Identification of Persons with Cardiorespiratory Conditions Who Are at Risk of Dying from the Acute Effects of Ambient Air Particles

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This study was undertaken to identify subgroups of the population susceptible to the effects of ambient air particles. Fixed-site air pollution monitors in Montreal, Quebec, Canada, provided daily mean levels of various measures of particulates and gaseous pollutants. Total sulfates were also measured daily (1986–1993) at a monitoring station 150 km southeast of the city (Sutton, Quebec, Canada). We used coefficient of haze (COH), extinction coefficient, and Sutton sulfates to predict fine particles and sulfates from a fine particles model for days that were missing. We used the universal Quebec medicare system to obtain billings and prescriptions for each Montreal resident who died in the city from 1984 to 1993. These data were then used to define cardiovascular and respiratory conditions that subjects had before death. Using standard Poisson regression time-series analyses, we estimated the association between daily nonaccidental mortality and daily concentrations of particles in the ambient air among persons with cardiovascular and respiratory conditions diagnosed before death. We found no persuasive evidence that daily mortality increased when ambient air particles were elevated for subgroups of persons with chronic upper respiratory diseases, airways disease, cerebrovascular diseases, acute coronary artery disease, and hypertension. However, we found that daily mortality increased linearly as concentrations of particles increased for persons who had acute lower respiratory diseases, chronic coronary artery diseases (especially in the elderly), and congestive heart failure. For this latter set of conditions, the mean percent increase in daily mortality (MPC) for an increase in the COH across its interquartile range (18.5 COH units per 327.8 linear meters), averaged over the day of death and the 2 preceding days, was MPC = 5.09% [95% confidence interval (CI) 2.47–7.79%], MPC = 2.62 (95% CI 0.53–4.75%), and MPC = 4.99 (95% CI 2.44–7.60%), respectively. Adjustments for gaseous pollutants generally attenuated these associations, although the general pattern of increased daily mortality remained. In addition, there appeared to be a stronger association in the summer season. The positive associations found for persons who had acute lower respiratory diseases and congestive heart failure are consistent with some prevailing hypotheses and may also be consistent with recent toxicologic data implicating endothelins. Further epidemiologic studies are required to confirm these findings. *Key words*: ambient air pollution, coefficient of haze, epidemiology, mortality, particulates, PM_{10}, $PM_{2.5}$, sulfates, time-series, total suspended particles. — *Environ Health Perspect* 109(suppl 4):487–494 (2001).
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Recent epidemiologic studies have shown that concentrations of ambient air particles are associated with a wide range of effects on human health, especially on the cardiorespiratory system (*1–5*). Some of the most persuasive data derive from epidemiologic time-series studies of acute effects that include *inter alia* investigations of daily increases in hospital and emergency room admissions (*6–17*) and increased daily mortality (*4,18–45*).

In addition to these studies of the short-term effects of air pollution, three large cohort studies that followed thousands of subjects prospectively have been published (*46–51*). The Six Cities Study (*50*) and the American Cancer Society's Cancer Prevention Study II (*51*) were used to estimate long-term associations between air pollution and survival and have reported increases in annual average total mortality associated with fine particles. The Seventh Day Adventist Health Study (*46–49*) showed increases in respiratory diseases associated with exposure to total suspended particles (TSP) and particulate matter having an aerodynamic diameter of 10 µm or less (PM_{10}), although no associations with mortality have been found (*49*).

The health effects associated with short-term increases in particulate pollution is relatively small (*1*). Should air pollution affect all individuals, this low risk would translate into a serious public health problem. There is some consensus that only persons in poor health should experience severe and acute effects (e.g., hospitalization, death) when levels of air pollution increase (*2,5,52,53*). Thus, the identification of susceptible subgroups is critically important for scientific and public health purposes, as it may provide information regarding mechanisms and may target certain subgroups to reduce exposure during episodes of high levels of air pollution. The present mortality time-series study addresses this issue by investigating whether individuals with specific respiratory and cardiovascular conditions diagnosed before death had a higher mortality when daily levels of particulate air pollution were increased.

Materials and Methods

The Study Population and Healthcare Utilization Databases

We have described previously the methodology used in this study as well as reported

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associations between cause-specific mortality and particles (*54–56*). In brief, the study population comprised all residents of Montreal, Quebec, Canada, who died in the metropolitan area from 1984 to 1993 and who were registered with the universal Quebec Health Insurance Plan (QHIP). Subjects were first identified from the information provided by the computerized provincial database of death certificates, then each deceased subject was linked to the population register of the QHIP. Ethics approval was obtained from the Institutional Review Board of McGill University and from the Commission de l'Accès à l'Information du Québec.

