Potential Role of Ultrafine Particles in Associations between Airborne Particle Mass and Cardiovascular Health

Ralph J. Delfino, Constantinos Sioutas, and Shaista Malik

Numerous epidemiologic time-series studies have shown generally consistent associations of cardiovascular hospital admissions and mortality with outdoor air pollution, particularly mass concentrations of particulate matter (PM) ≤ 2.5 or ≤ 10 µm in diameter (PM$_{2.5}$, PM$_{10}$). Panel studies with repeated measures have supported the time-series results showing associations between PM and risk of cardiac ischemia and arrhythmias, increased blood pressure, decreased heart rate variability, and increased circulating markers of inflammation and thrombosis. The causal components driving the PM associations remain to be identified. Epidemiologic data using pollutant gases and particle characteristics such as particle number concentration and elemental carbon have provided indirect evidence that products of fossil fuel combustion are important. Ultrafine particles < 0.1 µm (UFPs) dominate particle number concentrations and surface area and are therefore capable of carrying large concentrations of adsorbed or condensed toxic air pollutants. It is likely that redox-active components in UFPs from fossil fuel combustion reach cardiovascular target sites. High UFP exposures may lead to systemic inflammation through oxidative stress responses to reactive oxygen species and thereby promote the progression of atherosclerosis and precipitate acute cardiovascular responses ranging from increased blood pressure to myocardial infarction. The next steps in epidemiologic research are to identify more clearly the potential PM causal components and size fractions linked to their sources. To advance this, we discuss in a companion article (Sioutas C, Delfino RJ, Singh M. 2005. Environ Health Perspect 113:947–955) the need for and methods of UFP exposure assessment. Key words: cardiovascular diseases, cytokines, diesel, epidemiology, oxidative stress, particle size, toxic air pollutants. Environ Health Perspect 113:934–946 (2005). doi:10.1289/ehp.7938 available via http://dx.doi.org/[Online 16 March 2005]

Coronary heart disease (CHD) is the leading cause of death and hospitalization among adults 65 or more years of age (Desai et al. 1999), which makes the identification of preventable causes for heart disease morbidity and mortality an important research goal. Numerous epidemiologic time-series studies have shown generally consistent associations of outdoor (ambient) air pollution with cardiovascular hospital admissions (Burnett et al. 1995, 1997a, 1997b, 1999; D’Ippoliti et al. 2003; Le Tertre et al. 2002; Linn et al. 2000; Mann et al. 2002; Morris et al. 1995; Peters et al. 2001a; Poloniecki et al. 1997; Samet et al. 2000a; Schwartz 1999; Schwartz and Morris 1995; Zanobetti and Schwartz 2001; Zanobetti et al. 2000a, 2000b). Consistent associations of ambient air pollution have also been found with cardiovascular mortality (Clancy et al. 2002; Dockery et al. 1993; Goldberg et al. 2001a, 2001b; Hoek et al. 2001; Kwon et al. 2001; Laden et al. 2000; Pope et al. 2004a; Rossi et al. 1999; Samet et al. 2000b; Schwartz et al. 1996; Wichmann et al. 2000; Zanobetti et al. 2003). The National Research Council (NRC) Committee on Research Priorities for Airborne Particulate Matter has identified research needed to explain the morbidity and mortality associations in the time-series studies (NRC 1998, 1999, 2001, 2004). One priority is to identify the pathophysiologic mechanisms and causal pollutant components driving these associations (Seaton et al. 1995).

The causal components driving the relationship between particulate matter (PM) and cardiovascular morbidity and mortality remain to be identified. Historically, the difficulty in accomplishing this in epidemiologic studies is related to the common use of ambient air pollution data from monitoring stations located at central regional sites. This has led to both exposure misclassification and high correlations between different pollutants. Both of these problems can be addressed with measurements of personal and/or microenvironmental exposures (Sarnat et al. 2000, 2001). Another problem is that the importance of particle size and chemistry has been limited by reliance on the same government monitoring data. In the United States, these data generally include only particle mass concentrations in air at two particle size cuts, PM$_{10}$ (PM ≤ 10 µm in aerodynamic diameter) and more recently PM$_{2.5}$ (PM ≤ 2.5 µm). However, there is sufficient reason to believe that ultrafine particles (UFPs; PM ≤ 0.1 µm) are important in morbidity and mortality associations otherwise attributed to larger-size fractions.

Major characteristics of UFPs that support their potential importance include a high pulmonary deposition efficiency, magnitudes higher particle number concentration than larger particles, and thus a much higher surface area. The UFP’s surface can carry large amounts of adsorbed or condensed toxic air pollutants (oxidant gases, organic compounds, transition metals) (Oberdörster 2001). Many of these toxic air pollutants have been identified as having pro-inflammatory effects in part through the action of reactive oxygen species (ROS), but relevant exposure data are rarely available to epidemiologists. Available surrogate measures of fossil fuel combustion such as elemental carbon (EC) or black smoke are of some use in this regard. Results from a study in southern California showed that a large proportion of urban UFPs is made up of primary combustion products from mobile source emissions (particularly diesel and automobile exhaust) and includes organic compounds, EC, and metals (Kim et al. 2002). Because exposure to mobile emissions can be variable across short distances and depends on personal activity patterns, assessing such exposures requires methods that go beyond the use of government monitoring data alone. These issues regarding the characteristics of UFPs are more thoroughly discussed in a companion article (Sioutas et al. 2005).

In the present review we discuss evidence for adverse effects of air pollution on cardiovascular health with an emphasis on findings that suggest a role for UFPs and related toxic air pollutant components. To date, there are fewer direct epidemiologic data on UFPs.

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Evidence of Causal Pollutant Components in Epidemiologic Time-Series, Cohort, and Cross-Sectional Studies

The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) is the largest of the air pollution time-series studies to date (Samet et al. 2000a, 2000b). Results show positive associations of PM$_{10}$ with cardiopulmonary mortality and with hospital admissions for cardiovascular disease, chronic obstructive pulmonary disease (COPD), and pneumonia in patients 65 or more years of age living in varied environments across up to 90 cities in the United States. A subsequent analysis to correct for statistical errors showed an increase of 0.34% [95% confidence interval (95% CI), 0.1–0.57] in combined cardiorespiratory mortality for each 10 µg/m$^3$ of air increase in PM$_{10}$ (Dominici et al. 2003). Another reanalysis of hospitalizations in 14 U.S. cities by Janssen et al. (2002) broke down the PM$_{10}$ concentrations using information on source categories. The authors found that for cardiovascular admissions, and to a lesser extent COPD admissions, PM$_{10}$ from highway vehicle and diesel emissions and from oil combustion showed the strongest associations with the most stable regression coefficients in co-regressions with other source categories. These findings are supported by an analysis of PM data collected for the Harvard Six Cities Study (Dockery et al. 1993) by Laden et al. (2000) using elemental profiles of PM$_{2.5}$ samples. They showed that associations between daily total mortality and mobile source (largely traffic related) particles for the six metropolitan areas were twice those for sulfate-rich coal combustion particles. This difference was most clearly demonstrated for deaths from CHD.

