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Postural Changes in Blood Pressure Associated with Interactions between Candidate Genes for Chronic Respiratory Diseases and Exposure to Particulate Matter

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BACKGROUND: Fine particulate matter [aerodynamic diameter ≤ 2.5 µm (PM2.5)] has been associated with autonomic dysregulation.

OBJECTIVE: We hypothesized that PM2.5 influences postural changes in systolic blood pressure (∆SBP) and in diastolic blood pressure (∆DBP) and that this effect is modified by genes thought to be related to chronic lung disease.

METHODS: We measured blood pressure in participants every 3–5 years. ∆SBP and ∆DBP were calculated as sitting minus standing SBP and DBP. We averaged PM2.5 over 48 hr before study visits and analyzed 202 single nucleotide polymorphisms (SNPs) in 25 genes. To address multiple comparisons, data were stratified into a split sample. In the discovery cohort, the effects of SNP × PM2.5 interactions on ∆SBP and ∆DBP were analyzed using mixed models with subject-specific random intercepts. We defined positive outcomes as p < 0.1 for the interaction; we analyzed only these SNPs in the replicate cohort and confirmed them if p < 0.025 with the same sign. Confirmed associations were analyzed within the full cohort in models adjusted for anthropometric and lifestyle factors.

RESULTS: Nine hundred forty-five participants were included in our analysis. One interaction with rs9568232 in PHD finger protein 11 (PHF11) was associated with greater ∆DBP. Interactions with rs1144393 in matrix metalloprotease 1 (MMP1) and rs16930692, rs7955200, and rs10771283 in inositol 1,4,5-triphosphate receptor, type 2 (ITPR2) were associated with significantly greater ∆SBP. Because SNPs associated with ∆SBP in our analysis are in genes along the renin–angiotensin pathway, we then examined medications affecting that pathway and observed significant interactions for angiotensin receptor blockers but not angiotensin-converting enzyme inhibitors with PM2.5.

CONCLUSIONS: PM2.5 influences blood pressure and autonomic function. This effect is modified by genes and drugs that also act along this pathway.

KEYWORDS: aging and susceptible populations, blood pressure, environmental epidemiology, gene–environment interaction, particulate matter. Environ Health Perspect 117:935–940 (2009). doi:10.1289/ehp.0800279 available via http://dx.doi.org/ [Online 3 February 2009]
 meters). Questionnaires evaluated smoking habits and medication use, with responses confirmed by an on-site physician. Subjects indicated pulmonary disorders by a questionnaire based on the American Thoracic Society Division of Lung Diseases 1978 questionnaire (Ferris 1978). Participants provided written informed consent, and the study protocol was approved by the institutional review boards of all participating institutions. Subjects visited the study center during the study period from 1995–2006 one to four times: 945 subjects (45%) had one visit, 692 subjects (33%) had two visits, 425 subjects (20%) had three visits, and 36 subjects (2%) had four visits.

**Blood pressure measurements.** At each clinical visit, a physician measured blood pressure using a standard mercury sphygmomanometer. SBP and fifth-phase diastolic blood pressure (DBP) were measured in each arm to the nearest 2 mmHg while the participant was seated. The means of the right and left arm measurements were used as each participant’s SBP and DBP. A measure of standing blood pressure was recorded in the right arm 30 sec after standing. Previous studies have noted that most hemodynamic changes related to the assumption of standing posture occur within the first 30 sec (Akselrod et al. 1997; Smith et al. 1994), and the NAS protocol was designed to address these initial orthostatic changes. Postural changes in SBP and DBP were calculated as mean sitting minus standing for SBP (ΔSBP) and DBP (ΔDBP).

**Air pollution measurement.** Ambient PM$_{2.5}$ were measured beginning in 1995 on the roof of Countway Library at Harvard Medical School. PM$_{2.5}$ concentrations were measured using Tapered Element Oscillating Microbalance (model 1400A; Rupprecht & Paterson, Albany, NY) operated at 50°C with a PM$_{1.5}$ impactor (Air Diagnostics, Harrison, ME) with two plates. Air was drawn through the impactors at 4 LPM. Concentrations (microgram per cubic meter) were averaged into 30-min periods. For this study, we estimated exposures as the 48-hr average concentration before study visit and blood draw. This time period has shown to have strongest associations with heart rate variability, another measure of autonomic function, within this cohort (Park et al. 2005).

