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The Impact of Multi-pollutant Clusters on the Association between Fine Particulate Air Pollution and Microvascular Function

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Abstract

Background—Prior studies including the Framingham Heart Study have suggested associations between single components of air pollution and vascular function; however, underlying mixtures of air pollution may have distinct associations with vascular function.

Methods—We used a k-means approach to construct five distinct pollution mixtures from elemental analyses of particle filters, air pollution monitoring data, and meteorology. Exposure was modeled as an interaction between fine particle mass (PM_{2.5}), and concurrent pollution cluster. Outcome variables were two measures of microvascular function in the fingertip in the Framingham Offspring and Third Generation cohorts from 2003–2008.

Results—In 1,720 participants, associations between PM_{2.5} and baseline pulse amplitude tonometry differed by air pollution cluster (interaction p value 0.009). Higher PM_{2.5} on days with low mass concentrations but high proportion of ultrafine particles from traffic was associated with 18% (95% CI 4.6%; 33%) higher baseline pulse amplitude per 5 µg/m³ and days with high

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Conflicts of Interest

PLL, EHW, MBR, EA, JS, DRG, PK, JAV, RSV, EJB, MAM and NMH declare no conflicts of interest.

contributions of oil and wood combustion with 16% (95% CI 0.2%; 34%) higher baseline pulse amplitude. We observed no variation in associations of PM_{2.5} with hyperemic response to ischemia observed across air pollution clusters.

Conclusions—PM_{2.5} exposure from air pollution mixtures with large contributions of local ultrafine particles from traffic, heating oil and wood combustion was associated with higher baseline pulse amplitude but not PAT ratio. Our findings suggest little association between acute exposure to air pollution clusters reflective of select sources and hyperemic response to ischemia, but possible associations with excessive small artery pulsatility with potentially deleterious microvascular consequences.

Particulate air pollution exposure is associated with increased cardiovascular risk¹. Acute exposure to high air pollution levels has detrimental vascular effects that may be relevant to the development of cardiovascular events. Determining the particular air pollution mixtures and sources associated with vascular alterations has substantial public health implications. Abnormal vascular function contributes to the pathogenesis of atherosclerosis, hypertension, and stroke.^{2,3} Higher resting small artery pulsatility is associated with cardiovascular risk factors and has potential to induce microvascular damage.⁴⁻⁷ Impaired small vessel hyperemic response reflects endothelial dysfunction and has been associated with increased risk of cardiovascular events.³ Microvascular function can be assessed non-invasively in the fingertip circulation using peripheral arterial tonometry. Resting pulse amplitude reflects microvessel pulsatility influenced by blood flow, autonomic tone, and vascular wall compliance. Though longitudinal associations of resting baseline pulse amplitude and cardiovascular events have not been demonstrated in high-risk patients, higher small vessel pulsatility may have deleterious effects in the microcirculation.⁷ The peripheral arterial response to hyperemia reflects endothelium-dependent vasodilation and is associated with ischemic heart disease,⁸ cardiac events,^{7,9} and with coronary endothelial dysfunction.¹⁰

In a previous study of microvascular function in the Framingham Heart Study using peripheral arterial tonometry we investigated associations between levels of different individual air pollutants and both baseline pulse amplitude and hyperemic response.¹¹ We demonstrated associations between preceding 1-3 day exposure to higher fine particulate matter (PM_{2.5}, particles with an aerodynamic diameter of $\leq 2.5\mu\text{m}$), black carbon or particle number and higher resting pulsatility measured by baseline pulse amplitude. Air pollution levels were not associated with hyperemic response. Other studies of smaller size, comparing hyperemic response in the digital microvasculature before and after air filtration of homes or using controlled human chamber exposure to coal, wood, or traffic pollution, have shown mixed results.¹²⁻¹⁶

Similar to other studies of air pollution and microvascular function, in previous analyses we only considered each pollutant separately without examining potentially variable associations by air pollution mixture. Ambient particulate air pollution is composed of many constituents originating from a plethora of anthropogenic and natural sources. The specific mixture of sources and constituents contained in PM_{2.5} as well as the concurrent gaseous pollutants also vary from day to day depending on meteorology and emissions. Analyzing each pollutant separately does not take this into account and obscures interpretation of which

specific mixtures of pollution sources are more strongly associated with microvascular function. In conjunction with other accumulated knowledge, this understanding may lead to insights about the most important sources and constituents of air pollution to consider in regulation policy.

