Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution

Epidemiological Evidence of General Pathophysiological Pathways of Disease

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Background—Epidemiologic studies have linked long-term exposure to fine particulate matter air pollution (PM) to broad cause-of-death mortality. Associations with specific cardiopulmonary diseases might be useful in exploring potential mechanistic pathways linking exposure and mortality.

Methods and Results—General pathophysiological pathways linking long-term PM exposure with mortality and expected patterns of PM mortality with specific causes of death were proposed a priori. Vital status, risk factor, and cause-of-death data, collected by the American Cancer Society as part of the Cancer Prevention II study, were linked with air pollution data from United States metropolitan areas. Cox Proportional Hazard regression models were used to estimate PM-mortality associations with specific causes of death. Long-term PM exposures were most strongly associated with mortality attributable to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest. For these cardiovascular causes of death, a 10-μg/m^3 elevation in fine PM was associated with 8% to 18% increases in mortality risk, with comparable or larger risks being observed for smokers relative to nonsmokers. Mortality attributable to respiratory disease had relatively weak associations.

Conclusions—Fine particulate air pollution is a risk factor for cause-specific cardiovascular disease mortality via mechanisms that likely include pulmonary and systemic inflammation, accelerated atherosclerosis, and altered cardiac autonomic function. Although smoking is a much larger risk factor for cardiovascular disease mortality, exposure to fine PM imposes additional effects that seem to be at least additive to if not synergistic with smoking. (***Circulation***. 2004; 109:71-77.)

Key Words: mortality ■ pulmonary heart disease ■ cardiovascular diseases ■ smoking

Substantial epidemiological evidence suggests that fine particulate matter air pollution (PM) has adverse human health effects.[1] Although many studies have focused on respiratory health end points, there is growing evidence that PM is a risk factor for cardiovascular disease.[2] This evidence comes from studies that have observed increases in cardiovascular disease deaths during and immediately after pollution episodes, associations between daily changes in PM and cardiovascular deaths and hospitalizations, and increased risk of adult cardiopulmonary disease mortality associated with spatial differences in ambient PM concentrations.[3,4] Although epidemiologic observations provide compelling evidence of a link between PM and cardiopulmonary morbidity and mortality, our understanding of the underlying biological mechanisms remains limited.[5]

Previous analyses of mortality effects of long-term PM exposure[3,4] used broad cause-of-death classifications because of concerns about the use of death certificates to identify causes of death and because of potential cross-coding between pulmonary and cardiovascular deaths. These analyses linked PM exposure with cardiopulmonary mortality but provided no information about associations with specific diseases that might be helpful in understanding general pathophysiological pathways. In the present study, we use data from the largest presently available prospective cohort study of mortality collected by the American Cancer Society (ACS) linked with air pollution data for metropolitan areas throughout the United States. Statistical analysis focuses on evaluating patterns of associations with specific causes of

TABLE 1. Expected Patterns of PM Mortality Associations for Specific Causes of Cardiopulmonary Deaths Based on 3 Hypothesized General Pathophysiological Pathways

Cause of Death	Accelerated Progression of COPD	Inflammation/Accelerated Atherosclerosis	Altered Cardiac Autonomic Function
All cardiovascular diseases plus diabetes	...	↑	↑
Ischemic heart disease	...	↑ ↑ ↑	↑
Dysrhythmias, heart failure, cardiac arrest	...	↑ ↑	↑ ↑
Hypertensive disease	...	↑	↑
Other atherosclerosis, aortic aneurysms	...	↑ ↑	...
Cerebrovascular disease	...	↑ ↑	...
Diabetes	...	↑ ↑	...
All other cardiovascular diseases	...	↑	...
Diseases of the respiratory system	↑ ↑	...	...
COPD and allied conditions	↑ ↑ ↑	...	...
Pneumonia and influenza	...	...	...
All other respiratory disease	...	...	...

death that may provide guidance toward understanding general pathophysiological pathways linking PM with mortality.

Epidemiologic studies are not inherently designed to study biological mechanisms, yet they can be used to evaluate consistency between epidemiologic health end points and what is known about potential mechanistic pathways of disease. The plan of this study is to establish a priori expected patterns of PM mortality with specific causes of death based on hypothesized general pathophysiological pathways linking long-term PM exposure with cardiopulmonary mortality. The ACS cohort is used to empirically estimate these PM mortality associations with specific causes of death and evaluate the observed patterns of PM mortality in relationship to the a priori patterns. Because the database includes information on smoking history, we additionally evaluate mechanistic hypotheses of the relationship of smoking and air pollution effects.

