HFE Genotype, Particulate Air Pollution, and Heart Rate Variability
A Gene-Environment Interaction

Sung Kyun Park, ScD; Marie S. O’Neill, PhD; Robert O. Wright, MD, MPH; Howard Hu, MD, ScD; Pantel S. Vokonas, MD; David Sparrow, DSc; Helen Suh, ScD; Joel Schwartz, PhD

Background—Particulate air pollution has been associated with cardiovascular mortality and morbidity. Transition metals such as iron bound to the particles may be responsible for those associations. The protein product of the hemochromatosis (HFE) gene modulates uptake of iron and divalent cations from pulmonary sources and reduces their toxicity. Two HFE polymorphisms (C282Y and H63D) associated with increased iron uptake may modify the effect of metal-rich particles on the cardiovascular system.

Methods and Results—We investigated the association between particulate matter \(\leq 2.5 \mu m\) in aerodynamic diameter and heart rate variability in 518 older men from the Normative Aging Study who were examined between November 2000 and December 2004. Linear regression models were fit to evaluate interactions between HFE genotype and particulate matter \(\leq 2.5 \mu m\) in aerodynamic diameter in relation to heart rate variability, controlling for potential confounders. A 10-\(\mu g/m^3\) increase in particulate matter \(\leq 2.5 \mu m\) in aerodynamic diameter during the 48 hours before heart rate variability measurement was associated with a 31.7% (95% CI, 10.3% to 48.1%) decrease in the high-frequency component of heart rate variability in persons with the wild-type genotype, whereas no relationship in the high-frequency component was observed in persons with either HFE variant. The difference in effect of particulate matter \(\leq 2.5 \mu m\) in aerodynamic diameter on the high-frequency component between persons with and without HFE variants was significant \((P = 0.02)\).

Conclusions—The effect of particles on cardiac autonomic function was shielded in subjects with at least 1 copy of an HFE variant compared with wild-type subjects. Transition metals, including iron, bound to ambient particles and the related oxidative stress may play an important role in cardiac toxicity of particles. (Circulation. 2006;114:2798-2805.)

Key Words: air pollution ■ genes ■ epidemiology ■ nervous system, autonomic ■ metals

Particulate air pollution is associated with increased cardiopulmonary deaths and hospital admissions, especially among older people, people with diabetes mellitus, and individuals with cardiovascular conditions. Particulate matter \(\leq 2.5 \mu m\) in aerodynamic diameter (PM\(_{2.5}\)) is a complex mixture of compounds, including transition metals, sulfate salts, nitrate salts, and carbon. Certain fine particulate components, including metals, may be especially toxic. Genetic host factors that modify pathophysiological effects of particles may play an important role in predicting susceptibility to air pollution. Research on these factors can identify mechanisms of damage from specific particle sources (eg, vehicles, industrial facilities) that contribute particularly harmful constituents to the ambient pollution mix, allowing more finely targeted control measures.

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Iron is an element abundant in ambient PM\(_{2.5}\), often loosely bound on the surface. In humans, under physiological conditions, iron is bound to transferrin, the plasma iron transporter, which keeps iron soluble but compartmentalized and nontoxic. However, when present in excess, free iron can react with oxygen to yield highly reactive oxygen species, including the hydroxyl radical, through the Fenton reaction. Other divalent cation metals, such as nickel, may also play a role. Reactive oxygen species appear to be involved in the pathogenesis of cardiovascular disease.
Iron uptake across cell membranes is regulated by several proteins, including the hemochromatosis (HFE) gene product, transferrin, transferrin receptor (TfR), ferroportin, and possibly others. We focus on 2 well-characterized functional variants in the HFE gene associated with increased iron uptake into cells. The HFE gene, located at chromosome 6p, and 2 missense mutations of this gene, C282Y (cystein-282→tyrosine) and H63D (histidine-63→aspartate), alter iron binding and storage.11 Mechanistically, HFE variants increase intracellular iron via regulation of TfR even among heterozygous subjects, but in an allele dose-dependent manner.12,13 Because transferrin and TfRs mediate iron transport across cell membranes, the functional defect of HFE proteins increases TfR activity and facilitates iron transport into cells.14,15 Because iron stores are inversely associated with the gastrointestinal absorption of multiple potentially toxic metals (lead, cadmium, manganese, copper, and cobalt),16,17 HFE variants may modify the effect of particulate transition metals, and in previous studies, HFE variants were associated with lower blood and bone levels of lead, a toxic divalent metal.18