In the current study we incorporated data from elemental analyses of particle filters, several gaseous and particulate pollutant levels, and meteorology to cluster days into five distinct air pollution mixtures using a previously published k-means approach.¹⁷ We aimed to evaluate whether the preceding day's air pollution mixture modified the association of PM_{2.5} with digital vascular measures in the Framingham Offspring and Third Generation Cohorts. We hypothesized that mixtures composed of particulate species related to local combustion sources would be more strongly associated than those from other sources with changes in microvascular circulation.

Methods

Study sample

We included participants with valid peripheral arterial tonometry measurements and a primary residential address 50 km from the Harvard Supersite monitor in Boston in the eighth cycle of the Offspring (2005-2008) and first cycle of the Third Generation (2003-2005) Cohorts of the Framingham Heart Study (N=2,367).¹¹ All participants provided written informed consent for the Framingham Heart Study examinations, and both the Committee on Clinical Investigation at Beth Israel Deaconess Medical Center and the Boston University Medical Center Institutional Review Board approved this work. The detailed study protocol has previously been described.^{18,19} Observations were excluded on days with missing data in at least one of the variables used in the construction of the air pollution mixture clusters. A total of 1,720 participants were included for the current study.

Digital vascular function measurements

Digital pulse amplitude was measured at a single visit per participant as previously described in detail.⁵ Briefly, using a peripheral arterial tonometry device on the tip of each index finger (Endo-PAT2000, Itamar Medical, Caesarea, Israel) pulse volume changes were electronically measured and expressed as pulse amplitude. Baseline pulse amplitude, or resting pulsatility, was measured in the fingertips of both hands for 2 minutes and 20 seconds. Ischemia was induced by an inflated forearm cuff on one arm for 5 minutes. The hyperemic response was determined by the ratio of the post-deflation pulse amplitude (90-120 seconds after deflation) to the baseline pulse amplitude of the same finger divided by the ratio of the pulse amplitude measured in the control finger during the same interval to the baseline pulse amplitude of the control finger. For analyses, the natural logarithm of the mean of baseline pulse amplitudes from each finger was used. Likewise the hyperemic response was transformed such that peripheral arterial tonometry ratio = $\log_e[(X_{ht90-t120}/X_{ht0})/(X_{ct90-t120}/X_{ct0})]$ with X denoting pulse amplitude, h denoting hyperemic finger, t denoting time interval, 0 denoting baseline, and c denoting control finger.

Covariate assessment

Prevalent individual-level covariates that were expected to confound or be associated with the vascular measures but not causal intermediates were used in multivariable analyses including age, sex, body mass index, cohort (Offspring or Third Generation), smoking status (categorized as current, former or never smoker), systolic blood pressure (mean of two measurements taken by the physician administering the clinical exam), diabetes mellitus (defined as having a fasting glucose ≥ 126 mg/dL or oral hypoglycemic or insulin use at an exam or any previous history of diabetes, excluding gestational diabetes), triglycerides, total cholesterol to high-density lipoprotein ratio, and regular use of antihypertensive or statin medication classified according to their World Health Organization anatomical therapeutic chemical (ATC) codes. The participants were almost exclusively white and consequently race was not included as a covariate. Age showed evidence of a non-linear relationship with peripheral arterial tonometry measures and was therefore centered to the mean and entered as both a linear and quadratic term to accommodate non-linearity. To adjust for socioeconomic status we used individual-level data for years of education (categorized as no high school degree, high school degree, some college education, and college degree). Furthermore, we included median household income in the participants' residential census tract using data from US Census 2000 (categorized by quartiles). To account for seasonal and long-term time-trends in relating air pollutants to digital vascular function, we modeled the sine and cosine of the day of year and a linear time trend for date of examination. Finally, we adjusted for day of week, temperature, relative humidity and the cross-product term of ambient temperature and relative humidity to estimate associations with air pollutant exposures.