Methods

Hypothesized Pathophysiological Pathways

Before statistical fitting, expected patterns of PM mortality associations for specific causes of cardiopulmonary deaths were determined based on 3 hypothesized general pathophysiological pathways. These a priori patterns are explicitly provided in Table 1, and expected associations with PM are indicated by arrows. The first hypothesized pathway suggests that PM exposure results in accelerated progression of chronic obstructive pulmonary disease (COPD).[6] For this pathway, positive associations with respiratory disease deaths generally, but deaths from COPD and allied conditions more specifically, were expected. The second hypothesized pathway involves pulmonary and systemic inflammation and accelerated atherosclerosis. Inhaling PM may provoke a low-grade pulmonary inflammatory response, release of potentially harmful cytokines, changes in blood coagulability, and triggering of other related physiological responses, including increased risk of acute cardiovascular events and the potential for accelerated development of atherosclerosis and cardiovascular disease.[7,8] For the inflammation/accelerated atherosclerosis hypothesis, we expected PM associations with diseases of the cardiovascular system plus diabetes, which are associated with atherosclerosis or its complications but most specifically with ischemic heart disease. The third hypothesized pathway involves altered cardiac autonomic function. Studies have observed

that changes in cardiac autonomic function as measured by heart rate variability (HRV) are independent predictors of cardiovascular disease and mortality.[9] Recent epidemiological studies have observed associations between autonomic nervous system–related physiological measures and air pollution.[10–12] For this hypothesis, we expected the strongest associations to be with cardiac dysrhythmias and cardiac arrest.

Study Population

The empirical analysis is based on data collected by the ACS as part of the Cancer Prevention Study II (CPS-II), an ongoing prospective mortality study of ≈1.2 million adults.[4] Participants resided in all 50 states, the District of Columbia, and Puerto Rico and were enrolled by ACS volunteers in the fall of 1982. Enrollment was restricted to persons aged 30 years or older who were members of households with at least 1 individual aged 45 years or older. Participants completed a confidential questionnaire, which included questions about age, sex, weight, height, smoking history, alcohol use, occupational exposures, diet, education, marital status, and other characteristics.

Vital status of study participants was ascertained by ACS volunteers in September of 1984, 1986, and 1988. Reported deaths were verified with death certificates. Subsequently, through December 31, 1998, vital status was ascertained through linkage of the CPS-II study population with the National Death Index.[13] Ascertainment of deaths was >98% complete for the period of 1982 to 1988 and ≈93% complete after 1988. Death certificates or codes for cause of death were obtained for >98% of known deaths. Our analysis was restricted to those participates who resided in United States metropolitan areas with available pollution data. The actual size of the analytic cohort ranged from ≈319 000 to 500 000, depending on the specific pollution index (Table 2).

Pollution Exposure Estimates

Each participant was assigned a metropolitan area of residence based on his or her 3-digit ZIP code at time of enrollment. The specific

TABLE 2. Summary of Indexes of Fine Particulate Pollution Measures and Size of Analytic Cohorts

Fine Particulate Index	Mean (SD), $\mu g/m^3$	No. of Metropolitan Areas	No. of Participants in Thousands
$PM_{2.5}$ (1979–1983)	21.1 (4.6)	61	359
$PM_{2.5}$ (1999–2000)	14.0 (3.0)	116	500
$PM_{2.5}$ (average)	17.1 (3.7)	51	319

TABLE 3.   Specific Cause-of-Death Categories, ACS-CPS-II and ICD-9 codes, and Percent of Total Deaths for each Cause of Death