We hypothesized that the HFE genetic polymorphism modifies the effect of ambient PM$_{2.5}$ on cardiac autonomic function. We previously found a significant association between PM$_{2.5}$ and decreased heart rate variability (HRV), a marker of cardiac autonomic dysfunction and a predictor of sudden cardiac death and arrhythmia,19,20 among older men.21 In the present analysis, we expanded the period of follow-up originally reported in the study.21 The present analyses include additional follow-up data through 2004. A total of 1073 participants in the NAS cohort with archived blood samples were genotyped for C282Y and H63D. Between November 14, 2000, and December 22, 2004, 671 persons were examined for HRV. Of these individuals, 110 with irregular ECG patterns that interfere with HRV estimation and 5 with missing values of the potential confounding factors were excluded. In addition, 38 people with unreliable C282Y or H63D genotypes were also excluded. No important differences in subject characteristics according to reliable HFE genotype status were seen (data not shown). Hence, 518 participants with both HRV and HFE genotype were available for the analyses.

**HRV Measurement**

HRV was measured with a 2-channel (5-lead) ECG monitor (model Trillium 3000; Forest Medical, East Syracuse, NY). After a 5-minute rest period, each participant’s ECG was recorded (sampling rate of 256 Hz per channel) for ~7 minutes with the subject seated. We used the best 4-consecutive-minute interval for the HRV calculations. The ECG digital recordings were processed, and heart rate and HRV measures were calculated with PC-based software (Trillium 3000 PC Companion Software for MS Windows; Forest Medical), which conforms to established guidelines.23 We used only normal-to-normal (NN) beat intervals in the analysis. Standard deviation of NN intervals (SDNN) was calculated. We also computed high frequency (HF: 0.15 to 0.4 Hz), low frequency (LF; 0.04 to 0.15 Hz), and LF/HF ratio using a fast Fourier transform.

**HFE Genotyping**

Multiplex polymerase chain reaction assays were designed with Sequenom SpectroDESIGNER software (Sequenom, Inc, San Diego, Calif) by inputting sequence containing the single-nucleotide polymorphism (SNP) site and 100 bp of flanking sequence on either side of the SNP. For this assay, 4 SNPs were multiplexed: HFE RS1800562 and RS1799945, transferrin RS1049296, and ALAD RS1800435. Further details are available in the online Data Supplement.

**Air Pollution and Weather Data**

Ambient PM$_{2.5}$, black carbon, and sulfate were measured at a stationary monitoring site 1 km from the examination site with a tapered element oscillating microbalance (TEOM; model 1400A, Rupprecht & Patashnick Co, Albany, NY), aethalometer (Mage Scientific, Berkeley, Calif), and Harvard-EPA annular denuder system sampler, respectively. Ozone was obtained from a Massachusetts state monitoring site, and temperature and relative humidity were obtained from the Boston airport weather station. To control for weather variables, we used apparent temperature, defined as a person’s perceived air temperature.24 We used 48-hour moving averages for particle pollutants and 4-hour averages for ozone matched on the time of measuring ECG for each subject as our exposure indexes, because the strongest associations were seen previously in these exposure periods.21

**Statistical Methods**

We performed allele and genotype frequencies and Hardy-Weinberg equilibrium tests for each HFE and the joint genotypes. Measures of HRV were log$_{10}$ transformed to improve normality and stabilize the variance. Linear regression analyses were conducted to evaluate the relation of HRV with air pollution. The potential confounding variables considered were age, body mass index, mean arterial pressure, fasting blood glucose, high-density lipoprotein cholesterol, cigarette smoking, alcohol consumption (≥2 drinks/d), history of ischemic heart disease (IHD), use of β-blockers, calcium channel blockers and/or angiotensin-converting enzyme inhibitors, room temperature, season, day of week, and average of outdoor apparent temperatures 48 hours (4 hours for ozone) before the HRV measurement. A cubic spline with 3 degrees of freedom was used to model the nonlinear relationship between apparent temperature and HRV. To assess the potential modifying effect of HFE genotype, we ran regression models that included a cross-product term for interaction between HFE genotype and PM$_{2.5}$ along with the main effects and separate regressions stratified by HFE variants. We estimated the percentage change in each HRV parameter for each air pollutant.