Air pollution and Meteorology

Daily PM_{2.5} samples were collected on Teflon filters using Harvard Impactors and were analyzed by X-ray fluorescence for elements. Levels of PM_{2.5} and black carbon (BC), and particle number concentrations (number of particles per cm³) were measured continuously at the Harvard Air Pollution Monitoring Supersite, which is about one mile from downtown Boston. This site is on the rooftop of the Countway Library located five stories above ground level and 50 m from the nearest street. Daily means were computed using hourly data from 9 am to 9 pm. PM_{2.5} was measured using a tapered element oscillating microbalance (model 1400A, Rupprecht & Pataschnick Co, Albany NY) and BC using an Aethalometer (Magee Scientific, Berkeley, CA). Hourly particle number concentrations (particles per cm³) were measured with a Condensation Particle Counter (TSI Inc., Model 3022A, Shoreview, MN). Particle number is a measurement of ultra-fine particles because the majority of particles have an aerodynamic diameter of less than 100 nanometers (nm). Thus the terms particle number and ultra-fine particles are interchangeable. Hourly concentrations of the gaseous pollutants carbon monoxide (CO), nitrogen oxides (NO and NO₂), sulfur dioxide (SO₂), and ozone (O₃) were measured by state monitors located within the Greater Boston area, and exposures were estimated by averaging data from the available sites.²⁰ Finally, hourly temperature and relative humidity data were obtained from the Boston Logan Airport weather station located 12 km from the central monitoring site.

Pollutants and measures used in the clustering analyses included: particle number, CO, NO, NO₂, O₃, SO₂, BC, S, Cu, Zn, Ni, V, Ti, Mg, K, Si, Na, Cl, Ca, Br, Sr, Pb, Mn, and Fe. Other elements were considered but were excluded due to unreliable analytical measurement or a large proportion of measurements below the method detection limit. Days were grouped into five distinct clusters according to the method described by Austin et al.,¹⁷ with the goal of producing groups of days with similar multi-pollutant profiles and weather patterns. For each cluster of days, we then estimated pollutant and elemental average concentrations to better characterize differences among the five groups (eTables 1 and 2).

Cluster 1 occurred on 38% of the days and is characterized by the lowest levels of PM_{2.5} mass. Relative to these levels of PM_{2.5}, this cluster had high concentrations of O₃, NO₂, and particle number. High relative levels of elements Pb, Sr, Cl, and Mg indicated the presence of resuspended road dust. The ratio of particle number to PM_{2.5} was also high, indicating a high proportion of ultrafine particles. Taken together this mixture represents days of lower overall concentrations containing some road dust and a high proportion of locally generated particle contributions from traffic emissions.

Cluster 2 occurred on 19% of the days and less frequently in colder months. Most pollutant concentrations were within average ranges except Fe, K, Si, and Ca, which were all elevated. Low K/Si confirmed the prevalence of suspended crustal materials in this cluster such as soil and dust.

Cluster 3 occurred on 8% of days, almost entirely in the winter months. High relative concentrations of Ni, V, Zn, Br, CO, NO, and SO₂ with high NO/NO₂ and BC/PM_{2.5} ratios indicated the strong contribution of traffic and oil combustion emissions on these days. The particle number/PM_{2.5} ratio although elevated was lower than that in Clusters 1 and 5 indicating a mixture of ultrafine particles and fine particles.

Cluster 4 occurred on 14% of days, primarily during the warm season with the highest concentrations of PM_{2.5} as well as high S and Se concentrations. Note that Se was not included in the initial cluster analysis and its concentrations by cluster were determined after the clusters were defined. Se is a marker of secondary particles from coal. Furthermore, the lower particle number/PM_{2.5} ratio indicated relatively larger particle sizes consistent with aged agglomerated particles transported from regional sources.

Cluster 5 occurred on 21% of days, mostly in winter and had the lowest average daily temperatures. Relative to soil dust the high Fe/Si ratio suggested a strong contribution of road dust and the high K/Si ratio suggested a contribution of wood burning. This mixture had the highest concentrations of particle number and the highest particle number/PM_{2.5} ratio. The high Ni and V concentrations, which are associated with combustion of heating oil, were similar to Cluster 3 but the proportion of ultrafine particles was much higher. This indicated a higher proportion of local emissions than those in Cluster 3 although the lower NO/NO₂ ratio suggested a smaller traffic-related contribution compared to wood and heating oil combustion.

