Health and Respirable Particulate (PM_{10}) Air Pollution: A Causal or Statistical Association?

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Numerous studies have reported weak but statistically significant acute health effects of particulate air pollution. The associations are observed at levels below the current U.S. standard of 150 μg/m^3 (24 hr). Health effects include acute increased mortality from cardiopulmonary conditions and acute morbidity such as hospital admissions for related diseases. We reviewed recent epidemiology studies to evaluate whether criteria for causality are met, and we conclude that they are not. The weak associations are as likely to be due to confounding by weather, copollutants, or exposure misclassification as by ambient particulate matter (PM). The results from the same metropolitan areas are inconsistent, and PM explains such a small amount of the variability in mortality/morbidity that the association has little practical significance. Finally, experimental chamber studies of susceptible individuals exposed to PM concentrations well above 150 μg/m^3 provide no evidence to support the morbidity/mortality findings. None of the criteria for establishing causality of the PM/mortality hypothesis are clearly met at ambient concentrations common in many U.S. cities.
Key words: air pollution, air quality standards, causality, confounding, ecologic time–series studies, epidemiology, morbidity, mortality, particulate matter, weather. *Environ Health Perspect* 104:838–850 (1996)

Particulate matter (PM) refers to discrete particles in ambient air that exist as either solid or liquid droplets. There has been considerable interest in the potential health effects of particles 10 μm or less in aerodynamic diameter (PM_{10}). These particles are respirable and 80% or more will deposit somewhere in the respiratory system. Sources of PM_{10} in the environment include automobile and diesel exhaust, power plants, incinerators, and combustion of other fossil fuels. Fugitive dust (e.g., from farming and road construction) and wind blown dust from geological material (e.g., agriculture) are major sources of PM_{10}, often up to 50% of the average mass concentration.

The current U.S. air quality standard for PM_{10} is 150 μg/m^3 for 24 hr. There is also an annual PM_{10} standard of 50 μg/m^3, which is not considered here. Since the promulgation of this standard in 1987, a number of epidemiology studies have suggested acute adverse health effects caused by PM_{10} pollution at concentrations below the 24-hr standard. The association with PM_{10} pollution includes such health indices as increased acute mortality and increased respiratory morbidity (e.g., increased hospital admissions and emergency room visits and reduced lung function test performance). The alleged causal association has gained worldwide notoriety and is considered quite serious in the press, scientific circles, and health organizations. Reducing ambient PM_{10} concentrations based on the findings from epidemiology studies will have substantial costs to society; therefore, it is important to examine the science behind the data and to evaluate how well the results meet established criteria for assessing causality.

This report critically reviews the findings from time–series epidemiologic studies of PM_{10} and acute mortality and hospital admissions. Because the focus of this paper is on short-term acute effects and whether the 24-hr standard is adequate, studies of chronic effects of PM are not included.

Because correlation does not prove causation in observational studies, it is necessary to evaluate these associations using Hill's criteria (*1*). We also consider the role of confounding and bias and how they can obscure the true relationship. Studies included in this review have primarily examined the health effects of PM_{10}, although several studies involving other measures of PM [i.e., total suspended particulate (TSP) and coefficient of haze (COH)] have also been included. A recent review by Pope et al. (*2*) suggests that the burden of proof regarding a causal association has shifted to those who maintain that no causal inference is possible and requires them to explain the consistency and coherence of the evidence and put forward an alternative hypothesis. It is the purpose of this paper to evaluate the hypothesis that ambient PM levels less than 150 μg/m^3 (24-hr average) are causally associated with increased acute mortality and morbidity and to assess the evidence to determine whether the associations are statistical or whether they satisfy the criteria for establishing causality.

Assessing Ambient PM_{10} Health Effects

The interpretation for a causal association between acute health endpoints and PM_{10} is based on correlation studies, which in epidemiology are called ecological studies because no measures of personal exposure are available (only group exposure data). For acute mortality and morbidity, time–series studies using a 24-hr sampling period for PM is the relevant type of study.

