

Airborne Particulates and Hospital Admissions for Cardiovascular Disease: A Quantitative Review of the Evidence

Robert D. Morris

Department of Family Medicine and Community Health, Tufts University School of Medicine, Boston, Massachusetts, USA

This is a quantitative review of studies characterizing the relationship between exposure to airborne particulates and hospital admissions for cardiovascular disease. A MEDLINE search and a review of reference lists were conducted to identify time-series studies that considered particles less than 10 μm or 2.5 μm in diameter (PM_{10} and $\text{PM}_{2.5}$, respectively) and their association with day-to-day variation in cardiovascular admissions. The results of these studies were standardized to give estimates of the percentage increase in hospital admissions associated with an increase in ingestion of ambient particles of 10 $\mu\text{g}/\text{m}^3$. The results were grouped and compared on the basis of the specific outcomes and exposure measures. When studies that considered the association between PM_{10} exposure and specific cardiovascular outcomes were pooled (after exclusion of outliers), a 10- $\mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with increases in admission rates of 0.8% (95% confidence interval [CI]: 0.5, 1.2%) for congestive heart failure, 0.7% (95% CI: 0.4, 1.0%) for ischemic heart disease, and 0.2% (95% CI: -0.2, 0.6%) for cerebrovascular accidents. These effects tended to diminish substantially when gaseous co-pollutants were considered. The extent to which these effects are due to fine particles is unclear. The available studies indicate that exposure to airborne particles is associated with hospital admissions for cardiovascular disease; but the magnitude of this effect depends strongly on the specific disease category being considered, the time lag used in the analysis, and the type and amount of co-pollutants. Future studies should include careful consideration of the role of co-pollutants in this association, the interaction of particles with temperature, the impact of particle size on this effect, and the extent to which the observed effect involves short-term "harvesting." **Key words:** air pollution, cerebrovascular disease, congestive heart failure, ischemic heart disease, meta-analysis, myocardial infarction, particulates.

— *Environ Health Perspect* 109(suppl 4):495–500 (2001).

<http://ehpnet1.niehs.nih.gov/docs/2001/suppl-4/495-500morris/abstract.html>

The possibility that exposure to airborne particles can contribute to cardiovascular morbidity and mortality has generated a steady flow of published papers over the past decade. Recently, this has risen to flood proportions, mainly because of the emergence and the growing capacity of tools to conduct time-series studies using health outcomes data abstracted from records collected for other purposes.

These health outcomes can be grouped according to the type of health event being measured and the specific disease category being evaluated. Most published studies consider either measures of mortality or measures of morbidity. Mortality data were particularly important for early time-series studies because of their routine availability and the lack of ambiguity in death as a health end point. However, data related to morbidity are potentially more sensitive for time-series studies because they involve greater numbers of subjects. The only routinely and reliably collected data relevant to cardiovascular morbidity in the United States are derived from administrative medical data sets (i.e., billing records) of hospitalizations for specific hospitals or metropolitan areas. Records of outpatient physician contacts are not routinely available, and even where they are, they tend to provide less complete and accurate information than inpatient

records. Studies of the temporal relationship between hospitalizations for cardiovascular disease and the presence of ambient particulate air pollution were the focus of this study.

Early studies of the relationship between exposure to particles and cardiovascular disease relied on measures such as black smoke or total suspended particulates. Those cruder measures of particle exposure lack the specificity and physiologic relevance of measures of specific particle groups, particularly particulate matter smaller than 10 μm or 2.5 μm (PM_{10} or $\text{PM}_{2.5}$, respectively). I limited this review to studies that used size-specific measures of particles. In most cases, the studies have relied on single monitoring stations with daily pollutant measures as a surrogate for individual exposures.

Through a MEDLINE search for all papers published before August 2000 that considered PM_{10} or $\text{PM}_{2.5}$ exposure and cardiovascular disease together with a review of references listed in those articles, I identified 12 published studies of hospital admissions for cardiovascular disease (1–12). These studies are listed in Table 1. Although time-series studies seem to have taken on a numbing sameness, no two studies have used exactly the same method, and the differences among studies have major implications for their interpretation. Specifically, these studies

differ with respect to the health outcome or outcomes considered; the measure of particle exposure, including the consideration of time lags between exposure and outcome; and the covariates considered in the analysis.

In the following sections of this paper, I consider the impact of these characteristics on study results through a series of tables. Table 2 lists results pertaining to all cardiovascular admissions with respect to PM_{10} exposure without adjustment for co-pollutants. Succeeding tables provide results for specific cardiovascular diagnoses, results after adjustment for co-pollutants, and effects associated with subfractions of PM_{10} . This analysis provides some insight into how study results are influenced by the specific relationships being characterized and the methods used to define those relationships.