Statistical Methods

Air pollution clusters were constructed as a nominal variable such that each day during the study period was assigned one of the five distinct profiles. We therefore constructed 1-day moving averages for $PM_{2.5}$ prior to peripheral arterial tonometry examinations to temporally overlap cluster assignment. We fit multivariable linear regression models including an interaction term between preceding 1-day moving average of $PM_{2.5}$ (continuous variable) and preceding day air pollution cluster (categorical variable) and to assess whether the association between ambient exposure to fine particulate matter and microvascular function (baseline pulse amplitude and peripheral arterial tonometry ratio) varied by distinct mixture of air pollution.

Model:

$$\begin{aligned} \text{Log}_e(\text{outcome}) &= \beta_0 + \beta_1 PM_{2.5} + \beta_2 \text{cluster}_2 + \dots + \beta_5 \text{cluster}_5 \\ &+ \beta_6 \text{cluster}_2 * PM_{2.5} \\ &+ \dots + \beta_{10} \text{cluster}_5 * PM_{2.5} \\ &+ [\gamma(\text{covariates})] \end{aligned}$$

We constructed a model in which the dependent measure was either modeled as baseline pulse amplitude or peripheral arterial tonometry ratio and β_1 was the main effect of 1-day $PM_{2.5}$ and β_2 - β_5 were the main effects of each cluster, β_6 - β_{10} were the coefficients of interaction terms between $PM_{2.5}$ and each cluster, and γ represented the coefficients for each additional model covariate specified above. We computed the $PM_{2.5}$ estimates in each cluster by summing β_1 and each of the interaction coefficients β_6 - β_{10} , i.e., the $PM_{2.5}$ estimate for cluster 2 is $\beta_1 + \beta_6$ with standard error:

$$\sqrt{\text{var}(\beta_1) + \text{var}(\beta_6) + 2\text{cov}(\beta_1, \beta_6)}$$

The associations between $PM_{2.5}$ and baseline pulse amplitude or peripheral arterial tonometry ratio are expressed as percent change in the vascular measure per $5 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ by level of cluster. All estimates are presented with 95% confidence intervals (CI). We tested the statistical significance of the interaction between cluster and $PM_{2.5}$ using a single 5 degree of freedom global test for homogeneity and considered a two-sided p-value of < 0.05 as statistically significant. SAS 9.3 PROC GLM was used for all analyses.

Results

Study participants

Participants included similar numbers of men and women (Table 1). The mean age was 56 years old with standard deviation (SD) 16. Mean body mass index was $28 \text{ kg}/\text{m}^2$ (SD 5.4), mean ratio of total cholesterol/high density lipoproteins 3.6 (SD 1.2), mean triglycerides 119 mg/dl (SD 17) and mean systolic blood pressure 124 (SD 17). Thirty-eight percent of the

participants were using antihypertensive medication and 29% were using statins. A majority of participants were current or former smokers and had at least some college education.

Associations of PM_{2.5} with baseline pulse amplitude by air pollution cluster

Associations between a 1-day moving average of PM_{2.5} and baseline pulse amplitude varied according to daily pollution cluster (p-value for interaction 0.009) (Figure 1). A 5 µg/m³ higher PM_{2.5} on Cluster 1 days was associated with 18% (95% CI 4.6%; 33%) higher baseline pulse amplitude. Cluster 1 contains mixtures with the lowest levels of PM_{2.5} concentration but with contributions from road dust and traffic emissions and a high particle number/PM_{2.5} ratio. This ratio can be used as an indicator of particle size with higher ratios indicating a greater proportion of freshly generated smaller particles typically related to local combustion sources such as traffic and heating.¹⁷ Higher PM_{2.5} on Cluster 2, 3 and 4 days was not associated with higher baseline pulse amplitude. Cluster 2 consisted of mixtures of predominantly crustal sources. Cluster 3 days occurred exclusively in winter months and contained a mixture with a strong contribution of traffic emissions. Cluster 4 days were dominated by regionally transported pollution. Higher PM_{2.5} on Cluster 5 days was also associated with 16% (95% CI 0.2%; 34%) higher baseline pulse amplitude. PM_{2.5} in Cluster 5 had the highest proportion of ultrafine particles and was composed of elements suggesting contributions from wood and heating oil sources. These findings indicate that individual clusters of air pollutant mixtures from particular pollutant sources had distinct associations with higher baseline pulse amplitude, reflecting excessive microvessel pulsatility.