Cause-of-Death Groupings	ACS-CPS Codes	ICD-9 Codes	% of Deaths	Comments*
All cardiovascular diseases plus diabetes	01–10, 12, 0A, 0B	390–459, 250	45.1	...
Ischemic heart disease (acute myocardial infarction, coronary atherosclerosis, other chronic ischemic heart disease)	1	410–414	23.7	47% acute MI, 27% coronary atherosclerosis, 21% unspecified chronic ischemia
Dysrhythmias, heart failure, cardiac arrest (plus cardiomyopathy, unspecified with arteriosclerosis, and related)	5	420–429	8.2	33% unspecified, 20% heart failure, 14% cardiomyopathy, 13% cardiac arrest
Hypertensive disease	3	401–405	1.4	63% unspecified
Other atherosclerosis and aortic aneurysms	07, 08, 0B	440–441	1.7	36% generalized and unspecified atherosclerosis, 62% aortic aneurysms
Cerebrovascular disease	6	430–438	6.8	55% acute but ill-defined
Diabetes	12	250	1.9	...
All other cardiovascular diseases	02, 04, 09, 10, 0A	390–459, excluding those specified	1.4	30% pulmonary embolism and infarction, 20% rheumatic fever, 13% unspecified peripheral vascular disease
Diseases of the respiratory system	13–18	460–519	8.2	...
COPD and allied conditions	14–17	490–496	4.1	71% chronic airway obstruction not elsewhere classified, 20% emphysema
Pneumonia and influenza	13	480–487	2.8	87% pneumonia, organism unspecified
All other respiratory diseases	18	460–519, excluding those specified	1.3	...

*Based on 7 to 16 years of follow-up with available unconsolidated 4-digit ICD-9 coding.

measure of PM pollution used in this analysis was $PM_{2.5}$ (particles measuring <2.5 μm in diameter). Three constructed indexes for $PM_{2.5}$ were used in the analysis (Table 2). The first, $PM_{2.5}$ (1979 to 1983), was compiled by the Heath Effects Institute reanalysis team[14] using data from the Inhalable Particle Monitoring Network for 1979 to 1983. Widespread sampling of $PM_{2.5}$ was not available in the United States after 1983 and until after 1997, when the Environmental Protection Agency adopted ambient air quality standards for $PM_{2.5}$. As a consequence of the $PM_{2.5}$ standard, numerous sites began collecting $PM_{2.5}$ data in 1999. The second index, $PM_{2.5}$ (1999 to 2000), used $PM_{2.5}$ data that were extracted from the Environmental Protection Agency Aerometric Information Retrieval System database for 1999 and the first 3 quarters of 2000. For each site, quarterly averages for each of the 2 years were computed. The 4 quarters were averaged when at least 1 of the 2 corresponding quarters for each year had at least 50% of the sixth-day samples and at least 45 total sampling days available. Measurements were averaged first by site and then by metropolitan area. The integrated average of $PM_{2.5}$ concentrations was estimated by averaging concentrations for the early and later periods, providing the third index, $PM_{2.5}$ (average).

Cause-of-Death Coding and Categorization

Throughout the 16-year follow-up, 22.5% of the cohort participants died. For the first 6 years of follow-up, cause of death was coded using a 2-digit ACS-CPS code that was a consolidation of International Classification of Diseases, Ninth Revision (ICD-9) codes. For the remainder of the follow-up, ICD-9 codes were used. Specific cause-of-death categories with their corresponding ACS-CPS and ICD-9 codes are presented in Table 3. Based on unconsolidated ICD-9 codes available during the last 7 to 16 years of follow-up, it was clear that the specificity of information provided on the death certificates as interpreted by the nosologist was limited. Most deaths were coded for a relatively small number of specific causes of deaths, and a large percentage of the deaths were coded for relatively unspecific causes. An independent audit using a sample of 240 death

certificates and an independent nosologist found 93.7% agreement in cause-of-death coding.[14]

Statistical Analysis

Adjusted mortality relative risk ratios were estimated using the Cox proportional hazards regression model.[15] This approach has been used in previous studies of pollution-related mortality,[3,4] including analyses that extended the model by incorporating spatial random effects and nonparametric spatial smooth components.[4,14] Because pollution-related risk estimates were largely unaffected by these extended models, this analysis used the standard Cox proportional hazard model.