The published studies have presented results in a variety of formats and present results with respect to many different exposure ranges. Conversion to a standard range is essential to any meaningful comparison of results. For this reason, all results presented in this review have been converted to indicate the estimated percentage increase in hospital admissions associated with a 10- $\mu\text{g}/\text{m}^3$ increase in particulate matter.

Studies of the Relationship between PM_{10} Exposure and All Cardiovascular Admissions

The results of studies that considered the association between PM_{10} exposure and cardiovascular disease admissions are presented in Table 2 and stratified according to age group. These results by themselves refute any assertion of consistency among the observed associations between exposure to particles and hospital admissions. The effect size varies by a factor of 5 or more within each age group.

This article is based on a presentation at the Workshop on Inhaled Environmental/Occupational Irritants and Allergens: Mechanisms of Cardiovascular and Systemic Responses held 31 March to 2 April 2000 in Scottsdale, Arizona, USA.

Address correspondence to R.D. Morris, Dept. of Family Medicine and Community Health, Tufts University School of Medicine, 136 Harrison Ave., Boston, MA 02111 USA. Telephone: (617) 636-4074. Fax: (617) 636-4017. E-mail: robert.morris@tufts.edu

This work was supported by research grant R29-ES07204-01A2 from the National Institutes of Health. The author acknowledges the thoughtful comments of E. Naumova on this manuscript.

Received 22 December 2000; accepted 13 April 2001.

Table 1. Studies of the relationship between ambient particulates as PM₁₀ or PM_{2.5} and day-to-day variation in counts of hospitalization for cardiovascular disease.

Study (first author)	Location	Outcome diagnoses	Particle size	Exposure periods		Gaseous pollutants				Meteorologic covariates
				Lag (days)	Average (days)	NO ₂	CO	O ₃	SO ₂	
Schwartz, 1995 (7)	Detroit, MI	CHF, IHD	PM ₁₀	0	–		x			Temperature, humidity
Morris, 1997 (2)	Chicago, IL	CHF	PM ₁₀	0	–	x	x	x	x	Temperature, wind chill, humidity
Burnett, 1997 (3)	Toronto, Ontario, Canada	CVD	PM ₁₀ , PM _{2.5}	0–4	1–5	x	x	x	x	Temperature
Schwartz, 1997 (4)	Tucson, AZ	CVD	PM ₁₀	0	–		x			Temperature, humidity - S
Prescott, 1998 (5)	Edinburgh, Scotland	CVD	PM ₁₀	0 or 1	1 or 3	0	0	0	0	Temperature, humidity
Atkinson, 1999 (6)	London, England	CVD	PM ₁₀	1–3	Lagged 0–3	x	x	x	x	Temperature Temperature - S
Wong, 1999 (7)	Hong Kong	CVD, CHF, IHD, CVA	PM ₁₀	0–5	0–5	x		x	0	Temperature, humidity - S
Schwartz, 1999 (8)	Multiple cities	CVD	PM ₁₀	0	–		x			Temperature, humidity
Burnett, 1999 (9)	Toronto	DSR, CHF, IHD, CVD, AMI, CVA	PM ₁₀ , PM _{2.5}	0–4	1–5	x	x	x	x	Temperature
Moolgavkar, 2000 (10)	Los Angeles, CA; Phoenix, AZ; and Chicago	CVD, CVA	PM ₁₀ , PM _{2.5}	0–5	–	x	x	x	x	Temperature, humidity
Linn, 2000 (11)	Los Angeles	CVD, DSR, CHF	PM ₁₀	0	–	0	0	0	0	Temperature with indicators for hot, cold and rainy days - S
Gwynn, 2000 (12)	Buffalo, NY	CVD	PM ₁₀	0–3	–	0	0	0	0	Temperature, humidity

Abbreviations: AMI, acute myocardial infarction; O, pollutants specifically included in multivariate models; NO₂, nitrogen dioxide; O₃, ozone; S, stratification by temperature or related variable; SO₂, sulfur dioxide; x, pollutants specifically included in multivariate models.