Additional information regarding causal pollutant components has come from analyses of ambient gaseous air pollutants under U.S. federal regulation [carbon monoxide, nitrogen dioxide, sulfur dioxide, and ozone]. These pollutants can be strongly correlated with PM in ambient air. A European study by Katsouyanni et al. (2001) of 29 cities showed a positive association between total mortality and PM$_{10}$ and that this association was not confounded by SO$_2$ or O$_3$. However, they did find that in cities with higher versus lower average NO$_2$, the association with PM$_{10}$ was significantly greater (0.80% vs. 0.19% increase in mortality per 10 µg/m$^3$ PM$_{10}$, respectively). The NMMAPS study found that PM$_{10}$ associations with mortality were largely independent of NO$_2$, SO$_2$, and O$_3$ (Samet et al. 2000a). Goldberg et al. (2001a, 2001b), Moolgavkar (2000), and Venner et al. (2003) have also found robust associations between cardiovascular mortality and pollutant gases that often were stronger than particle associations. In a time-series study of the Los Angeles air basin, Linn et al. (2000) found that significant associations of daily cardiovascular hospital admissions were strongest for CO, followed by NO$_2$, and then much weaker associations for PM$_{10}$, but daily PM data were limited by fewer stations. Morris et al. (1995) and Morris and Naumova (1998) found that hospital admissions for congestive heart failure (CHF) were associated with CO independent of other gaseous pollutants in several large U.S. cities. Mann et al. (2002) also found significant associations of daily CHD hospital admissions with NO$_2$ and CO in Los Angeles, particularly among cases with a secondary diagnosis of CHF or arrhythmia. Lin et al. (2003) found that an interquartile range increase in CO was associated with an increase of 6.4% in daily angina and acute myocardial infarction (MI) emergency department visits in São Paulo, Brazil. A time-series study of seven European areas found cardiovascular hospital admissions, especially CHD, were associated with SO$_2$ (Sunyer et al. 2003). Associations between gases and hospital admissions for CHD and CHF have been found in several other studies (e.g., Burnett et al. 1997b, 1999; Koken et al. 2003; Morris et al. 1995, 1998).

Some of the time-series investigators have hypothesized that pollutant gases could be acting as indicators for a causal mixture of pollutants, including PM-related components. Ambient CO is highly correlated with UFPs near combustion sources such as freeways (discussed more fully below). Although it is possible that some of the effects detected with CO are due to the formation of carboxyhemoglobin in the blood and carboxymyoglobin in muscle, reported ambient concentrations are low (<6 ppm). A postulated mechanism for increased susceptibility to low CO doses is the attainment of a nominal threshold of reduced O$_2$ transport to the heart and further compromised cardiac myoglobin, particularly in CHF patients (McGrath 2000).

Additional evidence of causal components linked to UFPs comes from European studies that have used a nongravimetric PM measure called black smoke, which is roughly representative of EC. Le Tertre et al. (2002) conducted a time-series analysis of cardiovascular hospital admissions in eight European cities and found that CHD admissions were associated with PM$_{10}$ and black smoke. The association with PM$_{10}$ but not with black smoke, was reduced by adding CO to the model and eliminated by adding NO$_2$. Both Le Tertre et al. (2002) and the European study by Katsouyanni et al. (2001) reported above hypothesized that their results were attributable to traffic exhaust and its consequent high emissions of CO, NO$_2$, black smoke, and air toxics. It is relevant to point out that traffic exhaust, particularly from diesel engines, is a major contributor to UFP mass in urban areas (Kittelson 1998; Tobias et al. 2001), and in general, UFPs are both strongly linked to mobile source emissions and laden with toxic constituents (Kim et al. 2002; Shi et al. 2001).

Although time-series investigations have provided important information regarding the overall public health impact of ambient air pollutants on severe outcomes such as mortality, studies of individual subjects have provided insights into the underlying acute or chronic exposure–response relationships. Below we review studies of individuals using various epidemiologic designs, including cohort and panel studies, focusing only on findings for cardiovascular outcomes. Details for selected studies are presented in Table 1 and follow the discussion in the text.

Time-series studies have provided evidence for acute effects of air pollutants on cardiovascular morbidity and mortality. However, there are still gaps in the literature regarding chronic health impacts from long-term pollutant exposures. Cohort studies are best suited to address this gap. Dockery et al. (1993) reported evidence from the Harvard Six Cities Study that ambient PM$_{2.5}$ was associated with risk of cardiopulmonary mortality in a cohort of 8,111 adults (Table 1). Pope et al. (2004a) used 16 years of data from more than 500,000 adults in 151 U.S. cities that participated in the Cancer Prevention Study II of the American Cancer Society. The authors found that a 10-µg/m$^3$ elevation in PM$_{2.5}$ was associated with 8–18% increases in mortality due to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest. Mortality from various respiratory causes was not associated with PM$_{2.5}$ (Table 1). In contrast, a cohort study of 6,338 Seventh Day Adventists living in California found associations of long-term exposure to PM and O$_3$ with respiratory mortality but not with cardiovascular mortality (Abbey et al. 1999) (Table 1). Differences in findings might be due to exposure misclassification from the use of central regional air pollutant data. Hoek et al. (2002) tried to address this issue by evaluating effects of traffic exposures near the home in a cohort study of 5,000 adults followed 8 years in the Netherlands (Table 1). They showed that living near a major road was more strongly associated with cardiopulmonary mortality than...
Table 1. Cardiovascular effects associated with personal and ambient air pollution exposure: selected studies.

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<tr>
<td>Dockery et al. 1993</td>
<td>Cohort study examining ambient air pollution exposure and mortality in 8,111 adults in six U.S. cities with 14–16 years of follow-up</td>
<td>Cardiopulmonary mortality</td>
<td>Compared with the least polluted city, the most polluted city had an adjusted RR for cardiopulmonary mortality of 1.37 (95% CI, 1.11–1.68)</td>
<td>No association with O₃ but SO₂ and NOₓ tracked between-city trends in PM concentrations</td>
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<tr>
<td>Pope et al. 2004a</td>
<td>Cohort study examining ambient PM exposure and cardiovascular mortality in 319,000–500,000 persons in the Cancer Prevention Study II, with 16 years of follow-up across U.S. urban areas</td>
<td>Cardiovascular mortality: ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest</td>
<td>A 10-µg/m³ increase in PM₂.₅ was associated with 8–18% increases in mortality due to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest</td>
<td>Not assessed</td>
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<td>Abbey et al. 1999</td>
<td>Cohort study examining ambient PM₁₀ exposure, total suspended sulfates, SO₂, O₃, and NOₓ in relation to mortality in 6,338 non-smoking California Seventh-Day Adventists with 19 years of follow-up</td>
<td>Cardiopulmonary mortality</td>
<td>No associations</td>
<td>No associations</td>
</tr>
<tr>
<td>Hoek et al. 2002</td>
<td>Cohort study examining ambient traffic-related air pollutant exposure (black smoke, NOₓ) and cause-specific mortality in 5,000 persons with 8 years of follow-up in the Netherlands Cohort Study on Diet and Cancer</td>
<td>Cardiopulmonary mortality</td>
<td>Cardiopulmonary mortality was associated with living near high traffic density (100 m to freeway or 50 m to major urban road) adjusted RR = 1.95 (95% CI, 1.09–3.52) and was associated with an increase of 10 µg/m³ black smoke from background (central sites) plus local sources (street proximity), RR = 1.71 (95% CI, 1.10–2.67)</td>
<td>Cardiopulmonary mortality was associated with an increase of 30 µg/m³ background plus local NOₓ, RR 1.81 (95% CI, 0.98–3.34)</td>
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<td>Künzli et al. 2004</td>
<td>Cross-sectional study on the relationship between ambient PM₂.₅ and CIMT, using baseline data from two clinical trials in Los Angeles; annual mean PM₂.₅ exposure was estimated using data from 23 monitoring stations linked to home addresses with geostatistical models</td>
<td>CIMT</td>
<td>For each increase of annual mean 10 µg/m³ PM₂.₅, CIMT increased by 5.9% (95% CI, 1–11%), adjustment for age reduced the coefficients, but further adjustment for covariates indicated robust estimates in the range of 3.9–4.3%</td>
<td>Estimates for O₃ linked to ZIP code centroids were positive in relation to CIMT but not significant and smaller than PM₂.₅</td>
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Cardiac ischemia and related outcomes