The models controlled for available individual co-risk factors, as reported elsewhere.[4] To control for age, sex, and race, the models were stratified by 1-year age categories, sex, and race (white versus other), allowing each category to have its own baseline hazard. In addition, individual level covariates were included in the models to adjust for smoking, education, marital status, body mass index (BMI), alcohol consumption, occupational exposures, and diet. Both indicator and continuous variables were used to control for tobacco smoking. Smoking indicator variables included current cigarette smoker, former cigarette smoker, and pipe or cigar smoker only, along with indicator variables for starting smoking before or after age 18 years. Continuous smoking variables included linear and squared terms for current smoker's years of smoking, current smoker's cigarettes per day, former smoker's years of smoking, and former smoker's cigarettes per day, plus number of hours per day exposed to passive cigarette smoke. Variables indicating completion of high school or education beyond high school and marital status were included. BMI and BMI squared were included as continuous variables. Indicator variables for beer, liquor, and wine drinkers and nonresponders versus nondrinkers were included to adjust for alcohol consumption. Variables indicating occupational exposure included exposure to asbestos, chemicals/acids/solvent, coal or stone dusts, coal tar/pitch/asphalt, diesel engine exhaust, or formaldehyde and additional indicator vari-
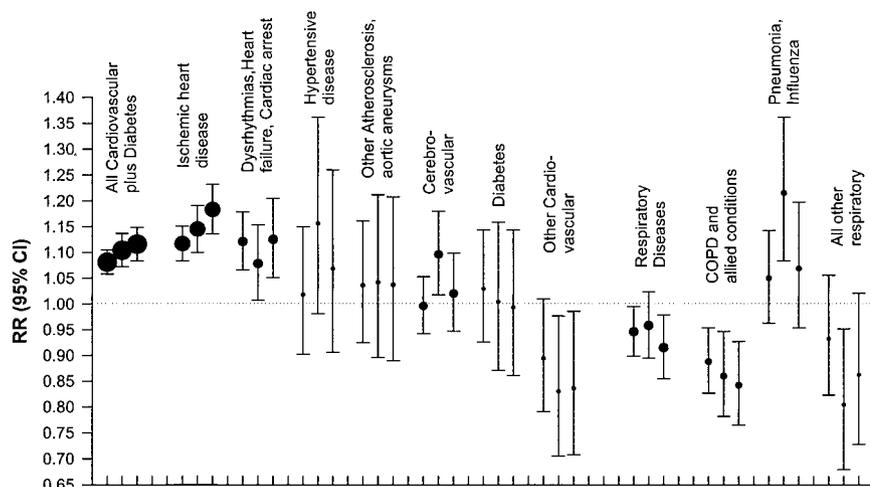
Adjusted relative risk ratios and 95% CIs for cardiovascular and respiratory mortality associated with a 10-μg/m^3 change in PM$_{2.5}$ for 1979 to 1983, 1999 to 2000, and average, respectively. Size of the dots corresponds to the relative number of deaths.

ables that indicated 9 rankings of an occupational dirtiness index described elsewhere.[14] Two diet indices that accounted for fat consumption and consumption of vegetables, citrus, and high-fiber grains were derived based on information given in the enrollment questionnaire.[16] Quintile indicator variables for each of these diet indices were also included in the models.

Models were estimated for each cause-of-death category listed in Table 3 using each of the PM indexes listed in Table 2. Models were also estimated in stratified analysis of smokers, former smokers, and never smokers. Pollution mortality effects were estimated while controlling for all of the smoking variables. However, to obtain simple risk estimates for cigarette smoking that are easily comparable to the risk estimates for pollution, models were also estimated, including only indicator variables for former smoker and current smoker.

Results

More than half of all deaths were attributable to cardiopulmonary disease generally—≈45% cardiovascular disease and 8% respiratory disease (Table 3). The largest specific cause of death was ischemic heart disease, accounting for almost one quarter of all deaths. Even with limited specificity regarding cause-of-death categories, substantial differences in response to PM were observed. The Figure illustrates adjusted relative risk ratios (RRs) and 95% confidence intervals (CIs) for the various cause-of-death categories associated with a 10 μg/m^3

difference in PM$_{2.5}$. Similar RRs were estimated for each of the 3 indexes of PM. The relative sizes of the dots are proportional to the relative number of deaths for each cause. Numerical RRs and CIs (for only PM$_{2.5}$ average) are provided in Table 4. Table 5 presents the numerical RRs and CIs for PM$_{2.5}$ stratified by smoking status.