Table 2. Results from single pollutant models of PM₁₀ and combined hospital admissions for cardiovascular disease.^a

Study (first author)	Age range (years)	Time lag (days)	% Increase per 10 µg/m ³	95% CI
Linn, 2000 (11)	> 29	0	0.64	0.41, 0.88
Burnett, 1997 (3)	All	1–4	2.30	0.29, 4.36
Prescott, 1998 (5)	All	1–3	4.80	0.90, 8.85
Wong, 1999 (7)	All	0–2	0.60	0.20, 1.00
Gwynn, 2000 (12)	All	1	0.62	–0.36, 1.61
Prescott, 1998 (5)	0–64	1–3	0.40	–2.63, 3.53
Atkinson, 1999 (6)	0–64	0	1.10	0.41, 1.81
Wong, 1999 (7)	5 to 64	0–5	0.50	0.20, 0.80
Moolgavkar, 2000 – LA (10)	20–64	0	2.20	1.12, 3.30
Linn, 2000-LA (11)	30–64	0	0.50	0.08, 0.92
Schwartz, 1997 (4)	> 64	0	1.19	0.22, 2.16
Prescott, 1998 (5)	> 64	1–3	2.37	0.45, 4.33
Atkinson, 1999 (6)	> 64	0	0.50	–0.04, 1.04
Wong, 1999 (7)	> 64	0–5	0.80	–0.30, 1.91
Schwartz, 1999 (8)	> 64	0	0.98	0.72, 1.25
Linn, 2000 (11)	> 64	0	0.62	–0.36, 1.61
Moolgavkar, 2000 (10)				
LA	> 64	0	1.60	0.59, 2.62
Cook	> 64	0	2.10	1.49, 2.71
Maricopa	> 64	0	–1.20	–3.51, 1.17

Abbreviations: Cook, Cook County; LA, Los Angeles County; Maricopa, Maricopa County.

^aAbstracted from studies of the relationship between exposure to ambient particulates and day-to-day variation in counts of hospitalizations for cardiovascular disease.

The reasons for this variability in effect size must involve some combination of chance variation and the impact of differences among the study designs. Study design could influence results either through actual differences in the effect being measured or through apparent differences arising as an artifact of the methods used in data collection and analysis. The underlying effect of exposure to particulate matter on cardiovascular morbidity may differ among locations because of local differences in the pollutant mixture, factors influencing individual exposure, or the characteristics of the population at risk. Even if the underlying effect were

constant, the estimated effect could vary because of the modeling approach including the adjustment for potential confounders and the consideration of time lags.

The major differences in consideration of confounders involved the evaluation of co-pollutants as discussed below. Approaches to considering time lags included evaluation of a range of values, evaluation of multiday averages of different durations and starting points, some combination of these approaches, or no consideration of time lags at all (i.e., a time lag of zero days).

Each approach has potential limitations. Studies in which a single time lag is evaluated

without a clear prior reason for doing so will not capture effects that occur at other times. Conversely, in those studies that consider multiple time lags the researchers often select the one with the strongest effect. This approach will tend to overestimate the effect of exposure to the particles to the extent that this effect is associated with a particular lag. Of particular concern, when there is no underlying effect, the theory of extreme value distributions shows that this approach can be expected to yield estimates of effect size with a magnitude similar to those routinely reported for particles (13). To test this relationship empirically, I performed a simulation to estimate the average effect size that would be reported from studies that considered time lags of 0–5 days and picked the maximum. A simulation based on 1,000 repetitions of the case in which the underlying effect had a true mean of 0 and a standard deviation of 1 yields an average predicted effect size of 1.3%.

The variability in these results makes it difficult to draw any meaningful conclusions from the aggregated cardiovascular disease data. The results suggest instead that we must look at groups of studies with greater homogeneity in health outcomes and modeling approaches. Therefore, as a first step, I considered studies that examined specific cardiovascular diagnoses.

Evaluation of Specific Cardiovascular Outcomes

Although cardiovascular diseases share many risk factors, particularly in chronic exposures that increase the risk of underlying disease, they do differ in the pathophysiology of acute morbidity. Therefore, consideration of individual disease groups may provide greater insight into the possible mechanisms by

which particulate matter might cause acute symptomatic disease.

The validity of considering specific diagnostic groups could be diminished by substantial inaccuracy or inconsistency in disease coding. Although there may be some regional and international variability in disease coding, the accuracy of these codes is relatively high for cardiovascular disease (14,15). Furthermore, misclassification would be likely to alter the effect size substantially only if the variability in coding resulted in a pattern of excluding cases related to patients' susceptibility to the cardiovascular effects of exposure to particulate air pollutants. Such misclassification is plausible if, for example, presence of associated respiratory disease resulted in coding the respiratory disease as the primary diagnosis in some areas but not in others. This could result in different effect sizes in different cities. However, there is no evidence to suggest that such a systemic misclassification occurred.

Table 3 lists the estimates of the effect of PM₁₀ with respect to four categories of cardiovascular disease: dysrhythmia (DSR), congestive heart failure (CHF), ischemic heart disease (IHD), and cerebrovascular accident (CVA). Two approaches were used to pool results. A random-effects model was used to pool all relevant studies. Then, the single study making the greatest contribution to heterogeneity among studies (as determined by its contribution to Cochran's Q statistic) was eliminated and the remaining studies were pooled using a fixed-effects model.

