 3.5% of each day outside.

The daily integrated 24 hour-long $PM_{2.5}$ exposures are presented in Table 3 and in greater detail elsewhere[38]. TPE exceeded community-level ambient exposures and was more variable. PEAO was on average greater than PENAO. Community ambient $PM_{2.5}$ levels were only weakly correlated with the personal exposures (all $r<0.25$) (Supplement Figure).

Community-level ambient $PM_{2.5}$ mass was not associated with any CV outcome (Table 4). No exposure was related to FMD. On the other hand, mean daily TPE was significantly associated with an elevation in systolic BP (lag day 1) with a trend towards an increase in diastolic BP (Table 5). For example, a 10 $\mu g/m^3$ increase in TPE led to a 1.41 mm Hg elevation in systolic BP one day later. There was a borderline non-significant association between TPE and a decrease in BAD (i.e. vasoconstriction) on lag day 2. Likely due to the reduction in the number of observations due to the high frequency of SHS exposures, there were no significant associations between BP and TPE when limited to subjects with low SHS exposure. To assess whether the BP-raising effect of TPE was due to SHS, we analyzed both exposures together in a model

controlling for the same-day level of the alternate exposure type. TPE was still associated on lag day 1 with an increase in systolic BP (+0.82 mm Hg per 10 $\mu g/m^3$ increase in $PM_{2.5}$ mass, p=0.05). In addition, a 10 $\mu g/m^3$ increase in the mean daily personal exposure to SHS was also associated with an increase in systolic BP of 3.94 (p=0.03) and 6.57 (p=0.02) mm Hg on lag days 1 and 2, respectively. Supplemental Table 2 provides more information regarding the effects of SHS and TPE.

PEAO and PENAO were not associated with BP (Supplement Tables 3 and 4), potentially due to reduced number of observations available. However, mean daily PEAO was significantly related to a decrease in BAD (-0.11 mm) consistent with vasoconstriction on lag day 2, even among subjects with low SHS exposure (-0.15 mm). PENAO showed a similar but non-significant trend. Both results on day 2 are similar to the trend in vasoconstriction (BAD reduction) associated with TPE on a similar time scale. On the other hand, there were non-significant earlier trends towards vasodilatation (BAD increase) in association with TPE, PEAO and PENAO on day 1.

In order to more adequately compare the effect sizes on systolic BP between changes in community and TPE levels that were typically encountered, we estimated a change in of 2.17 mm Hg (95% confidence interval (CI) 1.18, 3.17) per 15.4 $\mu g/m^3$ (IQR concentration) of TPE recorded on the day prior to testing. The corresponding change per 9.5 $\mu g/m^3$ (IQR concentration) of community ambient $PM_{2.5}$ levels was 0.49 mm Hg (95%CI -1.00, 1.61). During analyses of effect modification by available covariates (including subject demographics and factors in Table 1) using interaction terms in the linear mixed model, only systolic BP (average of measurements during the study) effected the association between TPE and systolic BP. When analyzed separately, subjects (n=38, 117 observations) with a mean systolic BP $\leq$ 140 mmHg had no association (0.02 mm Hg, p=0.98), while those with a systolic BP > 140 mm Hg (n=12, 36 observations) showed a significant and more robust response (2.4 mm Hg, p<0.001) per 10 per 10 $\mu g/m^3$.

Discussion

While community ambient $PM_{2.5}$ levels were not related to changes in the CV endpoints, each personal exposure metric was significantly associated with small alterations in either BP or vascular function from 1-2 days later. TPE and SHS were both related to modest increases in systolic BP (lag day 1), while PEAO was associated with arterial vasoconstriction (lag day 2). TPE and PENAO showed similar non-

significant trends toward vasoconstriction. These are the first findings to demonstrate that the method of assessing an individual's exposure to $PM_{2.5}$ influences the observed relationships with both BP and vascular function. The lack of responses induced by comparable elevations in community $PM_{2.5}$ suggests that fine particles encountered at the personal-level may elicit differing CV responses than background ambient levels. Whilst the explanation must remain speculative, it is likely that differences in the particle sources/characteristics (as they can vary considerably per exposure metric) may be important determinants of the capacity for $PM_{2.5}$ to elicit these adverse responses. Additionally, personal exposures can be impacted by source-proximity relationships that cannot be mimicked by a fixed-location sensor.[39]

Responsible Constituents

Though personal and community-level ambient $PM_{2.5}$ exposures are correlated longitudinally within individuals,[30] significant between subject differences can exist.[8,10] Many factors determine the TPE unique to individuals including time outdoors, indoor sources, and conditions that alter the indoor-outdoor air exchange.[10,26] We observed low cross-sectional correlations between personal and ambient community $PM_{2.5}$ (Supplement Figure). This suggests that these exposures occurred largely independent and are likely to differ in their characteristics and thus health effects -- as we observed.

While PEAO and PENAO showed some relationships with vasoconstriction they were not associated with BP, possibly due to less available observations and these metrics being secondary outcomes (i.e. the study was not a priori powered to explore their effects). Hence, we were unable to gain insight in this initial analysis into the personal-level particle components responsible. More knowledge into the specific PM constituents/sources, along with potential explanations for the discordant findings related to community ambient levels, will likely be gained in our on-going analysis. Nevertheless, these current results add to the evidence[3,5] that personal exposures to $PM_{2.5}$ may be capable of modestly increasing systolic BP within a day.