**TABLE 1. Frequencies of HFE Genotypes**

<table>
<thead>
<tr>
<th></th>
<th>DD</th>
<th>HD</th>
<th>HH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>14 (2.7)</td>
<td>92 (17.8)</td>
<td>336 (64.9)</td>
<td>442</td>
</tr>
<tr>
<td>CY</td>
<td>...</td>
<td>13 (2.5)</td>
<td>61 (11.8)</td>
<td>74</td>
</tr>
<tr>
<td>YY</td>
<td>...</td>
<td>2 (0.4)</td>
<td>399</td>
<td>518</td>
</tr>
</tbody>
</table>

CC indicates wild-type C282Y; CY, heterozygote C282Y; YY, homozygote C282Y; HH, wild-type H63D; HD, heterozygote H63D; and DD, homozygote H63D.

Values are n (%).
We previously found that people with IHD had a greater reduction in HF in association with PM$_{2.5}$ exposure than those without IHD, and in this population, IHD was more prevalent among those with HFE variants. Given these conditions, we expected to see an even greater difference in the effect of PM$_{2.5}$ by genotype in this subpopulation, with stronger positive point estimates among the HFE variant genotypes. Hence, we reran the regressions restricting them to the subpopulation without IHD.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

The overall prevalences for C282Y genotypes among those genotyped in the NAS cohort (n=1073) were wild-type, 85.3%; heterozygote, 14.1%; and homozygote, 0.6%. Prevalences of H63D genotypes were wild-type, 75.6%; heterozygote, 22.1%; and homozygote, 2.3%. The distributions of both genotypes were in Hardy-Weinberg equilibrium (C282Y: $\chi^2=0.08, P=0.78$; H63D: $\chi^2=2.34, P=0.13$). These prevalences are similar to those shown in Table 1 for the subjects included in this analysis (n=518). When collapsed into a single variable indicating the presence or absence of either mutation, 182 (35.1%) of subjects carried at least 1 copy of either HFE variant.

Table 2 shows demographic and clinical characteristics and HRV measurements according to HFE genotype. The study participants were male, with average age 73 years (SD, 6.7 years). Diabetes and hypertension prevalences were 15% and 70%, respectively. Subjects with an HFE variant had a lower level of high-density lipoprotein cholesterol and were more likely to have IHD. The mean concentration of PM$_{2.5}$ during the study period was 11.7 $\mu g/m^3$ (SD 7.8 $\mu g/m^3$), with a modest correlation between apparent temperature and PM$_{2.5}$ ($r=0.31$).
A dichotomous variable indicating the presence or absence of either HFE variant did not show an association with HRV in a model without PM_{2.5} (model I, Table 3). In a previous analysis, PM_{2.5} was significantly associated with reductions in HRV measures, especially in HF. In this expanded follow-up, we confirmed that PM_{2.5} was related to a decrease in HF. Coefficients for the HFE variant effects were not substantially changed after the addition of PM_{2.5} to each of the HRV models (model II, Table 3). In the multivariable regression models that included an interaction term between HFE variant and PM_{2.5}, we found a significant positive interaction for HF (\(P=0.02\)) and borderline-significant interactions for SDNN (\(P=0.06\)) and LF/HF ratio (\(P=0.07\); model III, Table 3). PM_{2.5} was significantly associated with SDNN in that model.

The Figure presents the estimated percent changes in HF according to HFE variants in stratified regression models. A 10- \(\mu\)g/m\(^3\) increase in PM_{2.5} was significantly associated with a 31.7% (95% CI, 10.3% to 48.1%) decrease in HF in persons with the wild-type genotype, whereas no relationship in HF was observed in persons with either HFE variant. The associations in SDNN, LF, and LF/HF ratio were similar to those in HF (data not shown).

### Table 3. Adjusted Regression Coefficients and SE for 48-Hour Average PM_{2.5} (10-\(\mu\)g/m\(^3\) Change), HFE Genotype (Either HFE Variant vs Wild Type), and the Interaction Between PM_{2.5} and HFE Genotype in the Association With HRV Measures