If we pool the results for CHF, admissions decrease by 1.6% [95% confidence interval (CI): 0.4, 2.8%] per 10 µg/m³ increase in PM₁₀. After elimination of the anomalous result from Wong et al. (7), the pooled effect drops to 0.8% (95% CI: 0.5, 1.2%), similar to the effect observed for IHD [0.7% (95% CI: 0.4, 1.0%)].

The four studies that considered CVA as an outcome provide little support for the underlying existence of substantial risk of CVA associated with PM₁₀ (7,9–11). The pooled effect from the three studies that provided data was 0.7% (95% CI: -0.2, 1.6%) and this effect dropped to 0.2% (95% CI: -0.4, 0.8%) when the outlying result from Moolgavkar's Cook County data was dropped (10). Furthermore, Burnett et al. (9) found a protective effect for CVA associated with PM₁₀ exposure but did not publish numerical results. Inclusion of these results would further reduce the pooled effect. Although this indicates that PM₁₀ exposure is not associated with an increase in overall hospital admissions for CVA, it is possible that this is too broad a category, as it includes hypertensive as well as occlusive strokes. When Linn et al. (12) limited their

analysis to occlusive strokes, they found a 1.3% (95% CI: 0.7, 1.9%) increase in admissions per 10 µg/m³ increase in PM₁₀. This appears consistent with the observed increase in IHD and suggests that studies including hypertensive strokes may underestimate of the effect of PM₁₀ exposure on CVA.

DSR was examined in only two studies, with substantially different results. Because the point estimates of the two studies do not fall within each other's confidence limits, pooling them seemed inappropriate. These studies do not provide sufficient basis for any conclusion as to the effects of PM₁₀ on conductive disorders of the heart.

In summary, CHF and IHD admissions appeared to be associated with PM₁₀ exposure with an increase of approximately 0.7% for an increase of 10 µg/m³ in the PM₁₀. The effect for DSR may have been of similar magnitude, but the data are too limited to draw firm conclusions. There appears to have been no relationship between CVA admissions and PM₁₀ exposure, but the conclusion might have been different if analyses were limited to occlusive strokes. The observed associations must be interpreted with caution. None of the results considered to this point included a full adjustment for covariates, particularly gaseous co-pollutants. No conclusions relevant to causality should be

drawn without careful consideration of these confounders.

Consideration of Potential Confounders

The factors associated with acute exacerbation of cardiovascular disease generally involve those that place acute stress on the heart or increase the coagulability of the blood. They can include short-term variations in diet, compliance with medications, exertion, physical stress, infections, and acute psychological stress. Time-series studies have the advantage over many other designs in that they limit relevant confounders to those that have a temporal correlation with air pollution. It is conceivable that any of the factors could be associated with exposure to particulate air pollution by virtue of the patients' relationship to weekly schedules, holidays, and other events related to the calendar. Adjustment for these types of cyclic patterns in the data should account for this source of confounding. Toward this end, well-conducted studies include an indicator for day of the week and a surrogate for seasonality in statistical models. Some studies have also included indicator variables for periods of known influenza epidemics. After these adjustments, gaseous pollutants and meteorologic factors remain the important potential confounders.

Table 3. Results from single pollutant models of PM₁₀ and hospital admissions for specific cardiovascular disease groups.

Study (first author)	Age range (years)	Time lag (days)	% Increase per 10 µg/m ³	95% CI
Congestive heart failure				
Schwartz, 1995 (7)	> 64	0	0.99	0.37,1.61
Morris, 1997 (2)	> 64	0	0.77	0.20,1.35
Wong, 1999 (7) ^a	All	0–3	4.80	3.20,6.42
Burnett, 1999 (9)	All	0–2	1.87	0.82,2.93
Linn, 2000 (17)	> 29	0	0.40	-0.19,0.99
Pooled (random effects)			1.60	0.40,2.81
Pooled (fixed effects) ^b			0.83	0.50,1.15
Ischemic heart disease				
Schwartz, 1995 (7)	> 64	0	0.56	0.16,0.96
Atkinson, 1999 (6)	> 64	0	0.97	0.15,1.80
Atkinson, 1999 (6)	0–64	0	1.33	0.25,2.41
Wong, 1999 (7)	All	0–3	0.70	-0.10,1.51
Burnett, 1999 (9) ^a	All	0–1	1.62	1.04,2.20
Linn, 2000 (17)	All	0	0.60	0.01,1.20
Pooled (random effects)			0.95	0.26,1.64
Pooled (fixed effects) ^b			0.68	0.41,0.96
Cerebrovascular accident				
Wong, 1999 (7)	All	0–1	0.30	-0.50,1.11
Linn, 2000 (17)	> 29	0	0.06	-0.43,0.55
Moolgavkar, 2000 (10)				
LA	> 20	0	0.59	-1.22,2.43
Cook ^a	> 64	0	6.00	2.69,9.42
Maricopa	> 64	0	0.50	-0.89,1.91
Pooled (random effects)			0.68	-0.24,1.61
Pooled (fixed effects) ^b			0.18	-0.21,0.57
Dysrhythmia				
Burnett, 1999 (9)	All	0	1.63	0.57,2.70
Linn, 2000 (17)	All	0	0.20	-0.39,0.79