Transient SHS exposure may also trigger acute CV events.[31] Our findings also suggest that mean SHS exposure over the previous day is also associated with an elevation in systolic BP 1 and 2 days later.. On a direct PM mass comparison basis, the BP raising effects of particulate SHS appeared to be larger than TPE not derived from tobacco smoke, though SHS did not entirely account for the effect of TPE (Supplement Table 2). Whether this is due to effects of nicotine or other components requires more

investigation. On the other hand, exposures to SHS on a particle mass basis were substantially smaller than to TPE as a whole (Table 3), and thus their comparative total contribution to the changes in BP may be more similar for this reason. This pressor effect of SHS occurred despite participants being non-smokers living in non-smoking households - yet approximately one third were exposed passively daily to SHS. No ordinance was in effect against smoking in public venues at the time of this study, potentially explaining this high frequency of exposure. These findings support the health importance of reducing exposure to SHS in public venues (e.g. indoor smoking bans).

Blood Pressure

Average 24-hour-long TPE was associated with a small increase in systolic BP approximately 8-10 hours later. Our findings are supported by similar responses following a few hour personal exposure to sub-micron particles[3] and 24 hour-long personal exposures to $PM_{2.5}$.[5] However, few studies have compared the BP responses elicited by air pollutants concomitantly measured at the personal and community level. Brauer et al.[7] reported borderline non-significant associations between ambient and personal $PM_{2.5}$ with a lower systolic BP 1 day later, which was attributed to PEAO.[8] Differences in the characteristics of their subjects (i.e. lung disease) and ambient $PM_{2.5}$ components might explain why they observed a discordant BP response compared to our increased BP. Nevertheless, we both observed stronger relationships between BP and personal exposure metrics compared to community ambient $PM_{2.5}$.

There are several possible explanations for the BP association with TPE and not community ambient $PM_{2.5}$ in contrast to earlier findings in Detroit[4] and by others elsewhere.[2,32] It is possible that TPE provided a more "accurate" exposure assessment and/or that there was some exposure misclassification by the community levels. The specific pollutants within TPE may have been capable of eliciting a larger and thus more observable BP elevation. However, we believe that a third possibility is the most likely. The particle compounds within the TPE may have been capable of triggering a more rapid increase in BP compared to a slower response induced by community ambient $PM_{2.5}$. Most earlier studies[2,4,32] illustrate that the BP-raising effect attributed to community ambient $PM_{2.5}$ occurs largely in a delayed fashion (>2-3 days post-exposure). On the other hand, similar to the current study, a more rapid response has also been shown to occur within 1 day following an increase in personal level exposures.[3,5] In tandem with our previous observations that community-level ambient $PM_{2.5}$ raised BP

within one but not other regions of Detroit,[4] these findings suggest that the particle components and/or sources may be important determinants of the capacity for $PM_{2.5}$ to alter BP. On-going analyses will investigate this in detail.

Vascular Function

PEAO was significantly associated with a decrease in BAD (i.e. vasoconstriction) 2 days post-exposure. TPE and PENAO showed similar non-significant trends. This agrees with the pro-vasoconstrictive effects of personal $PM_{2.5}$ exposure observed by Liu et al.[5] and adds to the evidence that personal-level exposures may be capable of triggering arterial vasoconstriction within days. On the other hand, there were non-significant trends among personal exposure metrics towards vasodilatation (increased BAD) occurring earlier (lag 1). These apparently discordant responses may represent chance, or result from a single mechanism, as discussed later.

No $PM_{2.5}$ exposure was associated with FMD. This is in contrast to previous studies demonstrating that community-level pollution is related to a lower FMD.[6,33] Though the reasons behind this discrepancy are unclear, it is possible that differences in susceptibility (i.e. diabetic and metabolic syndrome patients in previous reports) or differences in the characteristics of the $PM_{2.5}$ were responsible. However, our on-going analyses may yet uncover specific particle constituents associated with adverse FMD changes, as certain components (e.g. black carbon) were more strongly associated with FMD than particle mass in the previous "positive" studies as well.[33] As such, specific particle components/sources may be primarily capable of inducing endothelial dysfunction, which mass alone may not have adequately characterized in this study.

Biological Mechanisms

The acute increase in BP within hours of $PM_{2.5}$ exposure is likely mediated by autonomic nervous system imbalance.[29,34] On the other hand, we have ascribed the slower BP elevations initiated 1 or more days following exposure to lower levels of ambient particles to impaired vasomotor homeostasis induced by systemic inflammation.[29,35] Indeed, $PM_{2.5}$ exposure has proven capable of blunting nitric oxide-induced vasodilatation.[6,33] As brachial FMD was not reduced in this study, our findings do not directly support for this latter mechanism. Nevertheless, it cannot be excluded that $PM_{2.5}$ may have caused an isolated impairment of microvascular function 1 day post-exposure (not evaluated in this study), thereby promoting arteriole constriction and

consequently an increase in BP. For this scenario to be true, $PM_{2.5}$ would have had to elicit a more rapid vasoconstrictive response within the microvasculature than observed 2 days post-exposure in the brachial artery. This is plausible as conduit and resistance vascular territories can react discordantly. However, the final outcomes observed may in actuality reflect a more complicated biological situation resulting from the sum of multiple variable changes including reductions in vasodilators other than nitric oxide, augmentation of vasoconstrictor pathways (e.g. endothelins), or direct effects of PM components reaching the vasculature, each occurring in differing time frames and with discordant sensitivities among the various vascular territories.[1]

Chance alone may explain why BAD trended towards a non-significant increase on day 1 in relation to many of the personal exposures. On the other hand, there may be an alternative unifying mechanism potentially capable of explaining the responses. There is complex interaction between the autonomic nervous system and vascular function.[36] Resistance arteriole vasoconstriction mediated by sympathetic activity can cause a reflex increase in basal nitric oxide release in conduit vessels supplying skeletal muscles and β_2 receptor activation that cause vasodilatation (i.e. increased BAD) allowing for adequate blood flow under periods of stress. An increase in sympathetic tone lasting up to 24 hours following higher personal exposures[1] could have caused both conduit brachial artery vasodilatation[37] and the concomitant increase in systolic BP on lag day 1. In this scenario, the delayed vasoconstriction seen on day 2 may have also been elicited by the same 24-hour long imbalance in autonomic activity, as vascular function has been shown to be impaired one day following a short burst of enhanced sympathetic tone.[37] Regardless of the responsible mechanisms, both the acute elevation in systolic BP (day 1 after TPE) and the vasoconstriction (day 2 after PEAO) demonstrate that $PM_{2.5}$ encountered at the personal-level has the capacity to affect the systemic CV system. They are also credible mechanisms that could contribute to an increase in CV events in some individuals. The greater increase in BP among those with higher baseline systolic BP also suggests that certain individuals may be more susceptible.