**Table 1. Candidate genes included in our analysis.**

| Gene     | Name                                      | Chromosome position |
|----------|-------------------------------------------|---------------------|
| ITGB6    | integrin, beta 6                          | 2:q24.2             |
| ITGAV    | integrin alpha-V precursor                | 2:q32.1             |
| IL6      | interleukin 6 (interferon, beta 2)        | 7:p15.3             |
| DEFB1    | defensin, beta 1 preproprotein            | 8:p23.1             |
| TLH4     | toll-like receptor 4 preprotein           | 9:q33.1             |
| MBL2     | soluble mannose-binding lectin precursor  | 10:q21.1            |
| SFTPD    | pulmonary surfactant-associated protein D | 10:q22.3            |
| GSTP1    | glutathione transferase                   | 11:q13.2            |
| MMP1     | matrix metalloproteinase 1 preproprotein | 11:q22.2            |
| MMP12    | matrix metalloproteinase 12 preproprotein| 11:q22.2            |
| ITPK2    | inositol 1,4,5-triphosphate receptor, type 2 | 12:p11.23    |
| VDR      | vitamin D (1,25-dihydroxyvitamin D3) receptor | 12:q3.11    |
| DCN      | decorin isoform b precursor               | 12:q2.13            |
| PHF11    | PHD finger protein 1                      | 13:q13.4            |
| SERPINA1 | serpin peptidase inhibitor, clade A, member 3 | 14:q3.13     |
| SERPINA2 | serine (or cysteine) proteinase inhibitor, clade | 14:q2.13     |
| IL4      | interleukin 4 receptor alpha chain isoform b | 16:p12.1  |
| CHIR1    | corticotropin releasing hormone receptor 1 | 17:q2.13            |
| AZU1     | azurin 1 preproprotein                    | 19:p13.3            |
| ELA2     | elastase 2, neutrophil preproprotein      | 19:p13.2            |
| TGFBI    | transforming growth factor, beta 1        | 19:p13.2            |
| IL11     | interleukin 11 precuror                   | 19:q13.42           |
| ADAM33   | ADAM metallopeptidase domain 33 isoform alpha | 20:p13            |
| MMP9     | matrix metalloproteinase 9 preproprotein | 20:q13.12           |
| SLPI      | secretory leukocyte peptidase inhibitor   | 20:q13.12           |
Confirmed associations were then examined in models adjusted for age, BMI, smoking status (never, current, former), blood urea nitrogen, individual class of hypertension medication use (beta blockers, angiotensin receptor blockers (ARBs), alpha blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers), and diabetes diagnosis in the full cohort data.

The splitting of the sample and use of confirmation in the replication cohort provide protection against false positives. Because of the correlations in the data among SBP and DBP, repeated measures, and SNPs, the exact false discovery rate under this procedure cannot be computed theoretically. Instead, we examined false-positive predictive rates in a simulation study that preserved the correlation structure among SNPs and outcomes present in the data. The genotype data for each subject was randomly permuted, and then merged back into the repeated measures of phenotype. We created 10 new simulation data sets in which any associations observed in each individual simulation were random. We then identified all SNPs within each of the 10 discovery simulations that met our criteria of a \( p < 0.1 \) for the SNP × PM\(_{2.5}\) interaction and analyzed them in the simulated replication data set. We defined the probability of observing each of the associations we saw in the true data set as the probability of observing a greater absolute value \( t \)-statistic in the replication arm of the simulation study.

Results

A total of 945 individuals with a total of 2,098 study visits provided complete covariate and genotype data and are included in this analysis. A total of 480 subjects were randomly assigned to the discovery data set and 465 to the replicate data set. Table 2 presents the distribution of their demographics and anthropometrics. Age (mean ± SD) of study participants was 71.0 ± 7.3 years in the discovery cohort and 71.6 ± 7.1 years in the replication cohort, and most participants were former smokers. The distributions of a history of diabetes and use of medications for hypertension were similar in both cohorts.

We first examined the main effects of PM\(_{2.5}\) in mixed models adjusted for all covariates. The effect of PM\(_{2.5}\) in the model for ΔDBP was associated with a −0.018 mmHg change [95% confidence interval (CI), −0.45 to 0.41]. The main effect of PM\(_{2.5}\) in the model for ΔSBP was 0.69 mmHg (95% CI, −0.15 to 1.53). Both of these results were non-significant, although the ΔSBP change was more suggestive of an association.