Statistically robust associations between PM$_{2.5}$ and overall cardiovascular disease mortality were observed. Predominant PM mortality associations were with ischemic heart disease, but statistically significant associations were also observed with the combined category of dysrhythmias, heart failure, and cardiac arrest. Statistically significant, positive associations were not consistently observed for other cardiovascular causes of death or for respiratory disease deaths. In fact, COPD and related deaths were negatively associated with fine particulate air pollution exposure.

As also presented in Table 4, cigarette smoking was associated with far larger excess risks for both cardiovascular and respiratory disease mortality than air pollution. However, regardless of smoking status, statistically robust associations between PM$_{2.5}$ and overall cardiovascular disease mortality were observed with the predominant PM mortality associa-

TABLE 4.   Adjusted RRs and 95% CIs for a 10 μg/m^3 Increase in PM$_{2.5}$ (Average) and for Former and Current Smoker (vs Never Smoker) for Various Cause-of-Death Categories

Cause of Death	PM$_{2.5}$	Former Smoker	Current Smoker
All cardiovascular diseases plus diabetes	1.12 (1.08–1.15)	1.26 (1.23–1.28)	1.94 (1.90–1.99)
Ischemic heart disease	1.18 (1.14–1.23)	1.33 (1.29–1.37)	2.03 (1.96–2.10)
Dysrhythmias, heart failure, cardiac arrest	1.13 (1.05–1.21)	1.18 (1.12–1.24)	1.72 (1.62–1.83)
Hypertensive disease	1.07 (0.90–1.26)	1.21 (1.07–1.37)	2.13 (1.86–2.44)
Other atherosclerosis and aortic aneurysms	1.04 (0.89–1.21)	1.63 (1.45–1.84)	4.21 (3.71–4.78)
Cerebrovascular disease	1.02 (0.95–1.10)	1.12 (1.06–1.18)	1.78 (1.67–1.89)
Diabetes	0.99 (0.86–1.14)	1.05 (0.94–1.16)	1.35 (1.20–1.53)
All other cardiovascular diseases	0.84 (0.71–0.99)	1.22 (1.09–1.38)	1.78 (1.56–2.04)
Diseases of the respiratory system	0.92 (0.86–0.98)	2.16 (2.04–2.28)	3.88 (3.66–4.11)
COPD and allied conditions	0.84 (0.77–0.93)	4.93 (4.48–5.42)	9.85 (8.95–10.84)
Pneumonia and influenza	1.07 (0.95–1.20)	1.23 (1.13–1.34)	1.89 (1.70–2.09)
All other respiratory diseases	0.86 (0.73–1.02)	1.54 (1.36–1.74)	1.83 (1.57–2.12)

TABLE 5.   Adjusted RRs and 95% CIs Stratified by Smoking Status for a 10 μg/m^3 Increase in PM$_{2.5}$ (Average)

Cause of Death	Never Smokers	Former Smokers	Current Smokers
All cardiovascular diseases plus diabetes	1.11 (1.07–1.16)	1.09 (1.04–1.15)	1.16 (1.09–1.23)
Ischemic heart disease	1.22 (1.14–1.29)	1.15 (1.07–1.23)	1.16 (1.07–1.27)
Dysrhythmias, heart failure, cardiac arrest	1.04 (0.95–1.15)	1.14 (1.00–1.29)	1.31 (1.12–1.52)
Hypertensive disease	0.88 (0.69–1.12)	1.05 (0.76–1.44)	1.57 (1.12–2.19)
Other atherosclerosis and aortic aneurysms	1.18 (0.90–1.55)	0.91 (0.70–1.19)	1.08 (0.84–1.40)
Cerebrovascular disease	1.03 (0.93–1.15)	1.01 (0.88–1.17)	1.01 (0.86–1.20)
Diabetes	1.01 (0.83–1.23)	0.86 (0.66–1.12)	1.26 (0.91–1.74)
All other cardiovascular diseases	0.86 (0.67–1.09)	0.83 (0.61–1.13)	0.83 (0.59–1.15)
Diseases of the respiratory systems	1.03 (0.91–1.17)	0.89 (0.80–1.00)	0.85 (0.76–0.96)
COPD and allied conditions	0.96 (0.73–1.24)	0.86 (0.73–1.00)	0.81 (0.70–0.93)
Pneumonia and influenza	1.20 (1.02–1.41)	0.98 (0.80–1.20)	0.90 (0.69–1.18)
All other respiratory diseases	0.74 (0.56–0.97)	0.88 (0.68–1.16)	1.10 (0.76–1.60)

tions with ischemic heart disease (Table 5). One notable difference across smoking status was that, for never smokers, the PM mortality association with pneumonia and influenza was positive, statistically significant, and had RRs similar to those for ischemic heart disease.