Study Strengths and Limitations

This is the first protocol to measure FMD in the "field" (households) in relation to PM exposure. This provided a robust mechanism to investigate the "real" effect of routine daily personal and ambient $PM_{2.5}$ exposures without the extraneous effects of

doing so in a research laboratory (e.g. atypical commutes/exposures). However, the strengths of this design could have been partially mitigated by less reproducibly in FMD than can be anticipated in laboratory setting (Table 1),[28] possibly causing type 2 errors. On the other hand, few studies have evaluated the CV effect of both personal and community-level ambient $PM_{2.5}$ exposures.[8] This study is also highly unique in its ability to link multiple metrics of different exposures (while also substantially reducing exposure misclassifications with personal vest monitoring that accounts for patient adherence and SHS exposures) with both vascular function and BP. These strengths are likely important factors that bolster the veracity of our results as discussed elswhere[38].

There was potential for enrollment bias into the CV sub-study. However, the subject characteristics (except for more females) were consistent with the local demographics. On-going analyses are expected to elucidate remaining issues including the particle sources/components responsible as well as the effects of co-pollutants (e.g. gases such as ozone). Though the study was a priori designed and powered with the specific intent to investigate the effects of these 2 different exposures (TPE and community-level) on BP and FMD, multiple statistical comparisons were made. Some findings were found only in sub-sets of individuals (e.g. PEAO), potentially causing some type I errors in some of the reported positive associations in relation to these results in particular. The reduction in available observations on lag day 2 and in association with some personal exposure metrics may have alternatively resulted in some type II errors. Nonetheless, given the high level of significance of the systolic BP-TPE association in the main group and this being one of our pre-specified outcomes/analyses, at the very least this positive finding likely represents a real biological association. The consistency of the vasoconstriction with previous reports[5] lends credibility to its veracity as well.

The 24-hour integrated PM-based exposure measures and the home health-based CV outcomes were measured on the same days but not fully matched relative to their collection times. There was a brief period (4-9 hours) without PM measurement prior to the CV outcome measurement. This may be a source of exposure misclassification, even though we evaluated the effect of mean $PM_{2.5}$ exposure levels that are on lag days 1-2, as commonly done in panel studies[1-6]. We are currently recovering data from continuous personal PM measurements that were performed right up to the time of obtaining the CV outcomes. This will allow us to examine the effects of particles on the CV outcomes with much greater temporal resolution.

Conclusions

TPE encountered during routine daily activity and monitored with low-bias and minimally-confounded exposure metrics was associated with small elevations in systolic BP. The findings also suggest that PEAO may be related to arterial vasoconstriction. Both occurred in a manner potentially increasing CV risk among susceptible people. On the other hand, community ambient $PM_{2.5}$ was not related to any outcome. The findings demonstrate that fine particles encountered at the personal-level may elicit differing CV responses than background ambient levels. This supports the hypothesis that particle sources and/or characteristics, as they can vary considerably between exposures types, are likely important determinants of the CV responses induced by short-term exposure.

Sources of funding

The US EPA through its Office of Research and Development partially funded and conducted the research under contract 68-D-00-012 (RTI International), EP-D-04-068 (Battelle Columbus Laboratory), 68-D-00-206 and EP-05-D-065 (Alion Science and Technology). It has not been subjected to Agency review and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use. Carvin Stevens and Teri Conner (EPA) and Phil Lawless (RTI International) are acknowledged for their technical assistance regarding some of the exposure analyses.

This study was also supported by the Electric Power Research Institute (Contract EP-P15887/C7915) and from a National Institutes of Health General Clinical Research Center Grant: M01-RR000042.

References

1. Brook RD. Cardiovascular effects of air pollution. *Clin Sci* 2008;115: 175-87.

2. Auchincloss AH, Roux AV, Dvonch JT, Brown PL, Barr RG, Daviglus ML, et al. Associations between recent exposure to ambient fine particulate matter and blood pressure in the Multi-ethnic Study of Atherosclerosis (MESA). *Environ Health Perspect* 2008;116:486-91.

3. Chuang KJ, Chan CC, Shiao GM, Su TC. Associations between submicrometer particles exposures and blood pressure and heart rate in patients with lung function impairments. *J Occup Environ Med.* 2005;47:1093-8.

4. Dvonch JT, Kannan S, Schulz AJ, Mentz G, House J, Benjamin A, et al. 2009. Acute effects of ambient particulate matter on blood pressure: Differential effects across urban communities. *Hypertension* 2009;53: 853-9.

5. Liu L, Ruddy TD, Dalipaj M, Poon R, Szyszkowicz M, You H, et al. 2009. Effects of indoor, outdoor, and personal exposure to particulate air pollution on cardiovascular physiology and systemic mediators in seniors. *J Occup Environ Med* 51: 1088-98.

6. Schneider A, Neas L, Herbst MC, Case M, Williams RW, Cascio W, et al.. Endothelial dysfunction: associations with exposure to ambient fine particles in diabetic individuals. *Environ Health Perspect* 2008;116:1666-74.