The Quebec Health Insurance Plan. This record linkage provided detailed information regarding medical services rendered by physicians both in and out of hospital and reimbursed by the QHIP. The QHIP provides universal coverage for all costs of medical services dispensed in-province and provides complete or partial coverage for services and hospital admissions out-of-province. Individuals are given unique health insurance plan numbers that are recorded on each medical transaction and used administratively to check the validity of claims. Physicians in-province are paid by the QHIP on a fee-for-service basis, and out-of-province healthcare is paid by the patient and reimbursed partially or in full by the QHIP. This leads to almost complete reporting to the QHIP. Laboratory tests and results from these tests are not part of the database. When submitting each bill for service, the physician has the option to record one diagnostic code using the *International Classifications of Diseases, 9th Revision, Clinical Modifications* (*ICD-9-CM*) (*57*). Unlike the actual billing data, which are examined by the QHIP for consistency and accuracy, diagnoses are not verified. Most physicians use a restricted set of *ICD-9-CM* codes reflecting the mix of patients who consult them. In addition, the QHIP pays the costs of prescriptions for persons 65 years of age and older. The information on dispensed prescriptions includes date, name and generic type of medication, quantity, duration of prescription, and authorization for refills.

Ambient air pollution and weather data. During the study period, measurements of particulate air pollution TSP, particles having aerodynamic diameters of 10 and 2.5 μm or less [(PM_{10}, $PM_{2.5}$), and sulfates from these metrics] were measured every 6 days at several fixed-site monitoring stations in Montreal (*54–56,58,59*). From July 1992 to September 1995, the measurement schedule for PM_{10} and $PM_{2.5}$ was increased to daily sampling at one site (*58*). Coefficient of haze (COH), which measures organic and inorganic carbon, and gaseous pollutants were measured every 2 hr. For the purposes of this study we computed station-specific daily means from these data and then averaged these across all stations. We also used measurements of daily total sulfates (1986–1993) from an acid rain monitoring station at Sutton, Quebec, a rural community about 150 km southeast of the city (*54*). These data represent regional levels throughout southwest Quebec, including Montreal (*58*). The average correlation between sulfates measured at this station and the two Montreal stations was 0.9.

We also developed statistical models for the period from 1986 to 1993 to estimate fine particle mass and fine sulfate particles when measurements were not taken, using the predictor variables COH, the extinction coefficient, and total sulfates from Sutton. The R^2 for the prediction model for $PM_{2.5}$ was 0.72 and for sulfates from $PM_{2.5}$ it was 0.80.

Visibility, barometric pressure, temperature, total precipitation (distinguishing snow from rain), relative humidity, and dew point temperature were measured at Dorval International Airport in Montreal. Visibility at noon, or at other times of the day when there was no precipitation, was converted into an extinction coefficient (a measure of light scattering and absorption) after accounting for relative humidity (*25,54,55,60,61*).

Indicators of Disease Status

To define health conditions before death, we used information from diagnoses recorded on billing records, specific health services rendered, and filled prescriptions for drugs that are reimbursed by the QHIP. We had on hand data for a period of up to 5 years before each death but wished to use information as close to death as possible. We therefore needed to select suitable time periods that accounted for the typical course of each disease and the manner in which data were recorded on the billing and prescription databases. Most chronic diseases are not curable and persist for months or years after initial detection, although treatment can modify their natural history and relieve symptoms, suggesting that relatively long time periods could be used. On the other hand, acute diseases such as pneumonia can resolve in a very short time. In addition the average duration of a prescription in the province of Quebec is about 1 month, so using an interval of less than 1 month to define disease status would lead to a loss of important information. Also, diagnoses were recorded on only about half of the billing records. Because of the complex method by which diagnoses were recorded and drugs were prescribed, as well as the intricate patterns in the utilization of healthcare services, we felt that a 2-month interval was the minimum for which we could develop reasonably reliable indicators of illness. In the end we used data during a period of 2 months to define acute conditions and a period of 1 year before death to define chronic conditions.

Respiratory diseases. Table 1 shows the definitions for chronic upper respiratory diseases, acute upper respiratory diseases, acute lower respiratory diseases, and airways disease. In defining airways disease we assumed that the data from the QHIP were not sufficiently specific to discriminate between asthma, chronic bronchitis, and emphysema. In addition, because clinicians did not follow well-defined standards in prescribing drugs, we did not discriminate by severity using dose or quantity of drugs filled.

Table 1. Definition of the indicators of respiratory disease status.