In time–series studies, daily mortality (or morbidity) from a metropolitan area is correlated with PM_{10} concentration of the same or previous days. The causal hypothesis is that patients with chronic respiratory/cardiovascular diseases die prematurely (or show increased morbidity) because of the added stress of increased air pollution. PM_{10} concentrations are measured by one (sometimes several) ambient air sampler located in the metropolitan area. Other variables that may also cause increased mortality/morbidity are adjusted for in the statistical model and are therefore said to not confound the association. Potential confounders include weather (e.g., hot and cold temperatures), season, influenza epidemics, and other copollutants (e.g., SO_2, ozone, etc.). Table 1 summarizes selected time–series mortality studies.

Estimates of the Magnitude of Association between PM_{10} and Mortality

The relative risk of death or illness associated with PM can be expressed as a percent increase per unit increase in PM. Schwartz (*13*) estimates that a 50 μg/m^3 increase in TSP is associated with about a 3% increase in mortality; this is based on a meta-analysis of time–series studies. Ostro (*14*) estimates that a mean increase of 50 μg/m^3 in PM_{10} is associated with a mean increase in mortality of 4.8% (1.55–7.45% as lower and upper bounds, assuming a linear relationship). There are studies that show no apparent association of mortality/morbidity, i.e., the relative risk (RR) is less than one, and the association with PM is only observed in some analyses, seasons, models, etc.; these studies have not been included in the estimates described above.

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This work was partially funded by the Institute of Petroleum, London, England.
Received 27 October 1995; accepted 11 April 1996.

Evaluation of Epidemiology Studies of PM_{10} According to Hill's Causal Criteria

A major issue in the discussion of PM_{10} health effects is whether the observed associations demonstrate cause–effect relationships or are merely statistical associations that may be noncausal in nature. There are a number of accepted criteria in epidemiology to judge whether an association is causal, but only one criteria is definitive: the cause must precede the effect. It is not necessary that all criteria be met to support causality, and there are no statistical methods that can be used to establish causality.

For the purposes of this paper, Hill's causal criteria (*1*) will be used. These criteria include: temporality, consistency, strength of association, exposure-response (often referred to as dose-response), specificity, coherence, and plausibility. For the association to be qualitatively and quantitatively valid, the data must be largely free of bias; therefore, this issue is considered separately. Arguments for and against each of the causal criteria in the context of the studies referenced in Tables 1 to 3 are summarized below.

Temporality

Does cause precede effect? Are the time relationships plausible?

For. In different studies, death is correlated with PM concentrations ranging from lag periods of the same day to up to 4 previous days (the lag period refers to the time interval between when the exposure measure is taken and when the health outcome occurs). Effects are often adjusted for weather by using mean temperatures with lag periods similar to those of PM exposure. The event is acute mortality or morbidity, so exposure occurs before death (or hospitalization) except when there is no lag for 24-hr PM_{10} concentrations, and then the event and exposure take place the same day. These short lag times suggest PM may be lethal for persons already near death and who would have soon died even without increased PM exposure.

Against. When PM concentrations for the same day are used, it is not clear that there is enough time for exposure-related deaths to occur, especially if the deaths occurred before the full day's exposure is completed. Except for persons already near death, it is not obvious that low-level PM_{10} concentrations could cause such quick and severe effects. While deathbed effects may have an appropriate time frame, this type of death cannot explain all the deaths attributed to PM (*29*).

Increased susceptibility to infectious diseases such as influenza or pneumonia is a possible cause of PM-increased mortality among elderly people who have cardiorespiratory disease (*30*). Because these diseases develop and evolve over days and weeks, a 24–120-hr time frame is too short to meet this criterion (*29*).

Table 1. Summary of selected time–series mortality studies: susceptible populations and selected causes of death