All of the SNPs that met our criteria for an association in analyses were in Hardy–Weinberg equilibrium. Table 3 presents the distribution and Hardy–Weinberg equilibrium chi-square test results and \( p \)-values for SNPs that met the criteria in our models. The rs9568232 SNP in PHD finger protein 11 (PHF11) met our criteria for an SNP × PM\(_{2.5}\) interaction predictive of ΔDBP. Criteria for SNP × PM\(_{2.5}\) interactions predictive of ΔSBP were met by rs114493 in matrix-metalloproteinase 1 (MMP1) as well as rs16930692, rs7955200, and rs10771283 in the inositol 1,4,5-trisphosphate receptor, type 2 (ITPR2).

We examined SNP × PM\(_{2.5}\) interactions under additive, dominant, and recessive models of inheritance, and in our ΔDBP models 32 associations in 21 SNPs met criteria for ΔDBP in the discovery data set and were replicated. Of these associations, one SNP in the PHF11 gene met criteria for a significant SNP × PM\(_{2.5}\) interaction. Under a dominant model, the CT PHF11 rs9568232 SNP × PM\(_{2.5}\) interaction was associated with 2.29 mmHg higher DBP upon standing (95% CI, 0.72–3.86). Neither the main effect of PM\(_{2.5}\) (0.33 mmHg; 95% CI, −0.29 to 0.19) nor rs9568232 (0.37 mmHg; 95% CI, −0.49 to 1.23) was significant in the model.

In our SBP models, 46 associations in 34 SNPs met criteria at the 0.1 level for ΔSBP in the discovery data set. Of these associations, four SNP × PM\(_{2.5}\) interactions met criteria for significant changes in ΔSBP (Table 4). Under a recessive model of inheritance, the SNP × PM\(_{2.5}\) interaction for the rs114493 CT SNP in MMP1 was associated with a 3.40 mmHg higher ΔSBP (95% CI, 0.79–6.01). Both main effects for the SNP and PM\(_{2.5}\) were not significant at the mean level of PM\(_{2.5}\) exposure.

Three SNPs in ITPR2 met criteria for an association with ΔSBP modified by the effect of PM\(_{2.5}\). Under a dominant model, the SNP × PM\(_{2.5}\) interaction for the minor C allele of A/C rs16930692 was associated with 3.48 mmHg higher SBP upon standing (95% CI, 0.84–6.12). Similarly, under a recessive model, the SNP × PM\(_{2.5}\) interaction for the T variant of the C/T rs7955200 SNP in ITPR2 was associated with a 4.84 mmHg higher SBP upon standing (95% CI, 1.47–8.20). Finally, for the G minor allele of the rs10771283 A/G SNP, we observed 5.7 mmHg higher ΔSBP (95% CI, 1.71–9.69). For all three ITPR2

### Table 2. Anthropometric and clinical characteristics and postural change in blood pressure parameters of the study subjects.

| Characteristic | Discovery cohort (n=480) | Replication cohort (n=465) |
|---------------|--------------------------|---------------------------|
| Age (years)   | 71 ± 7.3                 | 71.6 ± 7.1                |
| BMI (kg/m²)   | 28 ± 3.9                 | 27.9 ± 4                  |
| ΔSBP (mmHg)   | 0.7 ± 6.4                | 0.5 ± 6.5                 |
| ΔDBP (mmHg)   | −2.7 ± 12.9              | −1.8 ± 12.5               |
| PM 40 hr (µg/mL) | 11.9 ± 6.1              | 11.8 ± 6                  |
| Smoking       |                          |                           |
| Never         | 157 (32.71)              | 143 (30.75)               |
| Current       | 25 (5.21)                | 29 (6.24)                 |
| Former        | 298 (62.08)              | 293 (63.01)               |
| Diabetes diagnosis |                      |                           |
| No            | 374 (77.52)              | 351 (75.48)               |
| Yes           | 106 (22.48)              | 114 (24.52)               |
| Alpha blockers |                          |                           |
| No            | 393 (81.88)              | 389 (83.66)               |
| Yes           | 87 (18.13)               | 76 (16.34)                |
| Angiotensin receptor blocker |          |                           |
| No            | 451 (93.96)              | 430 (92.47)               |
| Yes           | 29 (6.04)                | 35 (7.53)                 |
| ACE inhibitors |                          |                           |
| No            | 329 (68.54)              | 324 (71.83)               |
| Yes           | 151 (31.46)              | 121 (28.17)               |
| Calcium channel blockers |          |                           |
| No            | 358 (74.59)              | 360 (77.42)               |
| Yes           | 122 (25.42)              | 105 (22.58)               |
| Beta blockers |                          |                           |
| No            | 287 (59.79)              | 283 (60.86)               |
| Yes           | 193 (40.21)              | 182 (39.14)               |