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<td>Peikkanen et al. 2002</td>
<td>Panel study examining ambient PM, NOₓ, CO exposure and ischemia during 342 submaximal exercise tests in 45 subjects with CHD in Helsinki, Finland</td>
<td>ECG ST segment depression &gt; 0.1 mV</td>
<td>Increased risk for ST depression (72 events) was associated with a change of lag-2 1,000 particles/cm³ NC₁₀₋₁₅, OR = 3.29 (95% CI, 1.57–6.92), 10 µg/m³ PM₂.₅, OR = 2.64 (95% CI, 1.42–5.66), and 10,000 UFP/cm³ NC₀.₁₋₁₅, OR = 3.14 (95% CI, 1.56–6.32); UFPs were independent of PM₂.₅</td>
<td>NOₓ and CO were also associated with an increased risk for ST depression.</td>
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<td>de Hartog et al. 2003</td>
<td>Panel study examining ambient exposure to PM and NOₓ, SO₂, and CO in relation to HRV and BP in 131 subjects with CHD in Helsinki, Finland; Amsterdam, the Netherlands; and Erfurt, Germany</td>
<td>Cardiorespiratory symptoms: chest pain, shortness of breath, avoidance of activities</td>
<td>A 10-µg/m³ increase in PM₂.₅ associated with shortness of breath, OR = 1.12 (95% CI, 1.02–1.24) and avoidance of activities, OR = 1.10 (95% CI, 1.01–1.19)</td>
<td>Not assessed</td>
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<td>Peters et al. 2004</td>
<td>Case-crossover study examining ambient traffic-related air pollution exposure and MI in 691 subjects from the Augsburg Myocardial Infarction Registry who had survived 24 hr postinfarct; time–activity diary data on activities during the 4 days before symptom onset were used to assess traffic exposures</td>
<td>MI</td>
<td>Exposure to traffic was associated with onset of MI 1 hr afterward, OR = 2.92 (95% CI, 2.22–3.83); a significant association was also seen for exposure to traffic 2 hr before onset, and there was evidence for effects up to 6 hr; key exposures influencing overall associations with traffic included times spent in cars and in public transportation; associations changed minimally, adjusting for exercise, and there was no confounding by reports of extreme anger or joy</td>
<td>As with PM, gases were not directly assessed, but traffic exposures involve pollutant gases as well as particles</td>
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<td><strong>Blood pressure (BP)</strong></td>
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<tr>
<td>Linn et al. 1999</td>
<td>Panel study in Los Angeles, California, examining BP and lung function in 30 subjects with COPD, with only 4 consecutive days of air sampling:</td>
<td>BP</td>
<td>Systolic BP increased 0.172 mm Hg for every 1-µg/m³ increase in ambient lag-1 PM₁₀₀ (p = 0.006); diastolic BP increased 0.095 mm Hg for every 1-µg/m³ increase in PM₁₀₀ (p = 0.033); outdoor home PM₁₀₀ was similarly associated with BP, but no significant associations were reported for PM₂·₅ or any indoor or personal PM measurement</td>
<td>No association of BP with exposure to central site O₂, NO₂, or CO</td>
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<td>Brauer et al. 2001</td>
<td>Panel study examining personal exposure over 7 non-consecutive days to PM₂·₅ and sulfate, and ambient exposure to PM₂·₅, PM₁₀₀, sulfate, and gaseous pollutants, in relation to BP, HRV, and lung function in 16 COPD patients in Vancouver, Canada</td>
<td>BP, HRV, SVE</td>
<td>Weak associations were observed between particle concentrations and increased SVE and with decreased systolic BP; ambient PM₁₀₀ had the largest effect on cardiovascular end points and the only statistically significant association (SVE); use of personal exposure measurements did not show a larger or more consistent effect</td>
<td>CO was inversely associated with systolic BP and reduced estimates for ambient PM</td>
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<td>Ibald-Mulli et al. 2001</td>
<td>Retrospective analysis examining the relationship between ambient air pollution exposure (TSP, SO₂, and CO) and BP in 2,607 men and women 25–64 years of age from a general population survey in Augsburg, Germany</td>
<td>Systolic BP</td>
<td>A 90-µg/m³ increase in TSP was associated with an increase in systolic BP of 1.79 mm Hg (95% CI, 0.63–2.95); in subgroups with high plasma viscosity levels or increased HR, systolic BP increased by 6.93 mm Hg (95% CI, 4.31–9.75) and 7.76 mm Hg (95% CI, 5.70–9.82) in association with TSP, respectively</td>
<td>An 80-µg/m³ increase in SO₂ was associated with an increase in systolic BP of 0.74 mm Hg (95% CI, 0.08–1.40)</td>
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<tr>
<td>Ibald-Mulli et al. 2004</td>
<td>Panel study examining ambient exposure to PM and NO₂, SO₂, and CO in relation to HRV and BP in 131 subjects with CHD in Helsinki, Finland; Amsterdam, the Netherlands and Erfurt, Germany</td>
<td>BP and HR</td>
<td>A small decrease in systolic BP [−0.72 mm Hg; 95% CI, −1.92 to 0.49] and diastolic BP [−0.70 mm Hg; 95% CI, −0.92 to −0.49] was found to be associated with a 5-day average increase of 10,000 UFPs/cm³ [NC₀.₀₁–₀.₁]; slightly stronger and more significant associations were found for accumulation mode particle number concentration [NC₀.₁–₁.₀], but smaller associations were found for a 10 µg/m³ increase in PM₂·₅ mass; small decreases in HR were also found for PM exposures</td>
<td>The magnitude and significance of inverse BP associations with CO were similar to those of PM₂·₅; a small decrease in HR [−0.40 beats/min; 95% CI, −0.82 to 0.01] was found for an increase of lag-1, 5 µg/m³ SO₂</td>
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<td>Zanobetti et al. 2004</td>
<td>Panel study examining ambient PM₂·₅, O₃, NO₂, SO₂, and CO in relation to patients with preexisting heart disease using data from 631 repeated visits for cardiac rehabilitation in Boston</td>
<td>BP</td>
<td>Increasing from the 10th to the 90th percentile in 5-day mean PM₂·₅ (10.5 µg/m³) resulted in increases of 2.8 mm Hg (95% CI, 0.1–5.5) in systolic, 2.7 mm Hg (95% CI, 1.2–4.3) in diastolic, and 2.7 mm Hg (95% CI, 1.0–4.5) in mean arterial BP; black carbon was associated with diastolic BP</td>
<td>Diastolic BO was associated with 120-hr average SO₂ (3.9% increase; 95% CI, 0.3–76); O₃ (2.7% increase; 95% CI, 0.02–5.4)</td>
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<td>Autonomic control of cardiac rhythm</td>
<td>Holguín et al. 2003</td>
<td>Panel study in Mexico City examining indoor and outdoor nursing home measurements of PM₂·₅ and ambient exposure to O₃, NO₂, CO, and SO₂ in relation to HRV in 34 elderly residents followed every other day for 3 months; personal PM₂·₅ was predicted using indoor and outdoor home PM₂·₅ plus time–activity data</td>
<td>HRV, frequency domain</td>
<td>A 10-µg/m³ increase in predicted personal PM₂·₅ was associated with a 5.0% decrease in high-frequency HRV (β = −0.049; 95% CI, −0.090 to −0.007); associations with indoor PM₂·₅ were stronger than outdoor home PM₂·₅ among 13 subjects with hypertension, the association with predicted personal PM₂·₅ was stronger (−7.1%)</td>
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<tr>
<td>Pope et al. 2004b</td>
<td>Panel study of ambient exposure to PM and HRV and blood markers in 88 elderly subjects living in Salt Lake City and Provo/Orem, Utah</td>
<td>HRV</td>
<td>A 100-µg/m³ increase in PM₁₀₀ was associated with a 35 (SE = 8) msec decrease in SDNN and a 42 (SE = 11) msec decrease in r-MSSD</td>
<td>Not assessed</td>
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### Studies Design and population