Discussion

These results provide intriguing, but inconclusive, insights into general pathophysiological pathways that may link exposure to fine particulate air pollution and cardiovascular disease mortality. Although previous studies have observed that elevated exposures to PM are associated with measures of lung function[17] and prevalence of symptoms of obstructive airway disease,[18] the pattern of PM mortality associations in this analysis does not fit the a priori pattern presented for the accelerated progression of COPD hypotheses. Unfortunately, the reliance on cause-of-death coding from death certificates presents important limitations and the potential for estimation bias for specific causes of death. For example, COPD patients are predisposed to die of pneumonia. Inhalation of fine inert PM can cause bronchospasm even in healthy subjects[19] and could additionally reduce ventilatory reserve in patients with COPD, making death from pneumonia even more likely. COPD patients are also more likely to die from cardiovascular disease.[20] If PM exposure accelerates progression of COPD, but those most susceptible to PM are prematurely removed by pneumonia or cardiovascular disease death, the estimated PM effect on remaining COPD deaths may be misleading. Furthermore, the influence of medication use, especially antiinflammatory agents by COPD patients, on the physiological response to PM is unknown.

Given the robust PM association with ischemic heart disease, the empirical pattern of PM mortality associations is more consistent with the inflammation/accelerated atherosclerosis hypothesis. The proposition that PM-induced low-grade inflammation may increase the risk of adverse coronary events is supported by observations that PM exposure is associated with (1) elevated levels of C-reactive protein,[21] a marker of systemic inflammation that may be an important

and independent predictor of cardiovascular disease[22]; (2) inflammatory lung injury[23,24]; (3) bone marrow and blood cell responses[25]; (4) enhanced human alveolar macrophage production of proinflammatory cytokines[26]; (5) elevated blood plasma viscosity[27]; (6) endothelial dysfunction and brachial artery vasoconstriction[28]; and (7) triggering of myocardial infarction.[29] PM-induced inflammatory responses have also been observed in studies using animal models.[30] In a study of rabbits susceptible to atherosclerosis, repeated PM exposure induced progression of atherosclerotic lesions.[8] Low-level PM exposure from secondhand tobacco smoke has also been shown to promote inflammatory response and atherosclerosis, even at exposure to secondhand smoke of just 1 cigarette per day,[31] raising the possibility that PM and cigarette smoke may invoke similar pathophysiological mechanisms.

The association between PM and death attributable to dysrhythmias, heart failure, and cardiac arrest also supports the altered cardiac autonomic function hypotheses. Previous studies have observed that elevated PM exposure is associated with changes in autonomic function, as indicated by changes in HRV.[10–12] The proposition that exposure to PM is associated with changes in cardiac autonomic function is additionally bolstered by (1) observed changes in HRV after occupational PM exposure[32]; (2) HRV declines after just 2 hours of elevated PM from secondhand cigarette smoke in an airport smoking lounge[33]; (3) increases in systolic blood pressure during elevated exposure to PM and other pollutants[34]; and (4) animal studies that observed PM exposure-related changes in cardiac rhythm or function.[35] In addition, cardiac patients with implanted cardioverter defibrillators had higher rates of discharges, indicating potentially life-threatening arrhythmias, associated with air pollution.[36]

The likelihood of multiple mechanistic pathways with complex interdependencies must be considered when interpreting these results. For example, the role of the vasculature in response to PM has also received increased attention. Recent findings include (1) increased vasoconstriction in the pulmonary vessels of PM-exposed rats[37]; (2) enhanced acute

vasoconstriction in healthy adults as measured by brachial artery diameter with concomitant inhalation of PM and ozone[28]; (3) marked endothelial cell activation by ultrastructural criteria in small coronary vessels in stray dogs from Mexico City compared with those from 3 less polluted cities[38]; (4) increased circulating levels of the vasoactive peptide endothelin in rats exposed to urban particles,[39] indicating that vasoconstriction may be mediated by humoral factors; and (5) enhanced cardiac ischemia in PM-exposed dogs.[40] Taken together, these findings support the notion that particulate pollution may be associated with changes resulting from vasoconstriction.