Associations of PM_{2.5} with hyperemic response by air pollution cluster

Cluster type did not significantly alter the null association between PM_{2.5} and peripheral arterial tonometry ratio, reflecting the hyperemic response (p-value for interaction 0.10) (Figure 2). These findings indicate that cluster types did not have distinct associations with the vasodilator response to ischemia in the microvasculature. Excluding adjustment for systolic blood pressure or diabetes in the models did not materially change the results.

Discussion

In our large community-based Framingham Heart Study, we found a difference in the association between PM_{2.5} and baseline pulse amplitude according to the prevalent air pollution cluster, suggesting differing associations of specific air pollution mixtures with microvascular pulsatility. Associations were largely confined to days in clusters with a high relative or absolute content of ultrafine particles stemming from contributions from different forms of local combustion such as traffic, heating oil and wood burning. We did not observe statistically significant differences in the associations between PM_{2.5} and hyperemic response across the air pollution mixture clusters, suggesting that acute particulate air pollution is not associated with impairments in microvascular vasodilation response.

Other studies investigating associations between short-term air pollution exposure and microvascular function using peripheral arterial tonometry have to a limited degree explored sources of air pollution in controlled exposure settings. Consistent with our null results for

the hyperemic response, these studies did not observe associations between controlled exposure to coal,¹⁶ wood smoke^{15,16} or to 24 hour exposure to urban air from a busy street¹⁴ and hyperemic response. All studies included young volunteers, potentially less susceptible to air pollution exposure, and the two-hour exposure periods used in two of the studies may be of insufficient duration to affect the microvasculature. In contrast, two small interventional studies^{12,13} used air filtration in homes over a short period leading to lower levels of particle matter and demonstrated increases in the hyperemic response. None of these studies, however, assessed the association between air pollution and resting baseline pulse amplitude nor considered specific air pollution mixtures.

In our previous single-pollutant analysis we observed associations between the pollutants PM_{2.5}, black carbon, particle number, sulfate and ozone and baseline pulse amplitude.¹¹ The high correlation and multiple sources of these pollutants make it difficult to identify the true culprit or combination of culprits in this type of analyses. In our present study, however, we found that associations between PM_{2.5} exposure and digital baseline pulse amplitude varied according to concurrent air pollution mixture. Cluster 1, a mixture with low PM_{2.5} mass concentration but contributions from local traffic, demonstrated associations with higher baseline pulse amplitude. In addition PM_{2.5} on days with air pollutant mixtures dominated by local contributions of commercial heating oil and wood combustion (Cluster 5) was also associated with higher baseline pulse amplitude. The commercial heating oil used in Boston consists of heavier oil with longer-chain hydrocarbons and a greater concentration of impurities such as ash and metals including nickel and vanadium compared to home heating oil. Estimates for Cluster 3, containing a mixture of oil and traffic combustion with both aged and freshly emitted pollutants, were indicative of associations with higher baseline pulse amplitude, although confidence intervals overlapped the null, possibly reflecting reduced power due to a low number of days falling into this cluster (135 microvascular measurements). Taken together, these results are consistent with our primary hypotheses that air pollution mixtures dominated by local combustion emissions are most strongly associated with changes in the microvascular function and support our previous study results of strongest associations with air pollutants such as high particle number that are primarily derived from local combustion sources.¹¹

PM_{2.5} consists of a variety of species of particles from different sources, both local and regional, and since measurements consider mass concentration, larger particles with more mass will influence measured levels more than ultrafine particles. Agglomerated aged particles transported over hundreds of kilometers from regional sources are the major contributors to PM_{2.5} mass. Cluster 4 days contained a mixture with the strongest contribution of regionally transported pollution, which consisted of relatively larger fine particles and was the largest contributor to particle mass. Our results indicated no association between PM_{2.5} and microvascular function on days with this mixture, consistent with previously reported results¹¹ of weak associations between baseline pulse amplitude and sulfate, a marker of regional pollution, and a weaker association with PM_{2.5} compared to particle number.