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<td><strong>Autonomic control of cardiac rhythm</strong>&lt;br&gt;Magari et al. 2001, 2002a, 2002b</td>
<td>Panel study examining personal exposure to PM in relation to HRV in 20 (Magari et al. 2002a), 40 (Magari et al. 2001), and 39 (Magari et al. 2002b) healthy boilermakers exposed to welding fumes and residual oil fly ash</td>
<td>HRV</td>
<td>Each 100-µg/m³ increase in 3-hr average PM$<em>{2.5}$ (laser photometer light scatter) was associated with a 1.4% (95% CI, –2.1 to –0.6%) decrease in 5-min SDNN in the 20 subjects (Magari et al. 2002a); in the 40 subjects, each 1-mg/m³ increase in 4-hr average PM$</em>{2.5}$ was associated with a 2.66% (95% CI, –3.75 to –1.58%) decrease in 5-min SDNN SDNN (Magari et al. 2001); however, in 39 of these 40 subjects, PM$_{2.5}$ metals on filters, lead and vanadium, were associated with an increase in workday average of the 5-min SDNN (Magari et al. 2002b)</td>
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<tr>
<td>Riediker et al. 2004</td>
<td>Panel study of in-vehicle exposure to PM and HRV and blood markers of inflammation in 9 healthy male North Carolina Highway Patrol troopers</td>
<td>HRV</td>
<td>In-vehicle 10-µg/m³ PM$<em>{2.5}$ increase was associated with increased ectopic beats throughout exposure (20%, p = 0.005); PM$</em>{2.5}$ was positively associated with heart beat cycle length (6%, p = 0.01) as well as HF HRV and SDNN the next morning after exposure</td>
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<td>Chan et al. 2004</td>
<td>Panel study in Taipei, Taiwan, examining personal exposure to submicrometer particles and HRV over one 16-hr daytime period in 9 young healthy adults 19–29 years of age (2 females) and 10 older male subjects 42–97 years of age with lung function impairments (FEV$_1$/FVC &lt; 85%)</td>
<td>HRV</td>
<td>Personal exposure to NC$<em>{0.02–1}$ was associated with increased HRV indices; in young subjects, a 10,000 particles/cm³ increase in the last 1–4 hr average NC$</em>{0.02–1}$ was associated with 0.68–1.35% decrease in SDNN, 1.85–2.58% decrease in r-MSSD, and residual oil fly ash –3.75 to –1.58% decrease in 5-min SDNN SDNN (Magari et al. 2001); however, in 39 of these 40 subjects, PM$_{2.5}$ metals on filters, lead and vanadium, were associated with an increase in workday average of the 5-min SDNN (Magari et al. 2002b)</td>
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<tr>
<td>Tarkiainen et al. 2003</td>
<td>Panel study in Kuopio, Finland, examining personal exposure to carbon monoxide and HRV and hospital admissions for CHD in 6 subjects with CHD followed for three separate 24-hr ambulatory monitoring periods</td>
<td>HRV</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Peters et al. 2000</td>
<td>Panel study of arrhythmias in 100 subjects in eastern Massachusetts with implanted defibrillators (63,628 person-days of follow-up) with ambient measurements of PM mass, black carbon, NO$_x$, CO, O$_3$, and SO$_2$</td>
<td>Defibrillator discharge interventions for ventricular tachycardias or fibrillation (33 subjects with at least one)</td>
<td>Only 6 subjects with ≥ 10 defibrillator discharges had increased arrhythmias associated with black carbon and PM$_{2.5}$, which showed a weaker association; both PM metrics were confounded by NO$_2$, but the effect estimate of NO$_2$ was unchanged</td>
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<td><strong>Systemic inflammation and thrombosis</strong>&lt;br&gt;Seaton et al. 1999</td>
<td>Panel study examining 3-day personal exposure estimated (from a one 24-hr personal exposure measurement) and city center ambient exposure to PM$_{10}$ in relation to hematologic factors in 112 elderly subjects in Belfast and Edinburgh, UK</td>
<td>Hematologic factors: hemo-globin, packed red cells, reticulocytes, platelets, white blood cell count, CRP, fibrinogen, factor VII, IL-6</td>
<td>An increase of 100 µg/m³ in personal PM$<em>{10}$ and ambient PM$</em>{10}$ exposure resulted in significant decreased mean percentage changes of ≤ 1% in hemoglobin concentration, packed cell volume, and red blood cell count; only personal PM$<em>{10}$ was associated with an 11% increase in platelets and a 7% decrease in factor VII; CRP increased with ambient PM$</em>{10}$ (+147%, 95% CI, 20–477), but not with personal PM (p = 0.73); fibrinogen decreased with ambient PM$_{10}$ (–9%, 95% CI, –19 to 0)</td>
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*Continued, next page*
with ambient background air pollutant levels. This finding suggests that pollutants more closely associated with traffic, which include UFPs and associated toxic air pollutants, could be causal components in the mortality associations.

Künzli et al. (2004) conducted a cross-sectional study of 798 healthy adults with elevated low density lipoprotein (LDL) cholesterol or homocysteine living in Los Angeles (Table 1). Subjects were in a dietary supplement clinical trial with ultrasound data on carotid intima-media thickness (CIMT) as an estimate of atherosclerosis. Exposure included an estimate using geostatistical models to link subject address to annual mean PM2.5 from 23 local air-monitoring stations. They found positive associations between CIMT and PM2.5, adjusting for host risk factors.

**Evidence for Pathophysiologic Mechanisms and Causal Components in PM-Related Cardiovascular Effects**

The following section looks at epidemiologic panel studies designed to evaluate the relationship between repeated air pollutant exposures and cardiovascular outcomes in individual subjects. We augment this discussion with a few selected human clinical studies that extend the panel study findings using controlled exposures, particularly those that aim to replicate ambient air mixtures. The discussion is divided by related groups of cardiovascular outcomes.

### Systemic inflammation and thrombosis

<table>
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<th>Studies</th>
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<td>Schwartz 2001</td>
<td>Cross-sectional study examining the relationship between ambient PM10, NO2, SO2, and blood biomarkers using data from a cohort study (NHANES III)</td>
<td>Fibrinogen, and platelet and white blood cell counts</td>
<td>For an interquartile range change in PM10 (26 µg/m3), the relative odds for being above the 90th percentile of fibrinogen was 1.77 (95% CI, 1.26–2.49); platelets, 1.27 (95% CI, 0.97–1.67); and white blood cells, 1.64 (95% CI, 1.17–2.30)</td>
<td>SO2 was positively associated with white cell counts, and NO2 with platelet counts and fibrinogen, but both gases were confounded by PM10.</td>
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<tr>
<td>Pekkanen et al. 2000</td>
<td>Cross-sectional study examining the association between ambient PM10, NO2, CO, SO2, O3, and fibrinogen among 7,205 subjects in London at baseline enrollment in a cohort study</td>
<td>Fibrinogen</td>
<td>No association between PM10 and fibrinogen was seen after adjustment for confounders</td>
<td>NO2 increase from the 10th to the 90th percentile was associated with a 1.5% higher fibrinogen concentration (95% CI, 0.4–2.5%); similar increase for CO resulted in 1.5% higher fibrinogen concentration (95% CI, 0.5–2.5%); no association with SO2 or O3.</td>
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<tr>
<td>Peters et al. 1997a, 2001b</td>
<td>Cohort study in Augsburg, Germany, examining relationships of ambient TSP, SO2, and CO exposure to CRP in 631 men 45–64 years of age with no history of MI at their baseline assessment; two CRP measurements were 3 years apart</td>
<td>CRP</td>
<td>An increase of 26 µg/m3 (5-day mean) in TSP increased the odds of observing a CRP level above the 90th percentile. OR = 1.31 (95% CI, 1.09–1.56); CRP and plasma viscosity (Peters et al. 1997a) were increased during an air pollution episode in 1985</td>
<td>An increase of 30 µg/m3 (5-day mean) in SO2 increased the odds of observing a CRP level above the 90th percentile, OR = 1.24 (95% CI, 1.03–1.49).</td>
</tr>
<tr>
<td>Pope et al. 2004b</td>
<td>Panel study of ambient exposure to PM and HRV and blood markers in 88 elderly subjects living in Salt Lake City and Provo/Orem, Utah</td>
<td>CRP, white blood cell count, whole blood viscosity, granulocytes, lymphocytes, monocytes, basophils, eosinophils, red blood cells, platelets</td>
<td>A 100-µg/m3 increase in PM10 was associated with a 0.81 (SE = 0.17) mg/dL increase in CRP; one subject’s data had a strong influence on estimates; there was no association with other outcomes</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Riediker et al. 2004</td>
<td>Panel study of in-vehicle exposure to PM and HRV and blood markers of inflammation in 9 healthy male North Carolina Highway Patrol troopers</td>
<td>CRP, plasminogen, von Willebrand factor, lymphocyte count, lymphocytes, neutrophils, hematocrit, red blood cell indices, uric acid</td>
<td>In-vehicle 10-µg/m3 PM2.5 increase was associated with decreased lymphocytes (~11%, p = 0.02); increased red blood cell indices (1%, p = 0.03), neutrophils (6%, p = 0.04), CRP (32%, p = 0.02), and von Willebrand factor (12%, p = 0.02)</td>
<td>NO2 and CO were not significant</td>
</tr>
</tbody>
</table>