7. Brauer M, Ebelt ST, Fisher TV, Brumm J, Petkau AJ, Vedal S. Exposure of chronic obstructive pulmonary disease patients to particles: Respiratory and cardiovascular health effects. *J Exp Anal Environ Epidemiol* 2001;11: 490-500.

8. Ebelt ST, Wilson WE, Brauer M. Exposure to ambient and nonambient components of particulate matter. A comparison of health effects. *Epidemiology* 2005;16: 396-405.

9. Rodes C, Lawless P, Evans G, Sheldon L, Williams R. Vette A. The relationships between personal PM exposures for elderly populations and indoor and outdoor concentrations for three retirement center scenarios. *J. Exposure Analysis and Environmental Epidemiology* 2001;11: 103-115.

10. Wallace L, Williams R, Suggs J, Jones P. Estimating Contributions of Outdoor Fine Particles to Indoor Concentrations and Personal Exposures: Effects of Household Characteristics and Personal Activities. ORD Report (APM 214). EPA/600/R-06/023. NTIS# PB2006-11353, March 2006. Washington, DC.

11. Williams R. 2005. EPA's Detroit Exposure and Aerosol Research Study. EPA Research Highlights, *AWMA Environmental Manager*, October 2005, pp43.

12. Williams R, Rea A, Vette A, Croghan C., Whitaker D, Wilson H, et al. 2008a. The design and field implementation of the Detroit Exposure and Aerosol Research Study (DEARS). *Journal of Exposure Science and Environmental Epidemiology*. 2009;19: 643–59.

13. Baxter L, Barzyck T, Vette A, Croghan C, Williams R. Contributions of diesel truck emissions to indoor elemental carbon concentrations in homes proximate to the Ambassador Bridge. *Atmospheric Environment* 2008;42:9080-6.

14. Barzyk T, George B, Vette A, Williams R, Croghan C, Stevens C. Development of a distance-to-roadway proximity metric to compare near-road pollutant levels to a central site monitor. *Atmospheric Environment* 2009;43:787-97.

15. Thornburg J, Rodes C, Lawless P, Williams R. Spatial and Temporal variability of outdoor coarse particulate matter mass concentrations measured with a new coarse particle sampler during the Detroit Exposure and Aerosol Research Study. *Atmospheric Environment*. 2009;43:4251-8.

16. US EPA (2009).The US EPA Detroit Exposure and Aerosol Research Study (DEARS) website. (www.epa.gov/dears).

17. Williams R, Suggs J, Zweidinger R, Evans G, Creason J, Kwok R, et al. The 1998 Baltimore particulate matter epidemiology-exposure study: part 1-comparison of ambient, residential outdoor, indoor and apartment particulate matter monitoring. *J. Exposure Analysis Environmental Epidemiology* 2000;10:518-32.

18. Williams R, Suggs J, Zweidinger R, Evans G, Creason J, Kwok R, et al. Comparison of $PM_{2.5}$ and PM_{10} monitors. *J. Exposure Analysis Environment Epidemiology* 2000;10:497-505.

19. Williams R, Suggs J, Rea A, Leovic K, Vette A, Croghan C, et al. The Research Triangle Park particulate matter panel study: PM mass concentration relationships. *Atmospheric Environment* 2003;37:5349-63.

20. Lawless P, Rodes C. Maximizing data quality in the gravimetric analysis of personal exposure sample filters. *J Air Waste Management Association* 1999;49:1039-49.

21. Dzubay T, Stevens R, Gordon G, Olmez I, Sheffield A, Courtney W. A composite receptor method applied to Philadelphia aerosol. *Environmental Science and Technolology* 1988;22:46-52.

22. Landis M, Norris G, Williams R, Weinstein, J. Personal exposures to PM2.5 mass and trace elements in Baltimore, Maryland. *Atmospheric Environment*. 2001;35:6551-24.

23. Sarnat JA, Long CM, Koutrakis P, Coull BA, Schwartz J, Suh HH. Using sulfur as a tracer of outdoor fine particulate matter. *Environ Sci Tech* 2002;36:5305-14.

24. Wallace L, Williams R. Use of personal-indoor-outdoor sulfur concentrations to estimate the infiltration factor, outdoor exposure factor, penetration coefficient, and deposition rate for individual homes. *Environmental Science and Technology* 2005;39: 1707-14.

25. Williams R, Case M, Yeatts K, Chen F, Scott J, Svendsen E, et al. Personal coarse particulate matter exposures in an adult cohort. *Atmospheric Environment*, 2008;42: 6743-8.

26. Wallace L, Williams R, Rea A, Croghan C. Continuous week long measurements of personal exposures and indoor concentrations of fine particles for 37 health-impaired North Carolina residents for up to four seasons. *Atmospheric Environment* 2006;40: 399-414.

27. Lawless P, Rodes C, Ensor D. Multiwavelength absorbance of filter deposits for determination of environmental tobacco smoke and black carbon. *Atmospheric Environment* 2004;38:3373-83.

28. Brook RD, Grau M, Kehrer C, Rajagopalan S Intra-subject Variability of Radial Artery Flow Mediated Dilatation: Implications for Use in Prospective Clinical Trials. *Am J Cardiol* 2005;96:1345-8.

29. Brook RD, Urch B, Dvonch JT, Bard RL, Speck M, Keeler G, et al. Insights into the Mechanisms and Mediators of the Effects of Air Pollution Exposure on Blood Pressure and Vascular Function in Healthy Humans. *Hypertension* 2009;54: 659-67.

30. Janssen NAH, Lanki T, Hoek G, Vallius M, de Hartog JJ, Van Grieken R, et al. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. *Occup Environ Med* 2005;62:868-77.

31. Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation.* 2005;111:2684-98.

32. Zanobetti A, Canner MJ, Stone PH, Schwartz J, Sher D, Eagan-Bengston E, et al.. Ambient pollution and blood pressure in cardiac rehabilitation patients. *Circulation* 2004;110:2184-89.

33. O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, et al. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. *Circulation* 2005;111:2913-20.

34. Bartoli CR, Wellenius GA, Diaz EA, Lawrence J, Coull BA, Akiyama I, et al. Mechanisms of inhaled fine particulate air pollution-induced arterial blood pressure changes. *Environmental Health Perspectives* 2009;117:361-6.

35. Sun Q, Yue P, Ying Z, Cardounel AJ, Brook RD, Devlin R, et al.. Air pollution exposure potentiates hypertension through reactive oxygen species-mediated activation of Rho/ROCK. *Arterioscler Thromb Vasc Biol* 2008;29:1760-66.

36. Harris KF, Matthews KA. Interactions between autonomic nervous system activity and endothelial function: A model for the development of cardiovascular disease. *Psychosom Med*. 2004;66:153-64.

37. Hijmering ML, Stroes ESG, Olijhoek J, Hutten BA, Blankestijn PJ, Rabelink TJ. Sympathetic activation markedly reduces endothelium-dependent, flow-mediated vasodilation. *J Am Coll Cardiol* 2002;39:683-8.

38. Rodes, CE., Lawless, PA., Thornburg, JW, Williams, RW., Croghan, CW. DEARS particulate matter relationships for personal, indoor, outdoor, and central site settings for a general population. *Atmospheric Environment* 2010; 44: 1386-99.

39. Rodes, CE. and JW Thornburg, JW Breathing Zone Exposure Assessment, Chapter 5 in Aerosols Handbook: Measurement, Dosimetry, and Health Effects, 2005, CRC Press, *61-73*.

Table 1 Subject Characteristics (n=65)

FACTOR	Number of observations	MEAN (or number)	SD	Minimum	Maximum
Age (years)	65	44.6	15.7	19	80
Sex	65				
Female		50 (77%)			
Male		15 (23%)			
Race	65				
African American		35 (54%)			
Caucasian		29(45%)			
American Indian		1 (1%)			
Body mass index (Kg/m^2)	63	30.9	8.0	16.7	56.5
SBP (mm Hg)	352	126.6	18.2	91	205
DBP (mm Hg)	352	75.1	10.0	50	101
HR (beats/min)	351	74.4	11.0	50	103
BAD (mm)	319	4.0	0.8	2.1	6.5
FMD (%)	291	3.2	5.2	-12.2	19.7
NMD (%)	165	14.6	7.2	-6.6	36.9

Self Reported Diagnosis of:	**n (%)**	**Number of Subjects using Prescribed Medications**
Hypertension	28 (34)	23
Hyperlipidemia	19 (23)	10
Diabetes Mellitus	13 (16)	9
Family History of CAD	22 (27)	
Self-Reported Heart Disease History:	10 (12)	
Angina	3 (4)	
Myocardial Infarction	3 (4)	
Congestive Heart Failure	4 (5)	
Cardiovascular Medications Used:		
ACEI/ARB	12 (14)	
Diuretic	5 (6)	
Beta Blocker	7 (8)	
Calcium Channel Blocker	11 (13)	

SD, Standard deviation; SBP, systolic blood pressure (BP); DBP, diastolic BP; HR, heart rate; BAD, brachial artery diameter; FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation. ACEI, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Table 2. Daily $PM_{2.5}$ Exposure Concentrations ($\mu g/m^3$)*

	TPE**	Ambient	PEAO	PENAO	P-SHS***
Number of non-missing	312	339	225	225	313
Mean (± SD)	21.9 ± 24.8	15.4 ± 7.5	11.6 ± 8.5	5.8 ± 5.3	4.0±12.7
Median	15.6	13.3	9.4	4.4	0.8
IQR	15.4	9.5	10.5	4.3	2.1
Minimum	1.3	2.8	0.2	0	-0.03
Maximum	225.4	41.0	46.0	46.5	115.4

SD, Standard deviation; IQR, Interquartile range; TPE, total personal $PM_{2.5}$ exposure; Ambient, community-level ambient $PM_{2.5}$; PEAO, personal $PM_{2.5}$ exposure of ambient origin; PENAO, personal $PM_{2.5}$ exposure of non-ambient origin.

*24-hour long Teflon filter-based collections for $PM_{2.5}$ mass measured by gravimetric mass on personal vest (TPE, PEAO, PENAO) or closest community ambient monitor (Ambient).

**TPE was derived from 312 observations while ambient (community-level) exposures were derived from 339 observations, thus TPE may not exactly equal PEAO + PENAO.

***P-SHS, particle SHS (mass) as measured on vest filter. Low SHS is defined as ≤1.5 $\mu g/m^3$.

Table 3. Health Effects Associated with Community-Level Ambient $PM_{2.5}$ Mass

			All Subjects
Health Outcome (unit)	Lag (day)	N	Change in Outcome per 10 $\mu g/m^3$ (95% CI)*
SBP (mm Hg)	1	245	0.32 (-1.052, 1.692)
SBP (mm Hg)	2	169	1.37 (-1.041, 3.781)
DBP (mm Hg)	1	245	0.02 (-1.019, 1.059)
DBP (mm Hg)	2	169	-0.37 (-2.016, 1.276)
HR (beats/minute)	1	245	-0.04 (-1.236, 1.156)
HR (beats/minute)	2	169	-0.12 (-2.119, 1.879)
BAD (mm)	1	219	0.03 (-0.029, 0.089)
BAD (mm)	2	150	-0.01 (-0.108, 0.088)
FMD (%)	1	204	-0.74 (-1.661, 0.181)
FMD (%)	2	140	0.69 (-0.623, 2.003)
NMD (%)	1	120	-0.54 (-1.990, 0.910)
NMD (%)	2	81	-2.10 (-4.707, 0.507)

*Accounting for sex, age, race, temperature on day of measurement, and BMI.