Location, dates (reference)	PM measurement (lag)	Mean concentration, µg/m³ (range)	Change in relative risk per 50 µg/m³ change in PM (95% C.I.)				
			Total mortality	CVD	Respiratory	Cancer	≥65 Years
Chicago, IL, 1985–1990 (*3*)	PM_{10} (0–2 days)	37 (3–365)	F: 1.041 (1.001–1.082)	1.033 (0.981–1.087)	1.116 (0.988–1.262	1.084 (1.012–1.163)	1.0714 (1.030–1.124)
Salt Lake County, UT 1985–1990 (*3*)	PM_{10} (0–2 days)	48 (9–194)	No effects in any season	—	—	—	0.988 (0.945–1.030) W: 1.01 (0.96–1.07) Sp: 1.02 (0.93–1.11) S: 0.99 (0.87–1.11) F: 0.94 (0.85–1.03)
Utah County, UT, Apr 1985–1992 (*4*)	PM_{10} (0–4 days)	Similar to Pope et al. (*5*)	1.04 (0.98–1.10)	1.13 (1.04–1.24)	1.03 (0.86–1.25)	—	—
Utah Valley, UT, Apr 1985–Dec 1989 (*5*)	PM_{10} (0–4 days)	47 (1–365)	1.076 (1.044–1.110)	1.094 (1.019–1.74)	1.198 (1.035–1.386)	—	—
Birmingham, AL, 1985–1988 (*6*)	PM_{10} (0–4 days)	48 (98% = 80)	1.055 (1.01–1.10)	1.085 (1.02–1.55)	1.08 (0.87–1.375)	—	Nonrespiratory, non-CVD 1.03 (0.97–1.09)
Birmingham, AL, 1988–1993 (*7*)	PM_{10} (0–3 days)	39 (5%–95%) (14–81)	1.00 (0.95–1.05)	NS (<1.0)	0.94 (0.85–1.03)	—	—
Philadelphia, PA, 1973–1980 (*8,9*)	TSP (0–1 day)	77 (5–95%) 37–132	1.068 (1.038–1.099)	1.047 (1.029–1.066)	COPD 1.093 (1.002–1.193) PN 1.052 (0.983–1.127)	1.018 (0.993–1.044)	<65 = 1.014 (0.993–1.034); ≥65 = 1.047 (1.030–1.063)
Philadelphia, PA, 1973–1990 (*10*)	TSP	69 (5–95%) (32–120)	Only significant in W (≥65 years) and Sp (≤65 years)	0.997 (>65 years) 1.02 (<65 years)	PN 1.020 (≥65 years) COPD 0.994 (≥65 years)	1.006 (≥65 years)	Other 1.013 (≥65 years)
São Paulo, Brazil, May 1990–Apr 1991(*11,12*)	PM_{10} (0–2 days for <5 years, 0–1 day for ≥65 years); copollutants include SO_2, CO, NO_x, O_3	82	—	—	<5 years = 0.740 (0.370–1.479) (only significant association was with NO_x)	—	~1.065 with copollutants

The range equals minimum to maximum unless (%) = value at percentiles.
F, fall; W, winter; Sp, spring; S, summer; TSP, total suspended particulate; CVD, cardiovascular disease; NS, not significant; PN, pneumonia.
*p <0.05.

A third major possible cause of death due to PM is exacerbation of underlying cardiac or pulmonary disease. Chronic obstructive pulmonary disease (COPD) is the most common cause of nonmalignant respiratory disease. If ambient PM caused acute death from COPD, one would expect smoking one or several cigarettes a day to be quickly lethal to COPD patients due to the PM levels generated during cigarette smoking, which are many times higher than ambient PM levels. Although many susceptible patients with cardiorespiratory disease smoke until late in their disease, smoking does not result in acute hospital admission (*29*).

Cardiovascular disease (CVD) deaths may be misclassified as respiratory deaths (*29*). When such misclassification occurs, the time course for respiratory disease death does not appear to be appropriate to the 0–5 day lags of time–series studies.

The time period also may not be appropriate for morbidity-related effects. For example, data on hospital admissions of asthmatics also suggest that the lag periods may not be appropriate. Canny et al. (*30*) reported that children brought to the emergency room for acute asthma begin to have symptoms about 41 hr before arrival, suggesting that the 24–48 hr lag time is too restrictive (*30*). The duration of symptoms was longer than 72 hr for 16% of the patients. Major precipitating causes included respiratory infection (75%) and allergen exposure (7%) (*30*).