Age (years)	Diagnoses (*ICD-9-CM* codes[a]) in specified time interval	Prescriptions in specified time interval	Services/tests/procedures in the specified time interval
Airways disease			
< 65 and ≥ 65	AD[a] by a respirologist or AD by a general practitioner or	None None	None ≥ 2 pulmonary function tests
≥ 65	None	Any prescription for bronchodilators (beta agonists, etc.), inhaled corticosteroids, systemic corticosteroids, anticholinergics, sodium chromoglycate (chromolyn), theophylline	
Chronic upper respiratory			
< 65 and ≥ 65	472–478, 102.3	None	None
Acute upper respiratory			
< 65 and ≥ 65	460–465	None	None
Acute lower respiratory			
< 65 and ≥ 65	466, 480–487, 512, 513, 517.1, 518.0, 518.4, 518.5, 519.0	None	None

AD, airways disease.
[a]The following *ICD-9-CM* codes are used to represent AD: 490–496; 500–508; 518.1–518.3, 518.8; 519.1–519.3, 519.8, 519.9 (*57*).

Cardiovascular diseases. Table 2 shows the following indices of cardiovascular disease status: hypertension, congestive heart failure, acute coronary artery disease, chronic coronary artery diseases, cerebrovascular diseases, and chronic rheumatic heart diseases. A specific index was developed to capture coronary bypass procedures. This was combined with chronic and acute coronary artery disease to form a composite index referred to as any coronary artery disease (Table 3). Another composite index included all of these cardiovascular indices (referred to as any cardiovascular diseases).

Statistical Methods

We created subgroups among subjects who had any of the above-listed conditions and analyzed daily mortality for those subjects who did not die from accidents or injuries. For each separate group we used quasi-likelihood estimation within the context of the generalized additive models (*62*) to model the expected logarithm of daily counts of deaths, assuming Poisson variation with constant over- or underdispersion. We accounted for seasonal and subseasonal variations (temporal filter) using a locally weighted regression smoother (LOESS) on time, and we adjusted for annual trends in daily mortality and the potential confounding effects of relevant weather variables. We selected the temporal filter with a smoothing bandwidth (span for the LOESS function) that produced a filtered time series consistent with a white noise process using Bartlett's statistic (*63*). In most cases this filter minimized the serial autocorrelation and produced a minimum Akaike information criterion. We then selected the combination of weather variables that explained the most amount of residual variability in the data. Single-pollutant models using daily mean values across the fixed-site monitoring stations were considered first. We also estimated mortality with the previous day's level of air pollution (lag 1 day) as

Table 2. Definition of the indicators of cardiovascular disease status.

Age (years)	Diagnoses (*ICD-9-CM* codes[a]) in specified time interval	Prescriptions in specified time interval	Services/tests/procedures in the specified time interval
Hypertension			
< 65	401–405; ≥ 3 billings	None	None
≥ 65	401–405; ≥ 3 billings or	None	None
	≥ 401–405; 2 billings	Any prescription for diuretics, beta-blockers, calcium channel inhibitors, ACE inhibitors, vasodilators	None
Congestive heart failure			
< 65	428; ≥ 2 billings	None	None
≥ 65	428; ≥ 2 billings or	None	None
	428; ≥ 1 billing	Any prescription for diuretics	None
Acute coronary artery disease			
< 65 and ≥ 65	410, 411	None	None
Chronic coronary artery disease			
< 65	412–414 or	None	≥ 1 Coronary catheterization or stress test
	412–414; ≥ 3 billings or	None	None
	412–414; diagnosed by a cardiologist	None	None
≥ 65	412–414 or	None	≥ 1 Coronary catheterization or stress test
	412–414; ≥ 3 billings or	None	None
	412–414; diagnosed by a cardiologist or	None	None
	412–414	≥ 2 Prescriptions for nitroglycerine	None
Coronary artery bypass (chronic or acute)		None	1 PTCA or coronary bypass
Cerebrovascular diseases			
< 65 and ≥ 65	430–438	None	None
Chronic rheumatic heart disease			
< 65 and ≥ 65	393–396	None	None

Abbreviations: ACE, angiotensin-converting enzyme; ECG, electrocardiogram; PTCA, percutaneous transluminal coronary angioplasty.
[a]Diagnostic codes from *ICD-9-CM* (*57*).

Table 3. Composite cardiovascular indices.

Composite index	Specific cardiovascular indices included in the composite
Any coronary artery disease	Definite acute coronary artery disease Chronic coronary artery disease Coronary artery bypass
Any cardiovascular disease	Acute coronary artery disease Chronic coronary artery disease Hypertension Coronary artery bypass Congestive heart failure Cerebrovascular disease Chronic rheumatic heart disease

Table 4. Distribution of daily nonaccidental mortality by subgroup, Montreal, Quebec, Canada, 1984–1993.