<table>
<thead>
<tr>
<th>HRV</th>
<th>Model I*</th>
<th>Model II*</th>
<th>Model III*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HFE Variant</td>
<td>PM_{2.5}</td>
<td>HFE Variant</td>
</tr>
<tr>
<td>Log_{10} SDNN</td>
<td>0.0017</td>
<td>-0.032†</td>
<td>0.0020</td>
</tr>
<tr>
<td>SE</td>
<td>0.0231</td>
<td>0.019</td>
<td>0.0231</td>
</tr>
<tr>
<td>Log_{10} HF</td>
<td>0.0048</td>
<td>-0.101‡</td>
<td>0.0057</td>
</tr>
<tr>
<td>SE</td>
<td>0.0601</td>
<td>0.048</td>
<td>0.0599</td>
</tr>
<tr>
<td>Log_{10} LF</td>
<td>-0.0224</td>
<td>-0.053</td>
<td>-0.0219</td>
</tr>
<tr>
<td>SE</td>
<td>0.0494</td>
<td>0.040</td>
<td>0.0493</td>
</tr>
<tr>
<td>Log_{10} LF/HF</td>
<td>-0.0331</td>
<td>0.048</td>
<td>-0.0276</td>
</tr>
<tr>
<td>SE</td>
<td>0.0423</td>
<td>0.034</td>
<td>0.0423</td>
</tr>
</tbody>
</table>

All models adjusted for age, body mass index, mean arterial pressure, fasting blood glucose, high-density lipoprotein, cigarette smoking (never/former/current), alcohol consumption (\(<=2\) drinks/d), history of HHD, use of \(\beta\)-blockers, use of calcium channel blockers, use of angiotensin-converting enzyme inhibitor, room temperature, season, day of week, and outdoor apparent temperature.

*Model I includes a main effect of HFE variant without PM_{2.5}; model II includes 2 main effects of HFE variant and PM_{2.5}; model III includes 2 main effects of HFE variant and PM_{2.5}, and an interaction term between HFE and PM_{2.5}.

†\(P<0.1\), ‡\(P<0.05\).
We also evaluated the effects of other pollutants on HRV by HFE variants. Like PM$_{2.5}$, the effects of black carbon and sulfate were stronger in subjects with wild-type genotypes than in those with either HFE variant, but these differences were not statistically significant. The effect of ozone was almost identical regardless of HFE genotype (see Data Supplement). We conducted a sensitivity analysis restricted to the subpopulation without IHD (n = 373), and as expected, we found a greater and significant interaction with genotype (see Data Supplement).

**Discussion**

The present study demonstrates a significant modifying effect of HFE genotype on the association between PM$_{2.5}$ and HRV. Significant reductions in HRV in association with increasing PM$_{2.5}$ were observed only in individuals with the wild-type HFE genotype, and no relation with pollution was seen in subjects who had at least 1 copy of an HFE variant. The observed significant interaction between PM$_{2.5}$ and the HFE genotype suggests that transition metals bound to airborne particles may play an important role in influencing cardiac autonomic dysfunction.

Mutations in the HFE gene are the major risk factor for adult-onset hemochromatosis, an autosomal recessive genetic disease that increases absorption of ingested iron. Afflicted subjects develop iron overload, diabetes mellitus, heart disease, and liver disease due to excess body iron. The C282Y variant accounts for $\sim$85% of all hemochromatosis cases. Approximately 9% (95% CI, 8.1% to 10.0%) of the US general population are heterozygous for this allele. The SNP H63D is also associated with hemochromatosis but with a lower penetrance. Prevalence of the H63D heterozygous genotype in the US population is $\sim$22.8% (95% CI, 21.5% to 24.2%), and combined carrier prevalence of the 2 SNPs is $\sim$36.9% (95% CI, 35.4% to 38.5%).

Although the exact molecular mechanism remains unclear, HFE is thought to bind TfR and influence transferrin–iron–mediated intracellular iron transport. The wild-type HFE protein normally forms a stable complex with TfR and reduces its affinity for iron-loaded transferrin. The C282Y mutant protein does not associate with TfR and $\beta$-microglobulin, which enables high affinity of transferrin binding. The H63D mutant protein is capable of forming a complex with TfR; however, the H63D and C282Y mutations appear to lack the ability of the HFE protein to increase the rate of cell-association ($K_{\text{cell association}}$), compared with the wild type. This functional defect of HFE protein increases TfR activity and facilitates iron transport into cells.