*Abbreviations: FEV1/FVC, forced expiratory volume in 1 sec/forced vital capacity; HF, high frequency; RR, relative risk; SVE, supraventricular ectopic heartbeat.

*The focus is on cardiovascular outcomes. Although some studies may have examined other outcomes, they are not reported.*
Cardiorespiratory symptoms potentially related to cardiac ischemia were assessed by de Hartog et al. (2003) in elderly patients with CHD. The authors found that although chest pain was not associated with PM exposure, a 10 µg/m³ increase in ambient PM₂.₅ was associated with shortness of breath and avoidance of activities (Table 1). A case-crossover study of 691 subjects from the Augsburg Myocardial Infarction Registry found a 2- to 3-fold increased risk of MI for time-activity diary reports of hours exposed to traffic, particularly for times spent in cars and public transportation in the hours leading up to cardiac symptom onset (Peters et al. 2004) (Table 1). No direct air pollutant measurements were available. However, as discussed in our companion article (Sioutas et al. 2005), exposures to UFPs can be magnitudes higher than background levels within vehicles and near busy highways, and to a much greater degree than larger particles. Accumulation-mode PM, volatile organic compounds, and gases such as CO could have also played a role in the findings of Peters et al. (2004).

**Blood pressure.** Two studies showing associations between air pollution and blood pressure (BP) followed subjects with COPD (Brauer et al. 2001; Linn et al. 1999; Table 1). Linn et al. (1999) found that for only 120 total person-observation times in 30 subjects, an increase of 33 µg/m³ ambient PM₁₀ (study mean) was associated with a 5.7 mm mercury (Hg) increase in systolic BP. In contrast, Brauer et al. (2001) found systolic BP was inversely but weakly associated with personal PM₂.₅ in a pooled regression analysis of 16 subjects with COPD monitored on 7 separate days. This association was not confounded by inverse associations with ambient CO. Inverse associations with ambient PM₁₀ were larger but were confounded by CO. Another study examined 2,607 German adults younger than 65 years evaluated on two occasions 3 years apart and found a positive association of systolic BP with ambient concentrations of both total suspended particulates (TSP) and SO₂ (Ibald-Mulli et al. 2001) (Table 1).

Ibald-Mulli et al. (2004) conducted one of the few panel studies to focus on the relationship between UFPs and BP (Table 1). They followed 131 adults with CHD in three European centers every 2 weeks for about 11 clinic visits. An increase of a 5-day average of 10,000/cm³ UFPs (PM₀₋₁) was associated with small decrease in systolic BP (–0.72 mm Hg; p < 0.01) and diastolic BP (–0.70 mm Hg; p < 0.01). Comparable small associations were also found for CO, 1,000/cm³ accumulation-mode particles, and 10 µg/m³ PM₂.₅. The authors hypothesized that BP medications in these CHD patients might have blunted or modified the response to air pollution exposure. However, these results contrast those of a panel study by Zanobetti et al. (2004), who found that ambient 5-day average PM₂.₅ was positively associated with BP among 62 patients with preexisting heart disease, using data from 631 repeated visits for cardiac rehabilitation in Boston (Table 1).

Panel study results for PM₂.₅ can be compared with two experimental human studies (Brook et al. 2002; Gong et al. 2003; not shown in Table 1). Gong et al. (2003) studied the effects of PM₂.₅ concentrated ambient particles (CAPs) from Los Angeles air versus clean air on systolic BP in 12 healthy versus 12 asthmatic adults using a 2-hr rest–exercise period in a chamber. CAPs were used to approximate the effects of “real-world” particles. They found inverse associations of PM₂.₅ CAPs with systolic BP in asthmatics, but positive associations in healthy subjects. Results from two small studies by Brauer et al. (2001) and Gong et al. (2003) with relatively good exposure data show that PM₂.₅ mass is inversely associated with BP in subjects with obstructive lung diseases. Brook et al. (2002) also studied the vascular effects of 150 µg/m³ PM₂.₅ CAPs from Toronto air, adding 120 ppb O₃ in 25 healthy adults using a 2-hr exposure period in a chamber. They found a significant but small 0.1 mm decrease in brachial artery diameter by ultrasonography for the joint exposures versus the controls. In the latter study, the authors hypothesized that the organic and EC fractions of PM₂.₅ might have blunted or modified the response to air pollution exposure. Therefore, the potential mechanisms for the observed associations in the epidemiologic studies used or underlying pathology (healthy, COPD, asthma, CHD, etc.). There is also a lack of data in most studies on other influences on BP, namely, emotional states and physical activity, which could have sustained influence on nonambulatory BP measurements. The above factors may result in contrasting shifts in vasoconstriction, leading to maintenance of basal vascular tone and BP (Haynes and Webb 1998) and accentuating BP elevation in more severe, sodium-sensitive hypertension (Schiffrin 2001). It is directly associated with the severity of CHF and risk of subsequent cardiac death in CHF patients (Galatius-Jensen et al. 1996; Tsutamoto et al. 1995). Endothelin-1 is produced and cleared in the lung and is generated in response to the presence of ROS (free radicals) and their metabolites (Haynes and Webb 1998). This leaves open the possibility that pollutants could induce an excess production of endothelin-1. Supporting evidence is that urban particles have been shown to increase endothelin-1 in rats (Bouthillier et al. 1998). Effects of endothelin-1 are partly counterbalanced by vasodilatory influences of endothelial nitric oxide (NO; Vanhoutte 2000). Endothelial NO synthase produces NO, which traverses the extracellular space to induce smooth muscle relaxation in the vessel wall. One ROS that can be produced in the presence of certain pollutant components is superoxide, which can react with NO to form the potent oxidant peroxynitrite. Peroxynitrite is likely involved in lipid peroxidation (D’Onofrio and Freeman 2001). Therefore, an additional potential mechanism whereby pollutant components can increase BP includes superoxide-mediated inhibition of the actions of NO in inducing vasodilatation.