If there are systemic toxic endothelial responses to ambient particles, this should be reflected with cardiac and systemic vascular responses. The fit for inflammation/accelerated atherosclerosis was expected to be best for ischemic heart disease, and it was. However, it was only marginally better for ischemic heart disease compared with the dysrhythmias group or the category of all cardiovascular diseases plus diabetes. The a priori predictions in relationship to all other cardiovascular groups were not correct. Because these other diagnosis groups were not strongly associated with ambient particle mortality, it is less likely that systemic toxic endothelial responses are the basis for the underlying mechanism, but it does not rule out a cardiac-specific endothelial response.

The autonomic nervous system also influences determinants of ischemic heart disease. Changes in sympathetic and parasympathetic nervous system activity have effects on vascular tone. For example, whereas increased parasympathetic activity normally leads to coronary vasodilation, in the presence of coronary artery disease, parasympathetic stimulation may lead to net coronary constriction.[41] PM effects on autonomic nervous system function have been documented in the elderly[10–12] and in animals experimentally.[35] The distinction between ischemia arising from atherosclerotic/inflammatory mechanisms and ischemia attributable to coronary vasoconstriction driven by particulate-induced changes in autonomic function in the presence of endothelial damage, therefore, cannot be distinguished easily.

In acute studies, the time course of response provides information on the biologic mechanism. Increased risk of myocardial infarction,[29] reduced HRV,[33] and vasoconstriction all within 2 hours of exposure[28] support the importance of acutely reacting mechanisms, as might be associated with the sympathetic nervous system. In animals, enhanced ST-segment elevation on the day of a 6-hour concentrated PM exposure[40] is indicative of a short latency response (such as neural/sympathetic). Inflammatory mechanisms that take 24 hours or longer to develop are also supported.[29,40] In both human and experimental animal studies, there is evidence for both acute and protracted mechanisms in response to ambient particles, so that defining dominance between the inflammation/accelerated atherosclerosis and the altered cardiac autonomic function mechanisms may be difficult in the chronic exposure study reported here.

Smoking was associated with substantially greater elevated risks for all of the causes of death (Table 4). Nevertheless, cardiovascular disease, especially ischemic heart disease, fatal dysrhythmias, heart failure, and cardiac arrest, was associated with $PM_{2.5}$ even after controlling for smoking. Significant positive associations between $PM_{2.5}$ and pneumonia/influenza deaths were only observed for never smokers. The interpretations of the effect of $PM_{2.5}$ using stratification by smoking status are intriguing and may be assessed in relationship to specific mechanisms of response. For example, similar RRs of the pollution effect for all cardiovascular diseases plus diabetes and ischemic heart disease were estimated for current smokers and for never smokers (Table 5). For the dysrhythmias, heart failure, and cardiac arrest group and hypertensive disease, there were larger RRs from air pollution for smokers compared with never smokers. The substantial excess risk associated with smoking and similar or even larger RRs from air pollution for smokers compared with never smokers implies that the absolute risks of air pollution are larger for smokers than for nonsmokers. Mechanisms by which cigarette smoke and air particulate exposure operate for these cardiovascular causes of death may be complementary and seem to be at least additive if not synergistic.

Cigarette smoking was a large and important risk factor for respiratory disease mortality. Air pollution was not. Only pneumonia and influenza deaths in never smokers were associated with PM. In contrast, numerous daily time-series mortality studies[1] have observed that daily mortality counts for both cardiovascular and respiratory disease are associated with day-to-day changes in PM. These results suggest that smoking contributes to the progression of both cardiovascular and respiratory disease. Whereas long-term exposure to PM pollution may contribute to the long-term progression of cardiovascular disease, for respiratory disease, air pollution's primary role is the exacerbation of existing disease.

In conclusion, this analysis provides evidence that long-term exposure to fine particulate air pollution is an important risk factor for cause-specific cardiovascular disease mortality. Although it is challenging to make empirical observations relating to potential mechanistic pathways of disease from epidemiologic studies, the results of this analysis are largely consistent with the proposition that the general pathophysiological pathways that link long-term PM exposure and cardiopulmonary mortality risk include pulmonary and systemic inflammation, accelerated atherosclerosis, and altered cardiac autonomic function.

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