Subgroup	Total number of deaths	Number of days in which there were no deaths	Mean	Variance	Percentiles 25th	50th	75th	100th
All nonaccidental causes of death	133,904	0	36.7	51.5	32	36	41	89
< 65 years of age	31,756	0	8.7	9.1	7	8	11	22
≥ 65 years of age	102,148	0	28.0	40.2	24	28	32	79
Respiratory diseases								
Acute upper respiratory disease	1,432	2,514	0.4	0.4	0	0	1	7
Chronic upper respiratory disease	2,541	1,869	0.7	0.8	0	0	1	6
Acute lower respiratory disease	15,775	85	4.3	6.0	2	4	6	17
Airways disease	29,030	7	7.9	11.0	6	8	10	23
Cardiovascular diseases								
Acute coronary artery disease	9,900	258	2.7	2.9	1	3	4	12
Chronic coronary artery disease	22,176	12	6.1	6.4	4	6	8	17
Congestive heart failure	16,794	61	4.6	5.5	3	4	6	16
Hypertension	7,977	468	2.2	2.4	1	2	3	10
Cerebrovascular diseases	10,861	207	3.0	3.3	2	3	4	13
Any coronary artery disease	29,209	3	8.0	8.8	6	8	10	20
Any cardiovascular disease	52,357	0	14.3	17.7	11	14	17	34

well as with the average of lags 0–2 days (referred to as the 3-day mean). For those pollutants not measured daily, lags were taken by shifting the mortality time series forward. The 3-day mean could not be derived for pollutants that were not monitored daily.

We estimated parametric, linear terms for the relative increase in the logarithmic number of daily deaths per unit increase in the pollutant. We calculated the percent change in the mean number of daily deaths for an increase of the interquartile range (IQ) for each index of particle, i.e., as $[\exp(\beta \times IQ) - 1] \times 100\%$, where β is the estimated regression coefficient. We refer to this quantity as the mean percent change (MPC). Associated upper and lower 95% confidence intervals on the MPC were obtained assuming that the estimated regression coefficient was distributed normally, with the standard error corrected for non-Poisson dispersion.

Results

There were 133,904 nonaccidental deaths during the study period 1984–1993 (Table 4), with 76.3% of the deaths among the elderly. One year before death, about 22% of the population were attributed with airways disease, 17% with chronic coronary artery disease, and 12% with congestive heart failure; for the acute conditions (2 months before death), 12% had acute lower respiratory disease and 8% had strokes.

Table 5. Distribution of pollutant and weather variables, Montreal, Quebec, Canada,1984–1993.

	Units	Number of days of measurements	Mean	SD	Minimum	Percentiles 25th	50th	75th	100th	IQ
TSP	µg/m^3	603	53.1	22.6	14.6	37.0	48.7	65.6	211.1	28.57
PM_{10}	µg/m^3	624	32.2	17.6	6.5	19.7	28.5	41.1	120.5	21.32
$PM_{2.5}$	µg/m^3	636	17.4	11.4	2.2	9.4	14.7	21.9	72.0	12.51
Sulfate from PM_{10}	µg/m^3	437	4.7	4.4	0.3	1.9	3.6	5.7	30.7	3.84
Sulfate from $PM_{2.5}$	µg/m^3	446	4.3	4.2	0.2	1.6	3.1	5.1	29.2	3.51
Sulfate from TSP	µg/m^3	607	4.3	2.9	0.3	2.3	3.6	5.3	19.2	3.02
Sulfate from the Sutton monitoring station[a]	µg/m^3	2,680	3.3	3.6	0	1.3	2.2	3.8	30.0	2.50
COH	0.1 COH units per 327.8 linear meters	3,653	2.4	1.5	0.1	1.3	2.1	3.2	15.6	1.85
Predicted $PM_{2.5}$[a]	µg/m^3	3,653	17.6	8.8	4.6	11.5	15.4	21.0	71.7	9.50
Predicted sulfate from $PM_{2.5}$[a]	µg/m^3	3,653	4.1	3.6	0.02	1.9	3.1	4.8	30.1	2.90
Extinction	km^{-1}	3,454	0.15	0.10	0.01	0.06	0.15	0.17	1.87	0.11
Sulfur dioxide	µg/m^3	3,653	17.8	11.2	3.9	10.3	14.6	21.8	105.7	11.50
Nitrogen dioxide	µg/m^3	3,653	41.7	15.4	8.8	30.9	39.5	50.2	143.5	19.34
Nitric oxide	µg/m^3	3,653	41.8	29.0	2.7	21.9	34.8	52.3	281.4	30.41
Carbon monoxide	ppm	3,653	0.8	0.5	0.1	0.5	0.7	1.0	5.1	0.50
Ozone	µg/m^3	3,653	29.0	17.1	2.8	16.6	26.0	37.9	163.9	21.34
Mean temperature	°C	3,653	6.4	11.8	–27.3	–2.6	7.5	16.5	28.8	19.10
Change in maximum temperature from the previous day	°C	3,653	0.0	4.7	–25.0	–2.5	0.4	2.8	19.4	5.30
Mean dew point temperature	°C	3,653	1.2	11.6	–33.8	–6.6	2.0	10.8	23.1	17.40
Relative humidity	%	3,653	69.4	11.9	33.0	61.0	70.0	78.0	99.0	17.00
Change in barometric pressure from previous day	kPa	3,653	0.0	0.9	–4.2	–0.5	0.0	0.6	4.4	1.10

[a]For 1986–1993.