^aStudy with the greatest contribution to heterogeneity among studies as determined by Cochran's Q statistic. ^bFixed effects models were run after excluding the study making the greatest contribution to heterogeneity among studies.

Inclusion of gaseous pollutants in models of exposure to particles and development of cardiovascular disease is controversial because of the co-linearity inherent among air pollutants and the concern that multipollutant models will artificially diminish the true effect of exposure to particulates. Conversely, to the extent to which the observed association of cardiovascular disease and exposure to particles is simply a reflection of the correlation between particles and these gaseous pollutants, failure to consider these pollutants will lead to inaccurate estimates of effect size.

In the published studies, adjusting for co-pollutants consistently reduced the PM₁₀ effect, as summarized in Table 4. This reduction ranged from 10 to 320%, depending on the study, the outcome, and the co-pollutants considered. The reduction ranges from 10 to 25% with an average of 18% in the four analyses by Schwartz and co-workers (1,4) whereas the adjustments performed by three groups of researchers (2,3,9,10) produced reductions of at least 35% with an average of 82% (after excluding the extreme value of 320%).

The reasons for this variation are not clear. Possibly, it reflects differences between the analytical methods used by Schwartz and co-workers (1,4) and those used by the others. None of Schwartz's analyses includes a full set of gaseous criteria pollutants. In his study of eight cities, Schwartz (8) did not perform adjustments but instead presented the magnitude of the PM₁₀ effect as a function of the correlation of PM₁₀ with different co-pollutants. He argued that the consistency of the PM₁₀ effect among cities with differing correlations between PM₁₀ and co-pollutants demonstrates low likelihood that those pollutants would drive the PM₁₀ effect. This somewhat unorthodox approach to assessing confounding yields an interesting observation, but it should be interpreted in light of the relatively small magnitude of documented PM₁₀ effects together with the complex, non-linear relationships among pollutants, meteorologic variables and cardiovascular disease. For example, the correlation between carbon monoxide and PM₁₀ during cold weather (conditions when the association of carbon monoxide with cardiovascular disease appears to be strongest) (2) may be far more important than the annual correlation. This seasonal correlation may be lost in a simple correlation for the entire study period.

In contrast to Schwartz's assertions about co-pollutants, Burnett et al. (3,9), Morris and Naumova (2), and Moolgavkar (10) all reported substantial reductions in the PM₁₀ effect when gaseous pollutants were considered. Morris and Naumova included all co-pollutants, while Moolgavkar evaluated two pollutant models. Burnett used two different approaches to considering the impact of co-pollutants on the observed effect of exposure to particles. One set of models used stepwise regression to select a set of gaseous pollutants for each health outcome using the Akaike information criteria, then generated a model based on those pollutants together with specific particulate matter metrics (9). Those results are presented in Table 5. In a second set of analyses, he allowed all the pollutants to compete equally in a stepwise model (9). In the second approach, none of the particulate measures was even included in models for CHF or IHD.

Other researchers considered co-pollutants but did not present comparable numerical results. Atkinson et al. (6) stated that the PM₁₀ effect was reduced in all two-pollutant models, particularly for sulfur dioxide but did not provide any numerical results. Wong's consideration of co-pollutants was limited to estimating the PM₁₀ effect when ozone and nitrogen dioxide were elevated. The PM₁₀ effect was higher in both cases [1.7% (95% CI: 0.7, 2.8%) during high ozone and 0.7% (95% CI: -0.5, 2.0%) during high nitrogen dioxide

Table 4. Results from models of PM₁₀ and hospital admissions for specific cardiovascular disease groups after adjustment for gaseous co-pollutants.