Subjects who carry HFE variants are less likely to be iron deficient and can still appropriately downregulate gastrointestinal iron absorption. Downregulation of iron/metal absorption based on body iron stores may occur in lung epithelial cells, as occurs in the intestinal tract, possibly explaining the present findings. High exposure to reactive divalent metals induces a local inflammatory response in the lungs, because such metals catalyze oxidative reactions. Oxidative stress increases extracellular calcium influx through activation of calcium channels in the plasma membrane and inhibits nitric oxide production. Calcium influx and nitric oxide inactivation are associated with an elevation in sympathetic tone and a reduction in parasympathetic tone, which may be associated with sudden cardiac death and arrhythmia. Iron deficiency increases absorption of several divalent metals other than iron (eg, cobalt, manganese, lead, and nickel). The HFE gene variants, by lowering risk for iron deficiency, may modify the response to divalent metals found in particulate matter. Data on serum ferritin or transferrin saturation are not available for the NAS cohort, so we cannot consider biomarkers of iron stores in the present analysis. The present findings are consistent with our previous report that HFE variants were associated with lower levels of blood lead and bone lead in the same NAS cohort. The proposed mechanism for this effect was that HFE variants indirectly reduce lead exposure. Subjects with HFE variants are at lower risk for iron deficiency, and the overall increase in body iron stores among people with HFE variants may result in reduced expression of proteins that regulate divalent metal absorption, thus reducing the body burden of lead.

The present results suggest a similar mechanism with respect to the transport of divalent toxic metals across cell membranes in the lung. The HFE variant may reduce immediate absorption of toxic divalent metals in particulate matter, because subjects with this variant have higher iron stores and downregulated iron absorption. Recently, Heilig et al demonstrated that iron-deficient rats will absorb increased levels of manganese instilled in the lungs. The present findings are consistent with those results and support the hypothesis that genes that regulate intestinal absorption of divalent metals also regulate pulmonary metal absorption.

Although reduced toxic metal absorption may be one mechanism, alternative explanations for the present findings exist. The mechanisms by which particles reduce HRV are not well established, and lung inflammation may indirectly promote these cardiovascular events. Under this scenario, the effects of HFE variants on metal absorption in the lung may reduce the local inflammatory response to particulate metals and indirectly reduce cardiac toxicity. If we postulate that instead of reducing metal absorption, HFE variant carriers increase pulmonary cellular uptake of metals, then the observed interaction might be due to reduced pulmonary toxicity of absorbed metals. This hypothesis is supported by evidence that local alveolar inflammation is increased among animals that absorb metals poorly via the lung. In Belgrade rats, which absorb iron poorly due to a functional defect in the iron-transport protein divalent metal transporter-1, metal transport after ambient exposure from the lower respiratory tract was diminished and lung injury increased compared with control littermates when both were exposed to oil fly ash. Because the functional defect of HFE leads to an increased expression of divalent metal transporter-1, this suggests that divalent metal transporter-1 could participate in detoxification of iron found in particulate air pollution by transporting iron into airway cells, where it can ultimately be sequestered in a detoxified form. If by detoxifying iron in pulmonary tissue, the expected dysregulation of sympathetic
and parasympathetic neuron activity from particle exposure is prevented, then cardiac function would be unimpaired. This alternative hypothesis suggests an opposite effect of the HFE variant on transmembrane metal transport compared with our first hypothesis. Further animal research is needed with varying iron stores to determine whether HFE variants upregulate or downregulate pulmonary metal transport, especially among elderly individuals.

Regardless of mechanism, the interaction between PM2.5 and the HFE genotype we observed is consistent with the hypothesis that cardiovascular effects of fine particles are due in part to a biochemical response to transition metals. In Boston, trace elements make up ≈16% of the ambient PM2.5. Transition metals including iron, vanadium, and nickel are present in high concentrations as water-soluble salts in fine particles from oil combustion. These divalent metals released from the particles have been linked to generation of reactive oxygen species and induction of inflammatory mediators. We have also reported a significant interaction between glutathione S-transferase M1 genotype and PM2.5 in relation to a decrease in HRV, which indicates that the glutathione detoxification pathway may play a role in the defense against particle exposures. Together with the present findings, these studies suggest that genetic polymorphisms in detoxification pathways of reactive oxygen species–generating particles may predict susceptibility to cardiac autonomic dysfunction from oxidative stress. Whether this effect is due to reduce oxidative toxicity in cardiac or pulmonary tissue cannot be determined yet.

Given the protective effect of HFE variants on the association between PM2.5 and HRV, one might expect a dose-dependent effect modification by number of HFE variants. We therefore examined the allele dose effect of the variants by coding the genotype on an ordinal scale (none, 1, or 2 variants present). There was no evidence of a graded difference in PM2.5–HRV effect, however, probably because of the small number of subjects with homozygosity for C282Y and H63D and compound heterozygosity (n = 29, data not shown).