N, number of observations; CI, confidence interval; SBP, systolic blood pressure (BP); DBP, diastolic BP; HR, heart rate; BAD, brachial artery diameter; FMD, flow-mediated dilatation; HR, heart rate; NMD, nitroglycerin-mediated dilatation.

Table 4. Health Effects Associated with Total Personal $PM_{2.5}$ Mass (TPE)

		Vest Compliance (≥60%) and low-SHS*		Vest Compliance (≥60%)	
Health Outcome (unit)	Lag (day)	N†	Change in Outcome per 10 μg/m³ (95% CI)**	N†	Change in Outcome per 10 μg/m³ (95% CI)**
SBP (mm Hg)	1	97	0.71 (-0.544, 1.964)	153	**1.41 (0.763, 2.057)**
SBP (mm Hg)	2	68	-0.57 (-2.295, 1.155)	108	**-0.80 (-1.643, 0.043)**
DBP (mm Hg)	1	97	0.49 (-0.451, 1.431)	153	**0.44 (-0.070, 0.950)**
DBP (mm Hg)	2	68	0.46 (-0.696, 1.616)	108	-0.28 (-0.848, 0.288)
HR (beats/minute)	1	97	0.18 (-1.251, 1.611)	153	-0.32 (-0.986, 0.346)
HR (beats/minute)	2	68	-0.84 (-2.741, 1.061)	108	-0.07 (-0.932, 0.792)
BAD (mm)	1	94	0.05 (-0.009, 0.109)	137	0.02 (0.000, 0.040)
BAD (mm)	2	62	**-0.08 (-0.158, -0.002)**	91	**-0.03 (-0.069, 0.009)**
FMD (%)	1	86	0.52 (-0.303, 1.343)	127	0.09 (-0.322, 0.502)
FMD (%)	2	59	-0.59 (-1.629, 0.449)	87	-0.10 (-0.649, 0.449)
NMD (%)	1	54	-0.39 (-1.938, 1.158)	72	-0.68 (-1.993, 0.633)
NMD (%)	2	36	0.13 (-1.771, 2.031)	48	0.64 (-1.163, 2.443)

*Low SHS defined as ≤1.5 μg/m³ of SHS components as measured on vest filter.

**Accounting for sex, age, race, temperature on day of measurement, and BMI

†The number of associations is reduced compared to the total available outcomes as in Table 3 because only patients with a vest compliance ≥60% (and with low SHS exposure when relevant) were included in the analyses as described in methods. Lag day 2 also had less available observations performed for most outcomes because there were fewer subjects with 3 days of CV measurements (Supplemental Table 1).

SHS, secondhand smoke; N, number of observations; CI, confidence interval; SBP, systolic blood pressure (BP); DBP, diastolic BP; HR, heart rate; BAD, brachial artery diameter; FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation.

Bold results are highlighted trends in associations where a p value is <0.1.

Supplement

Full Statistical Methods

Per the a priori design, the 4 main response variables were: systolic BP, diastolic BP, BAD, FMD. Two other responses were also evaluated as secondary outcomes: heart rate (HR) and NMD. A normal distribution was adequate in describing the stochastic structure of these variables after accounting for the suite of predictors. The repeated observations for each season within a subject are likely to be more similar to each other than observations on different subjects. These repeated measures can induce extra variation and intra-class correlation in the data. We accounted for this extra variation using mixed linear models for which unbiased and efficient estimates of effect and uncertainty are obtained. The subjects were considered to be selected at random from a population. Several predictors of the response were included in the model as fixed effects: age, gender, race, body mass index and ambient temperature. The relationship between these predictors and responses was assumed to be common to all subjects. All other available covariates including season (i.e. winter versus summer), personal-level environmental temperature measured by vest monitoring, and the subject's study day (e.g. first versus second day of monitoring during the 5 day period) and neighbourhood were not included in the final model as they did not predict responses individually or alter the significance of any results. We also assumed that the association between each of the responses evaluated and exposure to $PM_{2.5}$ is linear with an intercept varying at random over individuals and a slope assumed to be the same for all subjects.. The analysis was preformed by function "lme (linear mixed-effects model)" in R (version 2.8.1) with significance defined as a p value of <0.05.

Specifically, the model has the form:

$$y_{it} = \beta_0 + \beta_1 PM_{2.5} + \beta_2 Age + \beta_3 Sex + \beta_4 BMI + \beta_5 Temp + \beta_6 Race + \eta_i + e_{it} \quad (1)$$

where y_{it} represents the CV response for the i^{th} subject at the t^{th} repeated measurement time, $(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6)$ are unknown fixed effect regression parameters corresponding to the intercept, air pollution, age, sex, body mass index (BMI), and ambient temperature (Temp) predictor variables respectively. The random effects variable η_i represents a random intercept for the i^{th} subject and is assumed to be normally distributed with zero expectation and common variance among subjects. The

residual error term e_{it} is also assumed to be normally distributed with zero expectation and common covariance over time measurements for all subjects.