We found different patterns of association of air pollution cluster types with the two different measures of microvascular function: baseline pulse amplitude and hyperemic response.

There are several potential implications of the observed associations of baseline pulse amplitude but not hyperemic response with particular air pollutant mixtures. Baseline pulse amplitude reflects several factors including digital blood flow, vessel compliance, and sympathetic tone with a dynamic induction time over the course of minutes.^{21,22} Higher baseline pulse amplitude indicates higher small artery pulsatility that may induce damage to the microcirculation with chronic exposure. In prior studies traditional cardiovascular risk factors have been associated with higher baseline pulse amplitude.^{5,6} A recent study of high risk patients reported no associations between baseline pulse amplitude and large vessel cardiovascular events when adjusting for concomitant risk factors.⁷ The acute differences in baseline pulse amplitude seen here in association with particulate air pollution in mixtures dominated by oil and wood combustion and containing ultrafine particles may potentially reflect differences in resting sympathetic tone or small vessel compliance governing resting pulsatility.

In contrast, we did not observe associations of air pollution cluster types and hyperemic response, a measure of microvascular vasodilator function. Digital hyperemic response is a measure of response to shear stress in the microvasculature of the fingertip that has a short-induction time²² and is primarily endothelium dependent.²³ Reduced hyperemic response has been associated with several important risk factors for cardiovascular disease in the Framingham Heart Study^{5,24} and other studies^{6,25,26} as well as with future cardiac events.^{7,9} The lack of association of air pollution cluster types with the hyperemic response may indicate that acute air pollution exposure does not impair microvascular endothelial function. However, it remains possible that higher levels of exposure or longer exposure time may induce changes in microvascular endothelial function. Overall, our findings are consistent with the possibility that air pollution cluster types alter microvascular pulsatility but not microvascular vasodilatory response to shear stress. Our findings suggest that small vessel pulsatility may be a more sensitive marker of acute air pollution induced changes in microvascular function. Higher resting pulsatility in small vessels creates the conditions for microvessel damage that may be associated with end-organ damage particularly in the brain and kidneys.²⁷ Future studies are needed to determine whether microvascular dysfunction mediates the association of air pollution with cardiovascular events and the contribution of the observed increased microvascular pulsatility.

Other studies have investigated short-term exposure to air pollution and vascular function in other microvascular and conduit artery beds. Associations have previously been reported between particulate air pollution exposure and blunted endothelium-dependent arteriolar dilation in rat spinotrapezius muscle.^{28,29} In the retinal microvasculature of humans, short-term exposure to PM_{2.5}³⁰ and PM₁₀³¹ was associated with decreased retinal arteriolar diameter. Furthermore, for conduit artery function, observational studies of participants with diabetes have reported associations between particulate air pollution exposure and hyperemic response in the brachial arteries measured as flow-mediated dilation.^{32,33} Analogous to our findings however, exposure to particulates in non-diabetic people using chamber studies with controlled exposure did not demonstrate a hyperemic response in the brachial artery measured by flow-mediated dilation, but was associated with smaller brachial diameters.^{34,35} Although these studies taken together consistently point towards vascular reactivity to air pollution exposure, the disparate associations may reflect the intricacies of

vascular regulation with possible varying effects between conduit and resistance vessels or prevailing differences in exposure across studies.