### Table 3. Characteristics of SNPs with confirmed associations and their distribution among study participants.

| Characteristic | PHF11 | MMP1 | ITPR2 | ITPR2 | ITPR2 |
|---------------|-------|------|-------|-------|-------|
| Rs number     | rs9568232 | rs114493 | rs16930692 | rs7955200 | rs10771283 |
| Location      | chr13 | chr11 | chr12 | chr12 | chr12 |
| SNP           | C/T   | C/T   | C/T   | C/T   | A/G   |
| Functional role | Intron | Promoter | Intron | Intron | Intron |
| Wild type     | 814   | 351   | 802   | 480   | 571   |
| Heterozygote  | 120   | 439   | 119   | 362   | 307   |
| Homozygote    | 3     | 127   | 3     | 92    | 47    |
| Total         | 937   | 917   | 924   | 924   | 925   |
| HWE \( \chi^2 \) | 0.16  | 1.33  | 0.16  | 1.3   | 0.47  |
| \( p \)-Value  | 0.69* | 0.36  | 0.70* | 0.25  | 0.49  |

HWE, Hardy–Weinberg equilibrium. *Yates continuity corrected where expected value < 5.
SNPs, main effects of the SNPs and PM2.5 were not significant.

Because these ΔSBP associations for SNP × PM2.5 interactions were observed in genes related to the renin–angiotensin system, we hypothesized that blood pressure medications such as ARBs and ACE inhibitors might also be modified by the effects of PM2.5. We then examined associations for medication × PM2.5 interactions in the full cohort by adding interaction terms for medication × PM2.5 separately to the models that met our criteria for SNP × PM2.5 interactions (Table 4). Significant ARB × PM2.5 interactions (p < 0.05) were observed for all of the SNPs that met criteria for ΔSBP SNP × PM2.5 interactions, which were previously confirmed through our two-stage analysis utilizing the split-sample approach. In these models, the coefficients for the ARB × PM2.5 interactions were associated with significantly higher ΔSBP, whereby the magnitude of increase for an increase in 10 µg/m³ above the mean level of PM2.5 exposure was associated with 8–9 mmHg higher SBP. Similar results were observed for ARB × PM2.5 interactions in the absence of any SNP, where the interaction was associated with a 7.16 mmHg higher SBP (95% CI, 1.09–3.22). Figure 1 displays the relationship between SNP × PM2.5 interactions and ARB × PM2.5 interactions for ΔSBP. ACE inhibitors and their interactions with PM2.5 did not significantly alter ΔSBP.

Using our simulations, we found that the adjusted p-value for the SNP × PM2.5 association observed for the rs9568232 SNP in PPIA was 0.01. The rs1144393 MMP1 SNP × PM2.5 interaction associated with ΔSBP had an adjusted p-value of 0.02. The adjusted p-values for both the rs16930692 and rs10771283 ITPR2 SNP × PM2.5 interactions were 0.012, and for rs7955200 the adjusted p-value for the SNP × PM2.5 interaction was 0.004.

**Discussion**

In this study of the effects of SNP × PM2.5 interactions predicting postural changes in blood pressure, we observed several significant associations suggesting autonomic dysregulation and sensitization related to genes acting along the renin–angiotensin pathway in the presence of PM2.5, in contrast to the typical physiologic responses, in which we would expect to observe very small perturbations in blood pressure, and even negative associations with initial orthostatic change. Interactions in this analysis were consistently associated with increases in blood pressure from sitting to standing. In models of ΔDBP we observed one SNP × PM2.5 interaction that was a significant predictor, whereas in ΔSBP models, a single SNP in MMP1 and three SNPs in ITPR2 met our criteria. ITPR2 and MMP1 are activated downstream from angiotensin II and may be involved in altering responsiveness to renin–angiotensin and subsequent vasoconstriction with chronic exposure. Our analysis including PM2.5 interactions with antihypertension medication use among study participants showed similar effects where both SNP × PM2.5 interactions and ARB × PM2.5 interactions were associated with greater increase in blood pressure from sitting to standing position.