Study (first author)	Age range (years)	Diagnosis group	% Increase per 10 µg/m ³		95% CI	Effect ratio	Co-pollutants considered			
							CO	NO ₂	SO ₂	O ₃
Burnett, 1997 (3)	All	CVD	-0.28	-2.64,2.14	-0.12	x	x	x	x	
Schwartz, 1997 (4)	> 64	CVD	0.93	0.00,1.86	0.85	x				
Moolgavkar, 2000 (10)										
LA	20-64	CVD	0.70	-0.67,2.09	0.32	x				
LA	> 64	CVD	-0.90	-2.24,0.46	-0.56	x				
Cook	> 64	CVD	0.90	0.19,1.61	0.43		x			
Burnett, 1999 (9) ^a	All	DSR	1.04		0.64	x			x	
Schwartz, 1995 (7)	> 64	CHF	0.74	0.12,1.37	0.75	x				
Morris, 1997 (2)	> 64	CHF	0.39	-0.20,0.98	0.50	x	x	x	x	
Burnett, 1999 (9)	All	CHF	0.59		0.32	x	x			
Schwartz, 1995 (7)	> 64	IHD	0.50	0.06,0.93	0.89	x				
Schwartz, 1995 (7)	> 64	IHD	0.47	0.03,0.90	0.94			x		
Burnett, 1999 (9)	All	IHD	-0.12		-0.08		x	x		
Moolgavkar, 2000 (10)										
LA	> 64	CVA	-1.10	-2.74,0.56	-2.20	x				
Cook	> 64	CVA	0.90	-0.03,1.84	0.15		x			

x, includes co-pollutants included in the model. ^aBurnett et al. (9) did not include confidence intervals in these analyses. The multipollutant model was a stepwise model that considered all co-pollutants for inclusion.

Table 5. Results from single pollutant models of the association of PM_{2.5} with admissions for specific disease groups and overall cardiovascular admissions both before and after adjustment for co-pollutants.

Study (first author)	Age (years)	Particle size	Diagnosis group	% Increase per 10 µg/m ³		Effect ratio	
						Relative to PM ₁₀	Relative to single pollutant
Burnett, 1997 (3)	All	PM _{2.5}	CVD	2.81	-0.25,5.97	1.22	
Moolgavkar, 2000 (10)							
LA	20-64	PM _{2.5}	CVD	1.40	0.73,2.08	0.64	
LA	> 64	PM _{2.5}	CVD	1.70	1.00,2.40	1.06	
Burnett, 1997 (3)	All	PM _{2.5} ^a	CVD	-0.64	-4.33,3.20	2.27	-0.23
Moolgavkar, 2000 (10)							
LA	20-64	PM _{2.5} ^a	CVD	0.90	-0.08,1.89	1.29	0.64
LA	> 64	PM _{2.5} ^a	CVD	0.30	-7.77,9.08	-0.33	0.18
LA	20-64	PM _{2.5}	CVA	0.40	-0.90,1.72	0.67	
LA	> 64	PM _{2.5}	CVA	0.60	-0.30,1.51	1.20	
LA	> 64	PM _{2.5} ^a	CVA	-0.30	-1.47,0.88	0.27	-0.50
Burnett, 1999 (9)	All	PM _{2.5}	DSR	2.38	0.77,4.02	1.46	
	All	PM _{2.5} ^a	DSR	1.36	^b	1.32	0.57
	All	PM _{2.5}	CHF	2.58	0.76,2.58	1.38	
	All	PM _{2.5} ^a	CHF	0.53		0.90	0.21
	All	PM _{2.5}	IHD	3.14	2.12,4.18	1.94	
	All	PM _{2.5} ^a	IHD	0.90		-7.31	0.29
Burnett, 1997 (3)	All	PM _{10-2.5}	CVD	3.27	1.38,5.19	1.42	
	All	PM _{10-2.5} ^a	CVD	-0.64	-1.37,0.11	2.27	-0.19
Burnett, 1999 (9)	All	PM _{10-2.5}	DSR	2.02	-0.09,4.17	1.24	
	All	PM _{10-2.5} ^a	DSR	1.36		1.31	0.67
	All	PM _{10-2.5}	CHF	3.08	1.18,5.01	1.65	
	All	PM _{10-2.5} ^a	CHF	1.35		2.29	0.44
	All	PM _{10-2.5}	IHD	1.48	0.52,2.45	0.91	
	All	PM _{10-2.5} ^a	IHD	-0.13		1.07	-0.09

^aAdjusted for co-pollutants. ^bBurnett et al. (9) did not provide confidence intervals for results of multipollutant models.

compared to 0.6% in the baseline model], suggesting a possible interaction between PM_{10} and ozone.

Overall, these results indicate that the confounding effect of other pollutants can explain a portion of the observed association between particles and cardiovascular disease, potentially a major portion. Given the relationship among these pollutants, fully isolating this confounding effect will be extremely difficult. Perhaps ongoing analyses looking at large numbers of cities will shed further light on this controversy.

Consideration of Temperature

Meteorologic factors are key covariates to consider in time-series studies and all the studies included in this analysis made some effort to do so. Temperature is chief among these weather-related variables considered in the studies. There is substantial evidence that extreme temperatures, particularly low temperatures, substantially increase the risk of acute cardiac events (16–18). A full consideration of temperature in a time-series analysis should take into account this U-shaped relationship. In addition, there is some evidence in studies of other relationships between air pollution and cardiac events that temperature may act as an effect modifier (19–21).