We considered the possibility that the within-subject errors (the e_{it} 's in the model (1) above) are auto-correlated. A covariance structure was employed in which the repeated responses within each subject over time were assumed to follow an autoregressive process of order 1, AR(1). Specifically, $corr(e_{it}, e_{i,t-k}) = \rho(k)$, the correlation between these two errors recorded k day apart is $\rho(k) = \lambda^{|k|}$, where $0 \le \lambda < 1$. However, there was no evidence that such a temporal correlation structure improved the fit to the data after including the fixed effect predictor variables (age, gender, race, body mass index, ambient temperature, and air pollution) in the model (p>0.5) and thus results are reported based on a model assuming the repeated observations are independent over time conditional on the subject random effects.

Supplement

Full Statistical Methods

Per the a priori design, the 4 main response variables were: systolic BP, diastolic BP, BAD, FMD. Two other responses were also evaluated as secondary outcomes: heart rate (HR) and NMD. A normal distribution was adequate in describing the stochastic structure of these variables after accounting for the suite of predictors. The repeated observations for each season within a subject are likely to be more similar to each other than observations on different subjects. These repeated measures can induce extra variation and intra-class correlation in the data. We accounted for this extra variation using mixed linear models for which unbiased and efficient estimates of effect and uncertainty are obtained. The subjects were considered to be selected at random from a population. Several predictors of the response were included in the model as fixed effects: age, gender, race, body mass index and ambient temperature. The relationship between these predictors and responses was assumed to be common to all subjects. All other available covariates including season (i.e. winter versus summer), personal-level environmental temperature measured by vest monitoring, and the subject's study day (e.g. first versus second day of monitoring during the 5 day period) and neighbourhood were not included in the final model as they did not predict responses individually or alter the significance of any results. We also assumed that the association between each of the responses evaluated and exposure to $PM_{2.5}$ is linear with an intercept varying at random over individuals and a slope assumed to be the same for all subjects.. The analysis was preformed by function "lme (linear mixed-effects model)" in R (version 2.8.1) with significance defined as a p value of <0.05.

Specifically, the model has the form:

$$y_{it} = \beta_0 + \beta_1 PM_{2.5} + \beta_2 Age + \beta_3 Sex + \beta_4 BMI + \beta_5 Temp + \beta_6 Race + \eta_i + e_{it} \quad (1)$$

where y_{it} represents the CV response for the i^{th} subject at the t^{th} repeated measurement time, $(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6)$ are unknown fixed effect regression parameters corresponding to the intercept, air pollution, age, sex, body mass index (BMI), and ambient temperature (Temp) predictor variables respectively. The random effects variable η_i represents a random intercept for the i^{th} subject and is assumed to be normally distributed with zero expectation and common variance among subjects. The

residual error term e_{it} is also assumed to be normally distributed with zero expectation and common covariance over time measurements for all subjects.

We considered the possibility that the within-subject errors (the e_{it}'s in the model (1) above) are auto-correlated. A covariance structure was employed in which the repeated responses within each subject over time were assumed to follow an autoregressive process of order 1, AR(1). Specifically, $corr(e_{it}, e_{i,t-k}) = \rho(k)$, the correlation between these two errors recorded k day apart is $\rho(k) = \lambda^{|k|}$, where $0 \le \lambda < 1$. However, there was no evidence that such a temporal correlation structure improved the fit to the data after including the fixed effect predictor variables (age, gender, race, body mass index, ambient temperature, and air pollution) in the model (p>0.5) and thus results are reported based on a model assuming the repeated observations are independent over time conditional on the subject random effects.

Supplement Table 1. Number of Tests and Subjects per Season

Session #	2	3	4	5	6	total
Season	Winter 2005	Summer 2005	Winter 2006	Summer 2006	Winter 2007	
CV Observations	32	57	94	117	57	357
Subject Obs periods	9	13	21	27	13	83

Obs, Observations; CV obs, number of visits per season where testing was performed that include a measurement of blood pressure and/or flow-mediated dilatation; Subject Obs periods, number of subjects enrolled to participate per season. There were 65 individual participants in the study with 18 subjects enrolled into 2 consecutive seasons leading to a total of 83 subject observation-periods.

Two subjects had 1, two subjects had 2, ten subjects had 3, twenty-four subjects had 4, and forty-five subjects had 5 days of CV observations per study season

Supplement Table 2. Health Effects Associated with Total Personal $PM_{2.5}$ Exposure and SHS

Vest Compliance (>60%)*					
Model (M)	Health Outcome	Air Pollutants	P values	n†	Change in Outcome 10 μg/m^3 (SE)**
lag1(M1)[1]	SBP (mm Hg)	TPE	<0.01	153	**1.41 (0.33)**
lag2(M1)	SBP (mm Hg)	TPE	0.07	108	**-0.8 (0.43)**
lag1(M2)[2]	SBP (mm Hg)	SHS	<0.01	153	6.06 (1.39)
lag2(M2)	SBP (mm Hg)	SHS	0.83	108	0.38 (1.75)
lag1(M3)[3]	SBP (mm Hg)	TPE with SHS	0.05	153	**0.82 (0.42)**
lag1(M3)	SBP (mm Hg)	SHS with TPE	0.03	153	3.94 (1.74)
lag2(M3)	SBP (mm Hg)	TPE with SHS	<0.01	108	**-2.08 (0.67)**
lag2(M3)	SBP (mm Hg)	SHS with TPE	0.02	108	6.57 (2.68)

* Only patients with a vest compliance >60% were included in the analyses as described in methods. Bolded results ($p \leq 0.1$)

**Accounting for sex, age, race, temperature on day of measurement, and BMI

†The number of observations.