Although angiotensin II sensitization is necessary for regulation of blood pressure, hyperreactivity is associated with harmful effects, including the development of hypertension. Recent studies suggest that PM2.5 introduces cardiovascular effects by blunting response to endothelial dependent agonists as well as increasing response to vasoconstrictors in animals (Sun et al. 2005). In humans, evidence has shown that PM alters vascular diameter and tone and is associated with narrowing of the brachial artery (Brook et al. 2002) in controlled laboratory settings. Although epidemiologic studies have observed conflicting results in response to the effects of PM2.5 on blood pressure, two recent reports have observed small but significant increases in blood pressure associated with exposure (Auchincloss et al. 2008; Zanobetti et al. 2004). Our results suggest that looking at main effects of genes alone may not be sufficient and also may help to explain why associations between PM2.5 and various cardiovascular outcomes have been inconsistent.

**Table 4. Results for ΔSBP SNP × PM2.5 interaction models and ARB and ACE inhibitor interactions.**

| Gene | Variable | Model 1: SNP × 10 µg/m³ PM2.5 β (95% CI) | Model 2: model 1 + ARB × 10 µg/m³ PM2.5 β (95% CI) | Model 3: model 1 + ACE inhibitor × 10 µg/m³ PM2 β (95% CI) |
|------|----------|-----------------------------------------|-----------------------------------------------|--------------------------------------------------|
| MMP1 | Recessive | Rs1144393 0.37 (–1.34 to 2.08) | 0.35 (–1.36 to 2.06) | 0.38 (–1.33 to 2.09) |
|      | 10 µg/m³ PM2.5 0.2 (–0.80 to 1.20) | 0.04 (–0.96 to 1.04) | 0.35 (–0.73 to 1.43) | 3.46 (0.85 to 6.07) |
|      | Rs1144393 × 10 µg/m³ PM2.5 3.4 (0.79 to 6.01) | 3.35 (0.74 to 5.96) | 0.26 (–1.75 to 1.23) | –0.83 (–3.20 to 1.54) |
|      | ARB | 2.76 (–0.57 to 6.09) | 8.64 (2.00 to 15.28) | –0.26 (–1.75 to 1.23) | –0.83 (–3.20 to 1.54) |
|      | ARB × 10 µg/m³ PM2.5 | | 8.64 (2.00 to 15.28) | –0.26 (–1.75 to 1.23) | –0.83 (–3.20 to 1.54) |
|      | ACE inhibitors | | | | |
|      | ACE inhibitors × 10 µg/m³ PM2.5 | | | | |
| ITPR2 | Dominant | Rs16930692 –1.07 (–2.75 to 0.61) | –1.06 (–2.74 to 0.62) | –1.07 (–2.75 to 0.61) |
|      | 10 µg/m³ PM2.5 0.28 (–0.72 to 1.28) | 0.12 (–0.89 to 1.12) | 0.42 (–0.67 to 1.52) | 3.45 (0.81 to 6.09) |
|      | Rs16930692 × 10 µg/m³ PM2.5 3.48 (0.94 to 6.12) | 3.47 (0.84 to 6.10) | | |
|      | ARB | 2.89 (–0.45 to 6.23) | 8.68 (2.03 to 15.32) | | |
|      | ARB × 10 µg/m³ PM2.5 | | | | |
|      | ACE inhibitors | | | | |
|      | ACE inhibitors × 10 µg/m³ PM2.5 | | | | |
|      | Rs7955200 –0.73 (–2.77 to 1.30) | –0.75 (–2.78 to 1.29) | –0.74 (–2.77 to 1.30) | –0.19 (–1.68 to 1.30) |
|      | 10 µg/m³ PM2.5 0.33 (–0.63 to 1.29) | 0.18 (–0.79 to 1.15) | 0.44 (–0.63 to 1.51) | 0.42 (–0.67 to 1.52) |
|      | Rs7955200 × 10 µg/m³ PM2.5 4.84 (1.47 to 8.20) | 4.65 (1.29 to 8.01) | 4.79 (1.42 to 8.16) | 3.45 (0.81 to 6.09) |
|      | ARB | 2.87 (–0.47 to 6.20) | 8.35 (1.69 to 15.01) | | |
|      | ARB × 10 µg/m³ PM2.5 | | | | |
|      | ACE inhibitors | | | | |
|      | ACE inhibitors × 10 µg/m³ PM2.5 | | | | |
|      | Rs10771283 –1.29 (–3.82 to 1.32) | –1.29 (–3.82 to 1.32) | –1.3 (–3.83 to 1.23) | –0.58 (–2.95 to 1.80) |
|      | 10 µg/m³ PM2.5 0.41 (–0.56 to 1.36) | 0.26 (–0.70 to 1.22) | 0.51 (–0.56 to 1.57) | 0.51 (–0.56 to 1.57) |
|      | Rs10771283 × 10 µg/m³ PM2.5 5.7 (1.71 to 9.69) | 5.43 (1.44 to 9.41) | 5.63 (1.63 to 9.63) | 5.63 (1.63 to 9.63) |
|      | ARB | 2.89 (–0.46 to 6.21) | 8.24 (1.58 to 14.90) | –0.31 (–1.81 to 1.18) | –0.54 (–2.91 to 1.84) |
|      | ARB × 10 µg/m³ PM2.5 | | | | |
|      | ACE inhibitors | | | | |
|      | ACE inhibitors × 10 µg/m³ PM2.5 | | | | |