Despite the above data on potential biologic mechanisms, reviewed epidemiologic studies have found both a decrease and increase in BP in relation to air pollutant exposures. This may be because of differences between subject populations, differences in the types of regional air pollutants, or possibly due to medications used or underlying pathology (healthy, COPD, asthma, CHD, etc.). There is also a lack of data in most studies on other influences on BP, namely, emotional states and physical activity, which could have sustained influence on nonambulatory BP measurements. The above factors may result in contrasting shifts in sympathetic and vagal tone in response to inhaled air pollutants, or contrasting shifts in the balance between mediators such as endothelin-1 and endothelial NO. The time course of exposure–response relationships is also ill-defined, particularly periods of exposure averaging times ranging from minutes to days. None of the epidemiologic studies used ambulatory BP monitoring to assess acute effects of real time changes in exposure. Ambulatory BP monitoring is more closely associated with end organ damage (heart, kidney, brain) than isolated systolic or diastolic BP readings taken in clinic offices (Mancia and Parati 2000).
been shown to be a predictor of increased mortality after MI (Kleger et al. 1987; La Rovere et al. 1998) and has been related especially to sudden arrhythmic death (Hartikainen et al. 1996; Omeduwiya et al. 1991). Fourier analysis of HRV can show the magnitude of variance in the heart’s rhythm across different frequency bands. Different autonomic influences on cardiovascular function (HR and BP) are reflected by different frequency bands. The high-frequency (HF) band (0.15–0.40 Hz) has been used to estimate cardiac vagal control and is linked to respiratory influences (Task Force 1996). Lower frequencies (0.04–0.15 Hz) are believed to represent mixed sympathetic and parasympathetic influences (Task Force 1996). Time domain measurements are also used (described below).

One controlled exposure study showed significant decreases in HRV in 10 healthy elderly adults for 2-hr exposures to CAPs from Chapel Hill, North Carolina (mostly mobile source) compared with clean air, and the decrease persisted 24 hr later (Devlin et al. 2003). In epidemiologic studies discussed below, ambient PM has been associated with decreased HRV (Chan et al. 2004; Creason et al. 2001; Gold et al. 2000; Holguin et al. 2003; Liao et al. 1999; Magari et al. 2001, 2002; Peters et al. 1999; Pope et al. 2004a, 1999) and cardiac arrhythmia (Peters et al. 2000). Only two studies to our knowledge have investigated effects of personal PM exposures on HRV (Chan et al. 2004; Magari et al. 2001), and one on personal CO (Tarkiainen et al. 2003).

Liao et al. (1999) showed that the largest inverse associations between nonambulatory HRV measures and PM$_{2.5}$ were for subjects with a history of cardiovascular conditions, although the number subjects (18) was small and the specific illnesses were not separated (not shown in Table 1). Another study of 56 elderly subjects showed inverse associations of nonambulatory high- and low-frequency HRV with indoor and outdoor 24-hr gravimetric PM$_{2.5}$ collected in a retirement home (Creason et al. 2001; not shown in Table 1). Using hourly ambient PM$_{2.5}$ data, they briefly reported that models using prior 4-hr average PM$_{2.5}$ and time-lagged 4-hr PM$_{2.5}$ were similar in magnitude to effects of the 24-hr PM$_{2.5}$ averages, suggesting a mixture of short-term and cumulative effects. Holguin et al. (2003) studied 34 elderly nursing home residents living in Mexico City and showed a strong decrease in the high-frequency component of HRV with high ambient PM$_{2.5}$ exposure, and the association was stronger for indoor home PM$_{2.5}$. Those with hypertension had the largest reductions in HRV (Table 1). Pope et al. (1999) also used ambulatory HR monitoring in 7 elderly subjects with respiratory and cardiovascular disease before, during, and after episodes of elevated pollution. They found that ambient PM$_{10}$ was associated with decreased in the standard deviation (SD) of normal-to-normal (NN) intervals (SDNN), a time domain measure of overall HRV. However, they also found an increase in the square root of the mean of squared differences between adjacent NN intervals (r-MSSD); time domain measurement that corresponds to high-frequency variability and parasympathetic tone. A larger study using ambulatory ECG monitors by Pope et al. (2004b) found that ambient PM$_{2.5}$ was associated with a decrease in both SDNN and r-MSSD in 88 elderly subjects in Utah (Table 1). Magari et al. (2001) studied 40 workers occupationally exposed to welding fumes and residual oil fly ash with 24-hr monitoring using ambulatory HR monitors and personal real-time PM$_{2.5}$ measurements from a TSI Inc. DustTrak (Shoreview, MN) (Table 1). They found significant decreases in SD of average 5-min NN intervals in relation to increases in prior 1-hr moving averages of PM$_{2.5}$. They also found increasingly greater decreases in SDNN for higher PM$_{2.5}$ across longer PM$_{2.5}$ averaging times up to 9 hr. Magari et al. (2001) suggested inhaled particles directly affect autonomic function through a sympathetic stress response, represented by their acute response finding, and/or secondarily through airway inflammation and cytokine release into the circulation, represented by their cumulative response finding. Riediker et al. (2004) placed portable air-quality monitors in patrol cars of nine healthy male North Carolina Highway Patrol troopers who wore ambulatory ECG monitors (Table 1). In-vehicle PM$_{2.5}$ was positively associated with ectopic beats, heart beat cycle length, HF HRV, and SDNN.

Chan et al. (2004) conducted the only study to date to assess the relationship between HRV and particle number concentrations (dominated by UFPs) for particles 0.02–1.0 µm in diameter (NC$_{0.02–1}$) (Table 1). They followed 9 young healthy adults (2 females) and 10 elderly male subjects with obstructive lung function impairment. This was also the first study to examine the effects of personal exposure to UFPs on HRV. Subjects were monitored over only 10 daytime hours using a P-Trak Ultrafine Particle Counter (TSI Inc.) for NC$_{0.02–1}$. Subjects also wore ambulatory ECG monitors for continuous 5-min beat-to-beat intervals to assess HRV. Using linear mixed-effects models, they found that decreases in HRV indices (SDNN and r-MSSD) were associated with exposure to 1- to 4-hr moving averages of NC$_{0.02–1}$ before the 5-min HRV measurements, adjusting for age, sex, body mass index, environmental tobacco smoke exposure, and temperature (Table 1). Associations were stronger for the elderly panel, with the strongest effects from 2-hr average NC$_{0.02–1}$. These results along with those of Magari et al. (2001) suggest that the effect of personal PM exposure on autonomic function is acute, although the monitoring period (10 hr) was too short in the Chan et al. (2004) study to assess longer-term effects. Tarkiainen et al. (2003) studied six patients with CHD for 1 day per week for 3 weeks with continuous personal CO exposure monitors, ambulatory ECG monitoring for HRV, and time–activity diaries and found r-MSSD increased in relation to high CO exposures (> 2.7 ppm peaks lasting 17 min, SD 8 min) (Table 1). This result contrasted results of most studies using PM exposures, except the study of Pope et al. (1999). No particle data were available, but it is again important to note that outdoor CO at sites close to dense traffic is highly correlated with UFPs (Zhu et al. 2002). It is conceivable that CO and/or UFPs increase vagal control and induce bradycardiacs.

In a study of arrhythmias and air pollution, investigators followed 100 subjects in eastern Massachusetts with implanted defibrillators (Peters et al. 2000; Table 1). They found that patients with 10 or more defibrillator discharge interventions for cardiac arrhythmias experienced increased arrhythmias in association with outdoor ambient NO$_2$, CO, and black carbon, but PM$_{2.5}$ was less strongly related. The most robust association was found for NO$_2$, which may have been a marker for local traffic-related pollution, whereas particle mass may have been additionally influenced by other sources. Exposure was represented by only one Boston monitoring site.