All studies listed in Table 1 included adjustments for temperature. In most cases, consideration of temperature was limited to including it as a covariate. Most studies sought to include the nonlinear nature of this association by using either a polynomial model or some form of piecewise model for temperature. Because of the clear evidence of increased cardiovascular morbidity during extreme weather, particularly cold weather, the potential interaction between PM_{10} and temperature is of interest.

A small number of studies considered this interaction using a variety of approaches. In London, England, Atkinson et al. (6) found that the PM_{10} effect was strongest in the lowest temperature tertile but did not provide numerical details of their analysis. In Hong Kong, Wong et al. (7) found that the effect of PM_{10} disappeared during the cold season, but, in this tropical climate, the cold season is the more comfortable time of year. In Tucson, Arizona, Schwartz (4) found that the PM_{10} effect was reduced during periods of warm temperature, but not significantly so. In Los Angeles, California, Linn et al. (11) found that the PM_{10} effect was stronger in winter than in spring for CVD [0.96 (95% CI: 0.48, 1.43) vs -0.3 (95% CI: -1.0, 0.42)]. The effect for CVA was stronger in summer than in winter [1.2 (95% CI: -0.6, 3.2) vs -0.2 (95% CI: -1.2, 0.81)], but the statistical power was clearly limited with respect to CVA. None of those studies was conducted in a city with severe winters and

only one was conducted in a temperate climate. Given the known relationship between cold temperatures and cardiovascular disease, the possibility of increased effects in winter warrants further investigation.

Effect of Particle Size

Data on the effect of $PM_{2.5}$ were limited. The only two cardiovascular disease morbidity studies that considered this association explicitly yielded inconsistent results. The single-pollutant models, particularly those of Burnett and co-workers (3,9), suggested that $PM_{2.5}$ might have a greater effect than PM_{10} . For the combined CVD admissions, the ratio of the $PM_{2.5}$ effect to the PM_{10} effect ranged from 0.67 to 1.65 for the single-pollutant models. This was even clearer from the analysis of specific outcomes by Burnett which yielded the effect ratios ranging from 1.38 to 1.94. Surprisingly, Burnett and co-workers (3,9) also found that the effect for coarse fraction (PM_{10} minus $PM_{2.5}$) was greater than for the PM_{10} alone when he looked at specific cardiovascular outcomes. In almost all cases, adjustment for co-pollutants dramatically reduced the effect size with reductions ranging from 33 to 150%. These results clearly support efforts to consider the fine particle fraction in future studies and provide further evidence of the importance of considering co-pollutants in these studies.

Summary

Time-series studies consistently show that PM_{10} is associated with overall hospital admissions for cardiovascular disease, but a careful review suggests that analyses at this level of aggregation do not accurately characterize the relationship. The magnitude of this effect is highly variable and depends on the specific disease category being considered, the time lag used in the analysis, and the role of co-pollutants.

These studies were inconsistent with respect to the choice of time lags used in the analysis. Selecting the time lag with the maximum effect could result in an overestimation of the true effect size. This is evident in a comparison of studies that depended on post hoc rather than a priori selection of the time lag to be considered. In two of three age groups for combined cardiovascular disease and in three of four categories for specific diseases, the largest effect was associated with studies using post hoc selection of time lags. It would be preferable for researchers to base the selection of time lag or time lags on a priori hypotheses. To the extent possible, selection of time lag should be based on an understanding of the physiologic basis for the adverse cardiovascular effect of air pollutants.

Perhaps the greatest area of confusion and controversy related to the published studies involves adjustment for co-pollutants.

Most researchers find that adjustment for co-pollutants tends to substantially reduce the effect of particles, but the importance of this reduction is controversial. Opinions range from the perspective that the PM_{10} effect may be entirely the result of co-pollutants and that PM_{10} is simply a surrogate for these pollutants (10,22) to the assertion that the other extreme that the PM_{10} effect is independent of co-pollutants (8). It is essential that future studies consider co-pollutants in an effort to shed further light on this apparent inconsistency.

Other covariates may also influence the relationship between PM_{10} and cardiovascular morbidity. Specifically, these studies suggest that either high or low temperature may modify the association of PM_{10} with hospital admission for cardiovascular disease. This interaction should also be considered in future studies. Temperature may also interact with other covariates, particularly carbon monoxide. Failure to consider these interactions may result in inaccurate estimates of the PM_{10} effect.