TPE, total personal PM2.5 exposure; SHS, secondhand smoke; SE, standard error; SBP, systolic blood pressure

[1]M1: sbp~PTE.lag+Sex+Age +Race+BMI+Temperature

[2]M2: sbp~PTE.lag+Sex+Age+Race+BMI+ Temperature

[3]M3: sbp~PTE.lag+SHS.lag+Sex+Age+Race+BMI+ Temperature

Supplement Table 3. Health Effects Associated with Personal $PM_{2.5}$ Mass of Ambient Origin (PEAO)

		Vest Compliance (>60%) and low-SHS*		Vest Compliance (>60%)	
Health Outcome	Lag (day)	n†	Change in Outcome per 10 μg/m^3 (SE)**	n†	Change in Outcome 10 μg/m^3 (SE)**
SBP (mm Hg)	1	80	1.12 (0.95)	108	0.67 (0.85)
SBP (mm Hg)	2	57	-0.50 (1.39)	75	0.54 (1.26)
DBP (mm Hg)	1	80	0.00 (0.67)	108	0.21 (0.62)
DBP (mm Hg)	2	57	0.46 (1.02)	75	0.32 (0.87)
HR (beats/minute	1	80	0.13 (1.19)	108	0.68 (0.97)
HR (beats/minute)	2	57	-0.77 (1.84)	75	-0.25 (1.55)
BAD (mm)	1	77	**0.09 (0.05) (p=0.07)**	103	0.04 (0.04)
BAD (mm)	2	53	**-0.15 (0.06) (p=0.03)**	69	**-0.11 (0.05) (p=0.047)**
FMD (%)	1	71	0.56 (0.61)	97	-0.05 (0.54)
FMD (%)	2	51	-0.25 (1.05)	67	-0.74 (0.97)
NMD (%)	1	42	-0.97 (1.34)	57	-1.20 (1.08)
NMD (%)	2	27	-1.24 (1.33)	37	-0.21 (1.08)

*Low SHS defined as <1.5 μg/m^3 of SHS components as measured on vest filter.

**Accounting for sex, age, race, temperature on day of measurement, and BMI

†The number of associations is reduced compared to the total available outcomes as in Table 3 because only patients with a vest compliance >60% (and with low SHS exposure when relevant) were included in the analyses as described in methods. Lag day 2 also had less available observations performed for most outcomes because there were fewer subjects with 3 days of CV measurements (Supplemental Table 1).

SHS, secondhand smoke; N, number of observations; SE, standard error; SBP, systolic blood pressure (BP); DBP, diastolic BP; HR, heart rate; BAD, brachial artery diameter; FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation.

Bold results represent associations with a p value <0.1

Supplement Table 4. Health Effects Associated with Personal $PM_{2.5}$ Mass of Non-Ambient Origin (PENAO)

		Vest Compliance (>60%) & low-SHS*		Vest Compliance (>60%)	
Health outcome	Lag (day)	n†	Change in Outcome per 10 μg/m^3 (SE)**	n†	Change in Outcome per 10 μg/m^3 (SE)**
SBP (mm Hg)	1	80	2.53 (2.51)	108	-0.15 (2.05)
SBP (mm Hg)	2	57	-0.98 (2.90)	75	-0.37 (2.64)
DBP (mm Hg)	1	80	2.12 (1.74)	108	1.58 (1.46)
DBP (mm Hg)	2	57	-0.62 (2.12)	75	-0.59 (1.82)
Heart Rate beats/m	1	80	4.89 (2.98)	108	2.95 (2.24)
Heart Rate beats/m	2	57	-1.19 (3.71)	75	-1.25 (3.08)
BAD (mm)	1	77	**0.23 (0.12) (p=0.07)**	103	0.05 (0.09)
BAD (mm)	2	53	**-0.24 (0.14) (p=0.09)**	69	-0.18 (0.11)
FMD (%)	1	71	0.83 (1.58)	97	-0.09 (1.22)
FMD (%)	2	51	0.44 (1.83)	67	-0.77 (1.63)
NMD (%)	1	42	-1.15 (3.79)	57	0.90 (2.45)
NMD (%)	2	27	4.72 (3.13)	37	**5.00 (2.00) (p=0.03)**

*Low SHS defined as <1.5 μg/m^3 of SHS components as measured on vest filter.

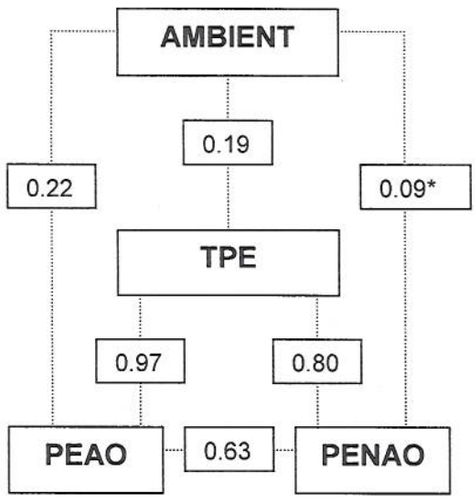
**Accounting for sex, age, race, temperature on day of measurement, and BMI

†The number of associations is reduced compared to the total available outcomes as in Table 3 because only patients with a vest compliance >60% (and with low SHS exposure when relevant) were included in the analyses as described in methods. Lag day 2 also had less available observations performed for most outcomes because there were fewer subjects with 3 days of CV measurements (Supplemental Table 1).

SHS, secondhand smoke; N, number of observations; SE, standard error; SBP, systolic blood pressure (BP); DBP, diastolic BP; HR, heart rate; BAD, brachial artery diameter; FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation.

Bold results represent associations with a p value <0.1

Supplement Figure. Pearson Correlations among $PM_{2.5}$ exposure metrics



TPE, total personal $PM_{2.5}$ exposure; Ambient, community-level ambient $PM_{2.5}$, PEAO, personal $PM_{2.5}$ exposure of ambient origin; PENAO, personal $PM_{2.5}$ exposure of non-ambient origin.

*All correlations are significant ($p<0.01$ except for between ambient and PENAO).