Systemic inflammation and thrombosis. The view that air-pollution–induced airway inflammation triggers systemic hypercoagulability (Seaton et al. 1995) has been supported in recent epidemiologic studies. It is relevant in this regard that, compared with unaffected people, patients with CHD (Lagrand et al. 1999; Mandell et al. 1997; Stec et al. 2000; Woods et al. 2000) or a complication of CHD, CHF (Pye et al. 1990; Torre-Amione et al. 1996), have increased levels of inflammatory cytokines such as interleukin (IL)-1B and IL-6, and tumor necrosis factor-α (TNF-α). They also have increased levels of circulating acute phase proteins such as C-reactive protein (CRP) and fibrinogen. In patients with CHD, CRP is also a strong independent predictor of future coronary events (Riisfjord and Ridker 2001). Cohort studies have shown that levels of acute phase proteins, cytokines, and hemostatic factors indicative of a thrombophilic state or endothelial activation are elevated at baseline in subjects at risk for future coronary occlusion or cardiovascular mortality (Cushman et al. 1999; Danesh et al. 2000; Folsom et al. 2001; Harris et al. 1999; Haverkate et al. 1997; Jager et al.
air pollution exposures that lead to acute increases in already elevated levels of inflammatory and hemostatic factors may also precipitate adverse health outcomes. This is a strong possibility in patients with diagnosed or underlying CHD, a population most likely driving the time-series associations. In addition, high air pollutant exposures that lead to chronic or repeated increases in systemic inflammation through oxidative stress responses to ROS may promote the progression of atherosclerosis in susceptible individuals.

Recent studies have shown acute associations between air pollutant exposures and systemic responses indicating inflammation and hypercoagulability. Seaton et al. (1999) studied 112 elderly individuals and used 1 day of personal PM$_{10}$ data per person to predict the remaining 2 days using ambient (city center) PM$_{10}$ data (Table 1). Results showed inverse associations of estimated personal PM$_{10}$ with albumin-adjusted hemoglobin, packed cell volume, red blood cell count, platelets, and factor VII levels. They found no associations between PM$_{10}$ and IL-6 or white blood cell count. Only ambient PM$_{10}$ was positively associated with CRP concentrations, but it was also inversely associated with fibrinogen. The authors hypothesized that particles enter lung endothelial cells or erythrocytes and subsequently influence red cell adhesiveness, leading to peripheral sequestration of red cells. Contrastings results were found by Schwartz (2001), who used health data from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States (Table 1). Results showed that outdoor PM$_{10}$ levels on the day of subject visits or previous day was positively associated with fibrinogen levels and counts of platelets and white blood cells. Fibrinogen increased by 13 µg/dL (95% CI, 4.6–22.1) for an interquartile range change in PM$_{10}$ of 26 µg/m$^3$. PM effects were independent of gaseous pollutants. Schwartz (2001) argued that the NHANES III results were consistent with data in controlled human exposure (Ghio et al. 2000) and animal studies (Gardner et al. 2000) that showed increased plasma fibrinogen after particle exposures. Peikkanen et al. (2000) found no association between PM$_{10}$ and fibrinogen using cross-sectional data from another cohort study of 7,205 subjects in London. However, they did find associations between fibrinogen and two pollutant gases, NO$_2$ and CO, but not SO$_2$ or O$_3$. Epidemiologic studies in Augsburg, Germany, have also shown positive associations of ambient air pollution with plasma viscosity (Peters et al. 1997) and with CRP concentrations (Peters et al. 2001b) (Table 1). Another study of people exposed to forest fire smoke showed increased circulating levels of IL-1β and IL-6 (Van Eeden et al. 2001; not shown). A panel study by Pope et al. (2004b) (Table 1) with 88 elderly subjects in Utah showed a 0.81 mg/dL CRP increase in association with a 100 µg/m$^3$ increase in ambient PM$_{2.5}$. There was no association with white or red blood cell counts, platelets, or whole-blood viscosity. Riediker et al. (2004; discussed above) assessed the relationship between in-vehicle PM exposure and markers of inflammation in nine healthy male state troopers. An in-vehicle 10 µg/m$^3$ PM$_{2.5}$ increase was associated with decreased lymphocytes (–11%), increased red blood cell indices (1%), neutrophils (6%), CRP (32%), and von Willebrand factor (12%)

Summary and biologic plausibility. To date only three studies have directly evaluated the effects on cardiovascular health by UFPs or particle number concentration (Chan et al. 2004; Ibald-Mulli et al. 2004; Peikkanen et al. 2002). Results of Peikkanen et al. (2002) showing ST segment depression in relation to UFPs are the most compelling findings. Associations of ambient NG$_{0.01–0.1}$ with ST segment depression were independent of ambient PM$_{2.5}$, but it is unclear whether the ambient exposure data represented personal UFP exposures of subjects. Other indirect evidence that components of fossil fuel combustion are important comes from studies using surrogate measures of particle composition such as black smoke, proximity of homes to traffic, or source apportionment data. Epidemiologic associations for pollutant gases also seem to support the idea that cardiovascular effects may be linked to primary products of combustion emissions that include UFPs.

Because hypertension, ST segment depression, and cardiac arrhythmias are well-known risk factors for cardiac morbidity and mortality, the above findings of acute associations with PM from individual-level studies are relevant to the reported findings of time-series and cohort investigations of mortality and hospital morbidity. However, mixed findings for BP have not provided a coherent view of particle effects. Findings for HRV are largely consistent in finding a decrease in HRV except for the increase in r-MSSD with ambient PM among elderly subjects found by Pope et al. (1999) and increased HF HRV for in-vehicle PM among healthy men found by Riediker et al. (2004). The clinical importance of HRV to cardiovascular disease is unclear however (Task Force 1996), and many technical issues regarding the influence of respiratory patterns (respiratory sinus arrhythmia) and psychosocial stress (both unmeasured in the reviewed studies) remain unresolved (Sloan et al. 1994).

The reviewed epidemiologic studies on circulating biomarkers of effect show inconsistent relationships between air pollution and blood markers of inflammation and hypercoagulability, possibly because all but two studies used ambient exposure to PM. Currently, only the studies of Seaton et al. (1999) and Riediker et al. (2004) used any personal PM exposure measurements, but results are not consistent. In addition, the reviewed studies of circulating biomarkers did not target people with cardiovascular diseases, who are expected to be among the most susceptible population, as indicated in the time-series investigations.

The main limitation of most epidemiologic studies is exposure misclassification from dependence on central site rather than on personal or microenvironmental exposure data. However, studies reported above that do have personal exposure data also have limited numbers of subjects or days monitored. In general, some major methodologic issues that remain involve choice of susceptible populations, personal exposure assessment, and timing of measurements to assess the temporality of exposure–dose–response relationships.

Despite the inconsistencies in epidemiologic data, sound postulated mechanisms support the biologic plausibility of many of the findings. Airway inflammation from PM likely involves inhalation of agents leading to the deposition or production in lung tissue of ROSs. The ROSs then induce subsequent oxidant injury and inflammatory responses (Pritchard et al. 1996; Schreck et al. 1991) both in the lungs and systemically. Inhalation of particle-bound airborne transition metals (copper, iron, nickel, vanadium) can lead to the production of ROSs in lung tissue. Residual oil fly ash containing high concentrations of transition metals but low in organic compounds have been shown to induce in vitro increases in IL-6 mRNA in human epithelial cells (Quay et al. 1998). Dogs exposed to CAPs from Boston air showed increased bronchoalveolar lavage macrophages and increased circulating neutrophils in relation to a vanadium/nickel factor, but no associations were shown with total mass (Clarke et al. 2000). This suggests that pollutant composition was important.

Organic constituents of PM are also capable of generating ROS. Nel et al. (2001) have presented evidence that polycyclic aromatic hydrocarbons (PAHs) from diesel exhaust particles (DEPs) and oxidized derivatives of PAHs, such as quinones, lead to the generation of ROSs and subsequent oxidant injury and inflammatory responses, including the production of nuclear transcription factor κB (NF-κB). NF-κB increases the transcription of cytokines and acute phase proteins (Schreck et al. 1991). Evidence has been presented that DEPs induce a broad polycyonal activation of cytokines from an adjuvant-like activity of DEP PAHs (Diaz-Sanchez et al. 1996, 1997; Fujieda et al. 1998; Nel et al. 1998, 2001).
Human pulmonary responses to DEPs include increased neutrophils and B-lymphocytes in lavage fluids, increased expression of endothelial adhesion molecules ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) in bronchial biopsies, and increased neutrophils and platelets in peripheral blood (Salvi et al. 1999). Such DEP-induced effects from oxidative stress mechanisms would be expected to lead to increased systemic hypercoagulability, but no data supporting this in humans are limited.