We also assessed interactions between HFE genotype and other air pollutants, including ozone, black carbon, and sulfate, but found no significant interaction. The effects of those pollutants were somewhat lower in persons with HFE variants than in wild-type carriers, perhaps because those pollutants were highly correlated with PM2.5. Furthermore, sulfate particles also have metals on their surface, and black carbon is a surrogate for traffic particles, which again include metals. We believe these results bolster our hypothesis that effects related to particulate metal metabolism underlie the observed interaction.

The present study has several limitations. Use of a single ambient monitoring site as a surrogate for recent exposure to PM2.5 may cause exposure misclassification. The extent of error depends on the spatial homogeneity of the exposure, because we have effectively assumed the only exposure contrast is temporal. PM2.5 concentrations in the eastern United States are relatively uniform over large areas, including metropolitan Philadelphia, Pa, and Boston, Mass. We have observed strong correlations between PM2.5 concentrations in Boston and in New Haven, Conn, which suggests that the use of temporal changes in PM2.5 exposure (and ignoring spatial variability) is reasonable. Similarly, sulfate concentrations are very spatially homogeneous on a regional level. A 1995 study found that sulfate concentrations at the Quabbin reservoir in western Massachusetts were essentially identical to those in Boston. We also assume, on the basis of evidence from previous studies in Boston and elsewhere, that outdoor concentrations are a good surrogate of personal exposure to PM2.5. Black carbon concentrations show considerable spatial variability depending on traffic exposure, however. We examined correlations between 24-hour concentrations at our monitoring location and concentrations at 6 monitoring stations operated for a year at a range of metropolitan Boston locations, from downtown to rural areas. Although the association was always significant, the median correlation coefficient was 0.8, which suggests greater exposure error for that exposure. The relative strength of the associations with the different particle metrics should be interpreted in this light.

We cannot rule out residual or unmeasured time-dependent and time-independent confounding factors and interactions with other genetic polymorphisms and/or environmental factors. Because PM2.5 concentrations vary daily, any factors that change over time and affect HRV measures, such as physical activity, may have the potential to confound the associations. Because such information was not available, we adjusted for day of week as a proxy of time-dependent confounding, and the association was unchanged. Given the age of the participants, we suspect that the range of physical activity was limited, but we have no direct data to address this question. We also checked whether people with HFE variants were less likely to have the glutathione S-transferase M1 null genotype, which also modified the PM2.5–HF relation in the same population. The proportion of the glutathione S-transferase M1 null genotype between HFE variants (45.4%) and wild types (46.4%) was essentially identical. Hence, these effect modifications are independent. As in any study of genetic association, population substructure might produce the observed interaction; however, the present study population is very homogeneous, with >95% being of European descent. Evaluation of functional variants that affect a biological pathway (divalent metal metabolism) chosen a priori also increases the likelihood that the effects are not due to confounding by ethnicity.

In conclusion, persons with either HFE genetic variant appear to be better protected from changes in cardiac autonomic dysfunction associated with particle exposure than wild-type carriers. The present study provides further evidence that transition metals, including iron, bound to ambient particles and the related oxidative stress may play a critical role in cardiac particle toxicity.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Metabolism of iron and other divalent metals is regulated by several proteins, including those whose expression is controlled by the *HFE* gene. *HFE* genetic mutations are the major risk factor for hemochromatosis, an autosomal recessive genetic disease that increases absorption of ingested iron. Approximately 9% and 23% of the US general population are heterozygous for the 2 single-nucleotide polymorphisms of this gene, C282Y and H63D, respectively. Ambient fine particles composed of reactive divalent metals, sulfate and nitrate salts, and carbonaceous materials have been associated with increased cardiopulmonary disease. Reactive oxygen species generated from those particle exposures may play a role in the pathogenesis of cardiovascular disease. Reduced heart rate variability is a marker of poor cardiac autonomic control and has been associated with increased risk of sudden cardiac death and arrhythmias. We investigated whether the effect of ambient particles on heart rate variability differed by *HFE* genotype in a population of elderly men. Exposure to fine particles significantly reduced heart rate variability in persons with wild-type *HFE* genotypes but not in those persons with either *HFE* variant. Although the mechanism is unclear, reduced metal absorption or indirect effects on autonomic function may play a role. The present study gives insight into a mechanism related to oxidative stress and metal metabolism that may explain how air pollution influences cardiovascular disease.
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