All persons represented by individual hospital admissions have serious underlying cardiovascular disease. It is likely that most of them would eventually be admitted to the hospital for acute disease. An association between air pollution and cardiovascular disease, to the extent that it is causal, means that the acute stress of air pollution either led to hospital admissions that would never have occurred otherwise or only influenced the timing of hospital admissions that would have occurred without a change in air quality. This is essentially the same issue that has been evaluated as a harvesting effect in the mortality studies. The extent to which the particle effect reflects a simple short-term shift in the timing of admissions has a major impact on any assessment of the public health impact of these pollutants. None of these morbidity studies explicitly considered the effect of harvesting. Future studies should do so.

Future research on the association between particulates and acute cardiovascular disease should focus on specific cardiovascular outcomes and should consider four key questions: a) To what extent do co-pollutants explain this association? b) Do temperature or other seasonal factors modify the particle effect and how might their interaction with other covariates influence the estimated particle effect? c) Do particle size and chemistry influence this relationship? d) To what extent does the observed effect reflect "harvesting" of pending admissions?

REFERENCES AND NOTES

1. Schwartz J, Morris R. Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. *Am J Epidemiol* 142:23–35 (1995).

2. Morris RD, Naumova EN. Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. *Environ Health Perspect* 106:649–653 (1998).
3. Burnett RT, Cakmak S, Brook JR, Krewski D. The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. *Environ Health Perspect* 105:614–620 (1997).
4. Schwartz J. Air pollution and hospital admissions for cardiovascular disease in Tucson. *Epidemiology* 8:371–377 (1997).
5. Prescott GJ, Cohen GR, Elton RA, Fowkes FG, Agius RM. Urban air pollution and cardiopulmonary ill health: a 14.5 year time series study. *Occup Environ Med* 55:697–704 (1998).
6. Atkinson RW, Bremner SA, Anderson HR, Strachan DP, Bland JM, de Leon AP. Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. *Arch Environ Health* 54:398–411 (1999).
7. Wong TW, Lau TS, Yu TS, Neller A, Wong SL, Tam W, Pang SW. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. *Occup Environ Med* 56:679–683 (1999).
8. Schwartz J. Air pollution and hospital admissions for heart disease in eight U.S. counties. *Epidemiology* 10:17–22 (1999).
9. Burnett RT, Smith-Doiron M, Stieb D, Cakmak S, Brook JR. Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. *Arch Environ Health* 54:130–139 (1999).
10. Moolgavkar SH. Air pollution and hospital admissions for diseases of the circulatory system in three U.S. metropolitan areas. *J Air Waste Manag Assoc* 50:1199–1206 (2000).
11. Linn WS, Szlachcic Y, Gong H Jr, Kinney PL, Berhane KT. Air pollution and daily hospital admissions in metropolitan Los Angeles. *Environ Health Perspect* 108:427–434 (2000).
12. Gwynn RC, Burnett RT, Thurston GD. A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. *Environ Health Perspect* 108:125–133 (2000).
13. Johnson NL, Kotz S, Balakrishnan N. Extreme value distributions. In: *Continuous Univariate Distributions, Vol 2* (Johnson NL, Kotz S, Balakrishnan N, eds). New York: John Wiley and Sons, 1995:1–112.
14. Fischer ES, Whaley FS, Krushat M, Malenka DJ, Fleming C, Hsia DC. The accuracy of Medicare's hospital claims data: progress has been made, but problems remain. *Am J Public Health* 82:243–248 (1992).
15. Baron JA, Lu-Yao G, McLerran D, Fisher ES. Internal validation of medicare claims data. *Epidemiology* 5:541–544 (1994).
16. The Eurowinter Group. Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. *Lancet* 349:1341–1346 (1997).
17. Wilmhurst P. Temperature and cardiovascular mortality. *Br Med J* 309:1029–1030 (1994).
18. Seretakis D, Lagiou P, Lipworth L, Signorello LB, Rothman KJ. Changing seasonality of mortality from coronary heart disease. *JAMA* 278:1012–1014 (1997).
19. Shumway RH, Azari AS, Pawitan Y. Modeling mortality fluctuations in Los Angeles as functions of pollution and weather effects. *Environ Res* 45:224–241 (1988).
20. Katsouyanni K, Pantazopoulou A, Touloumi G, Tselepidaki I, Moustris K, Asimakopoulos D, Pouloupoulou G, Trichopoulos D. Evidence for interaction between air pollution and high temperature in the causation of excess mortality. *Arch Environ Health* 48:235–242 (1993).
21. Yang L, Zhang W, He HZ, Zhang GG. Experimental studies of combined effects of high temperature and carbon monoxide. *J Tongji Med Univ* 8:60–65 (1988).
22. Moolgavkar SH, Luebeck EG. A critical review of the evidence on particulate air pollution and mortality. *Epidemiology* 7:420–428 (1996).