Epidemiologic evidence in humans that PM exposure increases biomarkers of oxidative stress in blood is limited to one study of 50 healthy young adults in Copenhagen using air samplers carried by subjects (Sorensen et al. 2003). They found a positive association between personal black carbon exposure and 2-aminoacidic semialdehyde in plasma proteins, a protein oxidation product. However, no association with personal PM2.5 mass was found, suggesting that traffic-related causal components may have been better represented by black carbon than by particle mass. A lipid peroxidation product (malondialdehyde), as well as red blood cell counts and hemoglobin concentrations, was positively associated with PM2.5 exposure in women only.

There are also plausible linkages between pulmonary and cardiovascular responses to PM. Airway inflammatory responses have been demonstrated in animals exposed to particulate air pollutants (U.S. EPA 2003). As discussed above, there is growing evidence that airway responses may trigger systemic inflammation and hypercoagulability. In addition, PM can induce neurogenic inflammation in the lungs from activation of capsaicin-sensitive irritant receptors, leading to the release of tachykinins from sensory terminals and then airway inflammation and bronchoconstriction (Veronesi and Oortgiesen 2001). This response could then affect cardiovascular autonomic function (Carr and Undem 2001; Yeates 2000), but it is not yet clear to what extent these mechanisms explain epidemiologic findings of air pollutant associations with cardiac rhythm and BP. There is limited evidence for an effect of tachykinins on cardiac function (Maggi 1996). In addition, the linkage between airway inflammation, cytokine/chemokine release, and autonomic stress response has not been directly demonstrated in humans. There are some in vitro data linking actions of pro-inflammatory cytokines IL-1β and TNF-α to myocardial cell changes in contractility and action potentials (DeMeules et al. 1992; Finkel et al. 1992; Li and Rozanski 1993; Yokoyama et al. 1993) and to induction of arrhythmias (Weisensee et al. 1993).

There are experimental data indirectly supporting a linkage between cellular inflammation in the lungs and cardiovascular responses to air pollutants. An experiment in hyperlipidemic rabbits showed that intrapulmonary instillation of ambient urban PM10 led to an increase in circulating polymorphonuclear neutrophils and caused an increase in the volume fraction of atherosclerotic lesions, which correlated with the number of alveolar macrophages that phagocytosed PM10 in the lung (r = 0.5) (Suwa et al. 2002). Particle-induced airway inflammation and translocation of UFPs and other pollutants into the circulation could lead to an increase in thrombogenic and inflammatory activity in the blood and to a disturbance in cardiovascular function. These extrapulmonary effects are expected to increase the risk of adverse cardiovascular outcomes such as hospitalization.

Other evidence links airway inflammation with cardiovascular effects. Cohort data have shown links of COPD with CHD risk independent of other risk factors (Jousilahti et al. 1999; Wedzicha et al. 2000), suggesting that inflammatory processes may have pro-inflammatory effects on the vascular endothelium. This could occur in individuals with asthma or COPD who have depleted antioxidant defenses from oxidative stress compared with normal subjects, and their defenses are further lowered during disease exacerbations (Rahman et al. 1996). Zanobetti et al. (2000a) have shown that a positive association between hospital admissions for cardiovascular diseases and ambient air pollution was nearly doubled in elderly patients admitted with concurrent respiratory infections. Diabetics appear to be another susceptible group, with stronger associations between cardiovascular hospital admissions and ambient air pollution (Zanobetti and Schwartz 2001).

Several excellent reviews of experimental data examining acute pulmonary and cardiovascular responses to inhaled UFPs and fine particles have proposed pathophysiologic mechanisms (American Thoracic Society 1999; Dhalla et al. 2000; Donaldson et al. 2001; Godleski et al. 2000; MacNee and Donaldson 2000; Nel et al. 2001; Ureil and Frampston 2000; Ureil et al. 2002; van Eeden and Hogg 2002). We have synthesized these and other data into the following proposed sequence of events for UFPs that link pulmonary and cardiovascular end points (Figure 1). Most of these mechanisms likely also apply to larger PM size fractions, particularly soluble components.

![Figure 1: Hypothesized pathways leading to adverse cardiovascular health effects from exposure to UFPs.](image-url)
of PM2.5, and retained nonsoluble particles in the lung that may stimulate the bone marrow to induce similar systemic responses (van Eden and Hogg 2002):

• UFP exposure is followed by high pulmonary deposition (Chalupa et al. 2004; Daigle et al. 2003; International Commission on Radiological Protection 1994). UFPs and associated air toxins translocate to the interstitium and gain entry into the circulation (Nemmar et al. 2002, 2004; Oberdörster et al. 2002).

• Redox-active components of PM lead to the production of ROSs in various cells in the lungs, blood, and vascular tissues.

• This is followed by oxidative stress responses in pulmonary epithelium and pulmonary vascular endothelium and in extrapulmonary vascular endothelium, leading to the production of oxidized phospholipids (especially LDL), lipid peroxidation (e.g., 8-isoprostanoid F₂), reduced antioxidant capacity (e.g., increase in the ratio of oxidized to reduced glutathione), and the production of superoxide anions by endothelial NADPH oxidase, all of which likely contribute to atherogenesis. Genetic polymorphisms in key metabolic enzymes likely play a role in susceptibility.

• Pulmonary and extrapulmonary peripheral vascular oxidative stress results in the activation and mobilization of mononuclear leukocytes and the expression of NF-κB, followed by increases in pro-inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) and endothelial cell activation.

• Emigration of inflammatory cells from blood to tissue sites involves up-regulation of adhesion molecules (VCAM-1, ICAM-1) on vascular endothelium and circulating leukocytes.

• Increased release of cytokines by activated mononuclear cells in the lungs and in the blood leads to initiation of hepatic synthesis of acute phase proteins (e.g., CRP and fibrinogen).

• A hypercoagulable state then occurs with platelet activation, hemostasis, and blood clot formation followed by fibrinolytic activity; this increases the risk of a coronary event. Cytokines may also have direct effects on cardiac function.

• Endothelial cell activation also leads the expression of endothelin-1, which induces vasoconstriction, and increased systolic and diastolic BP, and the expression of extracellular superoxide dismutase (SOD). SOD catalyzes superoxide (O₂⁻) to H₂O₂, which lowers endothelial NO-induced vasodilation. Neuroinflammatory responses involving tachykinins and catecholamines may also affect cardiovascular autonomic tone.

• The systemic inflammatory response also stimulates the bone marrow to release leukocytes and platelets, and polymorphonuclear leukocytes increasingly sequester in pulmonary capillaries to induce more inflammation.

Conclusion
As presented in this review, numerous studies have implicated particulate air pollution as an important contributor to morbidity and mortality from cardiovascular causes. Most of these data have been epidemiologic and have used available air pollution data from governmental monitoring stations. Because such data are collected to meet regulatory standards, they may not meet the needs of researchers trying to understand the causal pollutant components that lead to specific adverse health effects. UFPs and related toxic constituents and precursors are examples of air pollutants that have not been fully investigated, in part due to lack of available data. To date, data from epidemiologic studies indirectly implicate traffic- and other combustion-related pollutants, which include UFPs. Exposure assessment issues for UFPs are complex and need to be considered before undertaking epidemiologic investigations of UFP health effects (Sioutas et al. 2005).

A large body of evidence shows that inflammation and oxidative stress are related to both acute changes in cardiovascular health and chronic processes, including atherosclerosis. It is likely that redox-active components in UFPs from fossil fuel combustion reach target sites in the lungs, vasculature, and heart to induce inflammation and oxidative stress, adding to the burden of known lifestyle risk factors for cardiovascular disease such as diet, tobacco smoke, and stress.


Cardiovascular health and ultrafine particles