Table 6. Summary estimates of MPC in daily nonaccidental mortality for selected subgroups defined using billing and prescription data obtained from the QHIP for their respective period prior to death, for three selected measures of particulate air pollution, across the IQ and evaluated at the 3-day mean, Montreal, Quebec, Canada, 1984–1993.[a]

	COH		Predicted $PM_{2.5}$		Sutton sulfate	
Subgroup	MPC[b]	95% CI	MPC[b]	95% CI	MPC[b]	95% CI
All nonaccidental causes of death	1.98	1.07–2.90	2.17	1.26–3.08	1.29	0.68–1.90
Respiratory indices						
Acute upper respiratory disease	4.57	–4.06–13.98	7.28	–1.12–16.40	6.36	0.58–12.47
Chronic upper respiratory disease	2.39	–3.78–8.97	3.81	–2.19–10.17	4.34	0.32–8.51
Acute lower respiratory disease	5.09	2.47–7.79	4.72	2.23–7.28	2.25	0.56–3.98
Airways disease	1.53	–0.39–3.49	1.33	–0.45–3.15	0.51	–0.72–1.75
Cardiovascular indices						
Acute coronary artery disease	2.35	–0.91–5.70	2.27	–0.88–5.52	0.99	–1.17–3.19
Chronic coronary artery disease	2.62	0.53–4.75	2.20	0.14–4.31	0.63	–0.77–2.06
Congestive heart failure	4.99	2.44–7.60	4.02	1.61–6.48	1.91	0.28–3.56
Hypertension	3.35	–0.27–7.10	1.88	–1.56–5.44	0.53	–1.80–2.92
Cerebrovascular disease	1.73	–1.35–4.91	1.53	–1.40–4.55	0.63	–1.37–2.66
Any coronary artery disease	2.99	1.13–4.88	1.85	0.03–3.70	0.69	–0.55–1.95
Any cardiovascular disease	3.65	2.23–5.09	2.76	1.40–4.15	1.16	0.23–2.09

[a]The statistical model was $E(\log(y_i)) = \alpha + \text{loess}(i, \text{span} = 91/3653) + \text{loess}(\text{year}) + \text{loess}(\text{mean temperature}_0, \text{change in barometric pressure from the previous 24 hr}_0) + \beta \times \text{pollutant}$, where y_i is the number of nonaccidental deaths on day i for subjects included in each subgroup. [b]MPCs calculated for an increase of exposure equal to the IQ.

Table 5 shows that the levels of particulate and gaseous pollutants were fairly low. Measurements for TSP, PM_{10}, $PM_{2.5}$, and sulfates from these metrics were limited (varying from 12 to 17% of the total number of days on study), and there were 8 of 10 years of measurements of Sutton sulfates (1986–1993).

Table 6 shows detailed results for each morbidity subgroup (all age groups combined) of the regression analyses for three selected measures of particles evaluated at the 3-day mean. For the purposes of comparison we have included the results for all nonaccidental causes of death. (All positive associations were consistent with a linear response function.) We did not find any consistent positive associations (95% confidence intervals for the MPCs excluding zero across all metrics of particles) among persons who were classified before death as having airways disease, acute coronary artery disease, hypertension, or cerebrovascular disease. Although we found positive associations with Sutton sulfates among persons with acute and chronic upper respiratory diseases, no associations for this or any other pollutant were found at lag 0 or lag 1 days (Table 7). Consistent associations, when evaluated at the 3-day mean and for most measures of particles evaluated at lag 1 day, were found for the subgroup with acute lower respiratory disease. The subgroup with chronic coronary artery diseases was not found to be consistently associated across the different indices of particles or lags. We found a consistent association for congestive heart failure evaluated at the 3-day mean as well as at lag 0 days. Last, associations in the combined subgroup of individuals with any cardiovascular diseases were found across all indices of exposure and lags.

Figures 1–3 show results for selected measures of particles evaluated at the 3-day mean for deaths from acute lower respiratory disease, chronic coronary artery disease, and any cardiovascular diseases by age at time of death (< 65 and ≥ 65 years), respectively. We do not show results for congestive heart failure for the former age group as there were too few deaths. The figures show rather large confidence intervals that reflect the statistical noise inherent in these time-series analyses, particularly for the younger age groups. We did not find large differences between the age groups for subjects with acute lower respiratory diseases attributed within 2 months before their deaths (Figure 1). Although no consistent associations were found for chronic coronary artery diseases in the analyses of all

Table 7. Synthesis of selected results of the MPC for the different subgroups of disease status for selected measures of particulates evaluated at the IQ for lag 0 and lag 1 days, Montreal, Quebec, Canada, 1984–1993.