Our study has several limitations. We compared changes in exposure from one day to another for each participant's residence using central monitors for all primary addresses within 50 km of the central monitoring site. This most likely induced non-differential exposure misclassification with respect to the vascular measures leading to wider confidence intervals.³⁶ Earlier studies in Boston have shown that PM_{2.5} levels measured at the central site are good proxies for personal exposure to ambient particulate air pollution.³⁷ The results reported for air pollution mixtures in this study located in the northeastern United States may not be generalizable to other geographical areas with different sources and meteorology. Some days could not be characterized according to air pollution cluster due to missing monitor data or elements that could not be detected. This may have affected our power to detect associations. However, the missingness of these data is not expected to be related to whether participants came to their scheduled examinations and therefore would not cause bias. The Framingham study participants are almost all of non-Hispanic white origin and this may limit the generalizability of the results to other races or ethnic groups. Our design precluded a longitudinal analysis of change in exposure and change in vascular measures since we only had data from one tonometry examination and, because our study was observational, we cannot determine causal relations. We acknowledge the possibility for residual confounding by unmeasured factors affecting peripheral tonometry measures that also vary with short-term changes in air pollution levels. For the above-mentioned limitations and the novelty of the study, the findings will need to be replicated in other populations.

The Framingham Cohorts, however, offered the advantage of a large-scale community-based observational study with a standardized study protocol. Outcome assessment was collected independently and blinded to the air pollution measurements. Peripheral arterial tonometry has the additional advantage of yielding non-invasive measurements of micro-vessel function with little operator dependence. Although associations between ambient air pollution exposure and health outcomes are generally investigated by analyzing strongly correlated individual pollutants, personal exposure always consists of mixtures of several pollutants with possible interactions. We have attempted to address this challenge to inference by characterizing days with different mixtures of air pollution based on a previously published novel combination of analyses of elemental components from collected filters of particulate matter as well as gases and meteorology.

Air pollution mixtures with contributions from local combustion emissions like heating oil, wood, or traffic appeared to modify the association between PM_{2.5} and microvascular pulsatility but not hyperemic response. Furthermore, there did not appear to be an association between PM_{2.5} and microvascular function on days where air pollution was dominated regionally transported pollution. Characterizing particulate pollution in the context of an air pollution mixture appears to influence the association with microvascular function. If specific air pollution clusters are also associated with higher risk of clinical endpoints such as myocardial infarction or stroke in follow-up studies then this would provide valuable data to advise effective air quality regulation and implementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Relative difference and 95% confidence intervals (CI) in baseline pulse amplitude per 5 $\mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ by air pollution cluster. Cluster 1: Low $\text{PM}_{2.5}$ pollution levels with particle mixture dominated by ultrafine particles from traffic and other local combustion sources. Cluster 2: Average levels of most pollutants and particle components with a larger proportion of resuspended crustal particles. Cluster 3: High $\text{PM}_{2.5}$ mass concentrations with fine and ultrafine particles and high levels of Ni and V as well as high contribution of gaseous traffic emissions. Cluster 4: Regionally transported pollution mixture with highest $\text{PM}_{2.5}$ mass. Cluster 5: Highest contribution of ultrafine particles in a mixture with components of local heating oil and wood combustion with high levels of Ni and V.

Figure 2.

Relative difference and 95% confidence intervals (CI) in peripheral arterial tonometry ratio per $5 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$ by air pollution cluster. Cluster 1: Low $\text{PM}_{2.5}$ pollution levels with particle mixture dominated by ultrafine particles from traffic and other local combustion sources. Cluster 2: Average levels of most pollutants and particle components with a larger proportion of re-suspended crustal particles. Cluster 3: High $\text{PM}_{2.5}$ mass concentrations with fine and ultrafine particles and high levels of Ni and V as well as high contribution of gaseous traffic emissions. Cluster 4: Regionally transported pollution mixture with highest $\text{PM}_{2.5}$ mass. Cluster 5: Highest contribution of ultrafine particles in a mixture with components of local heating oil and wood combustion with high levels of Ni and V.

TABLE 1

Participant characteristics

Characteristic	(n=1,720)
Offspring Cohort, n (%)	1,021 (59)
Women, n (%)	867 (50)
Diabetes mellitus, n (%)	192 (11)
Smoking status, n (%)	
Current smokers	234 (14)
Former smokers	707 (41)
Never smokers	750 (44)
Missing	29 (2)
Education level, n (%)	
No high school degree	48 (3)
High school degree	421 (24)
Some college schooling	566 (33)
College degree	685 (40)
Anti-hypertensive medication, n (%)	646 (38)
Statin medication, n (%)	500 (29)
Both anti-hypertensive and statin medication, n (%)	361 (21)

n, number of observations.