*Models adjusted for age, BMI, smoking status, ACE inhibitors, ARBs, diabetes, alpha blockers, beta blockers, and calcium channel blockers. β is equivalent to mmHg.
We observed a number of associations for SNP × PM$_{2.5}$ interactions as predictors of ΔSBP, but only one SNP met criteria in our models for an association with ΔDBP. PHF11 is located on chromosome 13 and is most commonly cited as an asthma candidate gene. A chromosomal region of 13q4 is within which PHF11 is located has been previously associated with a linkage peak thought to be related to a site controlling both SBP postural change and BMI, a well-established predictor of blood pressure (Feitosa et al. 2002; North et al. 2004). One recent study has shown that asthmatics were 43% more likely to have heart disease and 36% more likely to have high blood pressure compared with nonasthmatics (Dogra et al. 2007), and adult-onset asthma has been demonstrated to be a significant predictor of atherosclerosis (Onufrai et al. 2007).

MMP1 has also been shown to induce expression of cardiovascular outcomes. Also, angiotensin II has been demonstrated to be a significant predictor of atherosclerosis (Onufrai et al. 2007). MMP1 regulates the renin–angiotensin pathway. Sun et al. (1998) recently noted that losartan, an ARB, inhibits the vasoconstrictive effect of urban PM on human pulmonary artery endothelial cells.

Although this study has produced a number of novel findings, we recognize that it also has some limitations. This study was not conducted using genomewide association techniques but rather was performed on a subset of genes. We took advantage of another project that had extensively genotyped genes thought to be related to chronic lung disease, based on our belief that heart disease and chronic lung disease share many pathways. This limited our ability to study all the genes we might have been interested in if we had been able to examine genes related to blood pressure and baroreceptor response. However, we believe that the genes chosen for asthma and COPD are plausible candidates for these measures of autonomic function. We also considered the possibility that we observed our significant interactions because of associations between the sitting SBP, DBP, and mean arterial pressure effects alone, but analysis confirmed no significant association for any of the SNPs that met our criteria. These SNPs also were not associated with antihypertension medication use.

Figure 1. Effect of PM$_{2.5}$, SNPs, Angiotensin receptor blocker (ARB), SNP × PM$_{2.5}$ interactions, and ARB × PM$_{2.5}$ interactions in models predicting ΔSBP. We adjusted all models for age, BMI, smoking status, ACE inhibitors, ARBs, diabetes, alpha blockers, beta blockers, and calcium channel blockers.

Conclusions

In this study of the effects of PM$_{2.5}$ interactions with asthma and COPD candidate genes and hypertension medication use on ΔSBP and ΔDBP, we observed significant effect modification by PM for several genes and for ARB use. Because we have examined these associations under a situation in which we are using outcomes measured on a continuous scale and with repeated measures, we have increased power to detect novel associations that might otherwise go unobserved. Response to air pollution and its effect on autonomic function may be mediated by...
the SNP variants we have identified and can be further investigated in case–control and cohort studies. Also, blunting of the effects of ARBs but not ACE inhibitors in response to air pollution merits increased attention in clinical settings.

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