Subgroup	COH	Extinction	Predicted $PM_{2.5}$	Sulfate from Sutton	Predicted sulfate from $PM_{2.5}$
			Lag 0 days		
All nonaccidental causes of death	1.44*	1.05*	1.86*	0.71*	1.15*
Respiratory indices					
Acute upper respiratory disease	1.66	–1.58	4.08	3.30	3.64
Chronic upper respiratory disease	–0.33	–4.15	–0.08	0.56	–0.08
Acute lower respiratory disease	1.04	1.42	2.12*	1.09	1.52
Airways disease	0.61	1.24	1.47*	0.14	0.90
Cardiovascular indices					
Acute coronary artery disease	1.51	1.06	1.94	0.43	0.95
Chronic coronary artery disease	1.76*	1.11	1.66	0.41	0.85
Congestive heart failure	2.88*	2.98*	3.44*	1.67*	2.61*
Hypertension	1.65	1.53	1.97	0.23	1.12
Cerebrovascular disease	0.69	0.53	1.72	0.42	0.88
Any coronary artery disease	1.40	0.66	1.74*	0.73	1.02
Any cardiovascular disease	1.82*	1.10*	2.05*	0.72	1.19*
			Lag 1 day		
All nonaccidental causes of death	1.12*	0.86*	1.48*	0.95*	1.15*
Respiratory indices					
Acute upper respiratory disease	3.72	0.68	5.14	3.73	4.11
Chronic upper respiratory disease	2.92	–2.32	1.39	1.64	0.63
Acute lower respiratory disease	4.38*	0.59	3.27*	1.83*	1.86*
Airways disease	1.44	1.41*	1.11	0.60	0.95
Cardiovascular indices					
Acute coronary artery disease	2.31	0.70	2.38	0.68	1.09
Chronic coronary artery disease	1.98*	0.25	1.82*	0.66	0.98
Congestive heart failure	4.17*	1.58	2.81*	1.18	1.53*
Hypertension	1.99	0.57	0.34	0.14	0.23
Cerebrovascular disease	1.71	0.96	1.77	1.03	1.13
Any coronary artery disease	2.56*	0.35	1.60*	0.30	0.61
Any cardiovascular disease	2.95*	1.14*	2.49*	1.11*	1.52*

*t > 1.96.

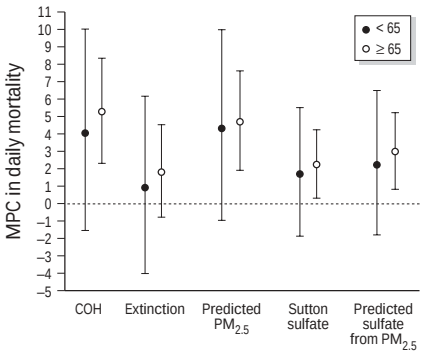

Figure 1. MPC in daily mortality among persons with acute lower respiratory diseases 2 months before death, evaluated at the 3-day mean for increases in the IQs of selected measures of particulates, by age group. The estimated MPC in daily nonaccidental mortality across the IQ is shown by the circles within the vertical lines (95% CIs).

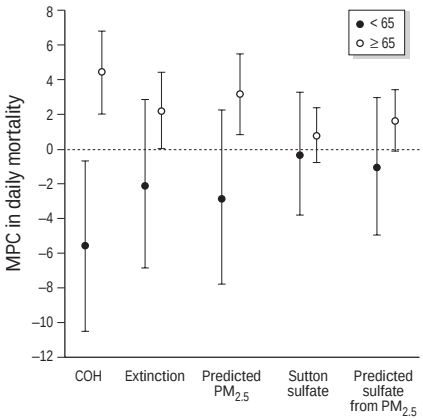

Figure 2. MPC in daily mortality among persons with chronic coronary artery diseases 1 year before death, evaluated at the 3-day mean for increases in the IQs of selected measures of particulates, by age group. The estimated MPC in daily nonaccidental mortality across the IQ is shown by the horizontal bars within the vertical lines (95% CIs).

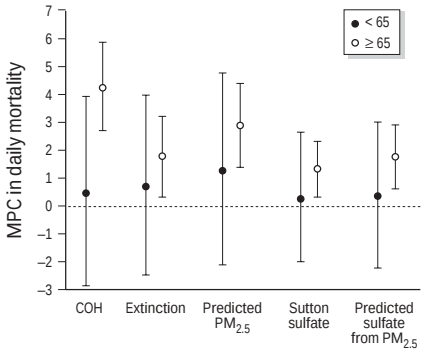

Figure 3. MPC in daily mortality among persons with any cardiovascular diseases 1 year before death, evaluated at the 3-day mean for increases in the IQs of selected measures of particulates, by age group. The estimated MPC in daily nonaccidental mortality across the IQ is shown by the circles within the vertical lines (95% CIs).

age groups, positive associations among the elderly were found (Figure 2). There was a clear increase in daily mortality among the elderly who had any cardiovascular diseases (Figure 3).

We also adjusted for the separate effects of sulfur dioxide and ozone (all pollutants evaluated at the 3-day mean). Figure 4 shows that the association for the subgroup with congestive heart failure (all age groups) was, in general, attenuated by these adjustments. Similar results were found for the subgroup with acute lower respiratory diseases (data not shown). Figure 5 shows that for congestive heart failure the positive associations were restricted to the summer season (April–September). Similar results were found for acute lower respiratory diseases but not for chronic coronary artery disease in the elderly (data not shown).

Discussion

In summary, statistically significant positive associations were found for individuals who, shortly before death, were classified as having acute lower respiratory diseases, congestive heart failure, and a combined group of cardiovascular diseases. There was reasonable evidence that individuals with chronic coronary artery disease (especially in the elderly) also had higher daily mortality when air pollution increased. (Positive associations were found for all measures of particles except sulfates.) In addition, there was evidence that the effects of air pollution in these subgroups were greater in the summer season than in the winter. These results need to be interpreted in terms of the study's strengths and limitations.

Methodologic Aspects

Pollution data. Data for particle mass were limited by the 6-day measurement schedule, so we relied on the COH, which is a reliable measure of the concentration of ambient carbon particles (mostly from internal combustion), the extinction coefficient (which primarily measures sulfate), and sulfate from the Sutton acid rain monitoring station. The extinction coefficient is likely to be misclassified more than particle mass because of the subjectivity of the measurements of visibility and the approximate formula used to convert visibility into an extinction measure. Measurements of total sulfate at the Sutton acid rain station captured regional levels of sulfates, but despite the high correlation with measurements of sulfate in Montreal, these regional levels did not fully reflect levels in Montreal because the measurements did not capture local fluctuations. As we did not have a complete series of fine particle measurements, we created one using a linear regression model that included COH, sulfate from the Sutton monitoring station, and the extinction coefficient. Although the statistical models provided reasonably good predictions, misclassification of this index should also have reduced power and attenuated estimates of effect.

Confounding. We adjusted for seasonal and subseasonal cycles in the mortality time series as well as the effects of weather on daily mortality. We could not control for the effects of infectious disease epidemics (e.g., influenza, which occurs mostly in the fall and winter, when particle levels are increased). However, because these epidemics generally follow seasonal and subseasonal weather patterns, it seems plausible that some or all of these potential confounding effects were removed during the temporal filtering. In a few other studies adjustment for influenza epidemics did not remove associations between mortality and suspended particles or sulfur dioxide (*64–66*).

We also adjusted for the effects of the gaseous pollutants. Many of these pollutants are generated from complex chemical reactions in air (e.g., ozone), and some gaseous pollutants (e.g., sulfur dioxide) act as precursors in the formation of particles. These atmospheric chemical processes create high correlations among levels of most pollutants. As the sources for the pollutants are the same, care must be taken in interpreting the results of these adjustments.

Morbidity data. The data used to construct the indices of disease status consisted of healthcare billing data, diagnostic codes recorded on the billing record, rendered healthcare services, and filled prescriptions for drugs that were paid for by the QHIP. Because the data are based on rendered services carried out both within and outside the hospital, they should, in principle, perform more accurately than simple hospital discharge summaries, which provide, at best, a snapshot of acute illnesses or exacerbations of chronic ones.

The key assumption in using the QHIP data was that they were sufficiently accurate to define most conditions before death. In defining these indices we used our knowledge of clinical practice in Quebec. For example, the requirement of having three diagnoses on the billing record to define hypertension was based on usual clinical practice guidelines. We also assumed that certain conditions could not be identified uniquely; for example, we defined airways disease but did not attempt to identify its individual components (e.g., asthma).

An essential element in defining most of the indices of disease status was the diagnosis recorded on the billing record. Although this was available for only about 50% of the billing records, over 97% of deceased subjects had at least one diagnosis coded in the 5-year period before death. There are no data regarding the accuracy of these diagnoses. However, it seems plausible that diagnoses for cancer and stroke should be accurate because of well-established investigative procedures used by specialists, whereas the accuracy of diagnosing asthma would be more problematic because appropriate tests would not be conducted by all physicians.

The next most important indicator was records of filled prescriptions. Although we had no information regarding compliance for taking drugs, this may be irrelevant in the context of defining subgroups, as we were only interested in whether a prescription indicated the presence of a specific health condition. On the other hand, we had no information regarding prescriptions written by physicians but never filled by patients; this kind of missing information will inevitably lead to misclassification that may vary by disease and socioeconomic status. Because the drug plan covered persons who were 65 years of age and older,

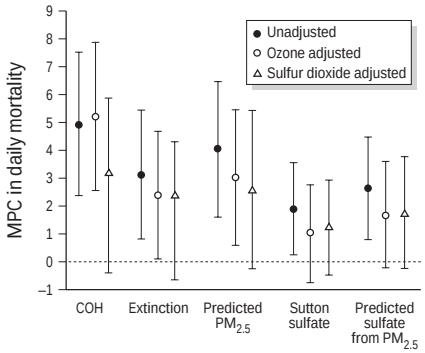

Figure 4. MPC in daily mortality among persons with congestive heart failure 1 year before death, evaluated at the 3-day mean for increases in the IQs of selected measures of particulates, adjusted for the effects of sulfur dioxide and ozone. The estimated MPC in daily nonaccidental mortality across the IQ is shown by the symbols within the vertical lines (95% CIs).

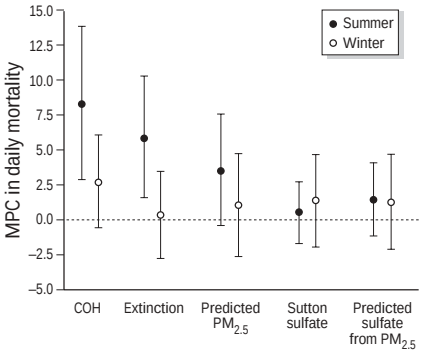

Figure 5. MPC in daily mortality among persons with congestive heart failure 1 year before death, evaluated at the 3-day mean for increases in the IQs of selected measures of particulates, by season. The summer season is defined as April to September. The estimated MPC in daily nonaccidental mortality across the IQ is shown by the circles within the vertical lines (95% CIs).

there was limited prescription data for persons who died at age 65. It would have been useful to carry out analyses excluding persons who died exactly at the age of 65 years, but this was not possible because the QHIP did not provide us with exact ages of subjects (only in groupings of 5 years; for reasons of confidentiality). Thus, it is likely that there were some inaccuracies in classifying subjects into subgroups based on prescriptions.

We used a 2-month interval to capture acute conditions and a 1-year period to capture chronic conditions. These intervals trade off specificity and sensitivity and account qualitatively for the complex manner in which information is recorded in the billing databases. Our analyses for chronic disease [data not shown; (*54*)] indicated that there could be substantial loss of information if too short a period was used. On the other hand, the 2-month period for acute diseases seemed justified, although it resulted in rather sparse time series of deaths for some conditions.

Mechanisms. Bates (*2*) suggested that exposure to air pollutants in persons with cardiac disease with myocardial damage may cause acute pulmonary disease such as bronchiolitis or pneumonia, thereby leading to congestive heart failure. In addition, Seaton et al. (*52*) hypothesized that in susceptible individuals, exposure to ultrafine particles will invoke alveolar inflammation, release inflammatory mediators, exacerbate lung conditions, and increase coagulability of blood, thereby leading to acute cardiovascular events. These hypotheses suggest that persons with congestive heart failure and acute myocardial infarctions should die at higher rates when air pollution increases. Based on this extension of these hypotheses, our results appear to be more consistent with the hypothesis of Bates (*2*), and the null association with acute coronary artery disease is not consistent with the hypothesis of Seaton et al. (*52*).

Other mechanisms may be at play. It has been shown that inhalation of urban particles in animals not having a structural lung injury increases the circulating levels of endothelins, the most potent vasoconstrictors known (*67*). Elevation of circulating endothelin-1 and endothelin-3 has been reported in a number of conditions, including cardiovascular disease, asthma, and diabetes. These peptides have vasoconstrictor as well as mitogenic effects and may be involved in the pathogenesis of a number of conditions. In particular, it has been reported that plasma endothelin levels correlate with severity of disease in congestive heart failure and predict cardiac death (*68*). Likewise, reduction of endothelin levels in congestive heart failure patients was associated with improvement of symptoms, suggesting a direct role of endothelins in the pathophysiology (*69*). The toxicologic data suggest that ambient particles and particle-associated chemical species may act principally as endocrine/paracrine modulators; host factors will modulate these and establish the nature and severity of the health effects.

One can postulate that ambient particles may affect the heart indirectly by a modification of endothelin homeostasis in the lungs. Conceivably, elevated circulating endothelins would impact on cardiac arrhythmia and dysrhythmia, exacerbate congestive heart failure, precipitate ischemic heart disease, and may affect persons with conditions involving endothelial dysfunction such as diabetes, atherosclerosis, and kidney diseases.

Because this study is the first of its kind, the findings need to be replicated. In addition, in-depth studies of individuals need to be undertaken to determine whether the association is causal. Specifically, if one can show in a panel study or other appropriate design that changes in essential indicators of health status that are precursors to acute crises (hospitalization, death) are associated with variations in levels of air pollution, then the case for causality is greatly strengthened.

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