Table 2. Respiratory morbidity: selected time–series studies of hospital admissions and particulate air pollution

Location, dates (reference)	Health effects	PM, % change (95% CI)[a]	Comments
Steubenville, OH, 1974–1977(*15*)	All respiratory diseases	Δ 50 μg/m^3 TSP, +1.5%	Explains only 1% of variation; no significant association
Southern Ontario, 1976–1983 (*16*)	Total admissions Respiratory admissions Asthma Nonrespiratory conditions	0.13[b] (not significant) Not significant Not significant Not significant	S: SO_4 and temperature account for 5% variance in respiratory or asthma admissions; significant association with respiratory admissions and O_3, SO_4, SO_2, and temperature W: all respiratory (but not asthma) admissions associated with SO_2
Vancouver, 1984–1986(*17*)	Asthma	No association with COH	S: total visits associated with temperature; ages 15–60: asthma and respiratory admissions associated with SO_2 and SO_4
5 German cities, 1983–1987 (*18*)	Croup	Δ70 μg/m^3 NO_2, +28% Δ70 μg/m^3 TSP, +27%	No pollutant associated with obstructive bronchitis
Seattle, WA, Sept 1989–Sept 1990 (*19*)	Asthma	<65 years: Δ50 μg/m^3 PM_{10}, +20% (6%–36%) >65 years: no association	Ozone and SO_2 not significant
Barcelona, Spain, 1985–1989 (*20*)	COPD	Δ25 μg/m^3 BS; S, +0.6% Δ25 μg/m^3 BS; W, +2.3%	S, W: SO_2 significant
Birmingham, AL, 1986–1989 (*21*)	>65 years Pneumonia COPD	Δ100 μg/m^3 PM_{10}, +19% (7%–32%) +27% (8%–50%)	Weaker association with O_3; no evidence of a threshold
Detroit, MI, 1986–1989 (*22*)	>65 years Pneumonia COPD	Δ32 μg/m^3 PM_{10}, +4% (1%–6%) +7% (3%–11%) Δ = 75%–25%	Pneumonia and COPD hospital admissions associated independently with both PM_{10} and O_3; O_3 association is strongest. No significant association with asthma
New Haven, CT, 1988–1990 (*23*)	>65 years Respiratory disease	Δ50 μg/m^3 PM_{10}, +6% (0%–13%)	PM_{10} followed by O_3 showed strongest association in hospital admission for elderly at concentrations below current guidelines
Tacoma, WA, 1988–1990 (*23*)	>65 years Respiratory disease	+10% (3%–17%)	

COH, coefficient of haze; BS, black smoke; TSP, total suspended particulate; COPD, chronic obstructive pulmonary disease; S, summer; W, winter.
[a]Association with PM as % change in morbidity per Δ in PM (95% CI).
[b]Only correlation for total admissions.

Consistency

Is the association observed repeatedly by different persons and in different places and circumstances? Is the association observed by different authors analyzing data from the same locations? Most importantly, are similar responses observed with study designs having personal exposure measurements rather than grouped exposure data? That is, are results of individual-level studies similar to those of ecologic studies?

Confounding from weather and other pollutants is a major concern because these factors are present to some extent in all locations and may consistently bias the association. Whether bias and confounding are adequately controlled is discussed in a separate section on bias.

For. Consistency is a major argument favoring a causal association. The associations of PM and mortality are consistently positive, statistically significant, and of similar magnitude as reported by different authors in different cities, different seasons, and in different pollutant mixtures (*13,14*).

Against. Whether there is a valid pattern of consistency is not known for two reasons. First, separate analyses of the same populations by different investigators have produced inconsistent results that are contrary to those of the original authors. Second, results from studies using different study designs (i.e., individual-level studies) do not support the results of the ecologic time–series mortality studies. Each of these issues is discussed below.

Additional analyses of time–series studies at five locations (Steubenville, Ohio; Philadelphia, Pennsylvania; London, England; Birmingham, Alabama; and two adjacent counties in Utah) by different authors have produced results inconsistent with those of the original reports. Samet et al. (*32*) replicated the findings of original authors for three of these locations (Philadelphia, Utah Valley, and Birmingham) but did not attempt an independent analysis (i.e., statistical models and variables different from those originally used were not evaluated). If the PM/mortality association is consistent, one would expect as a minimum that the results by different authors analyzing similar data from the same locations would be similar. The examples from these five locations, as

Table 3. Respiratory morbidity: selected time-series studies of respiratory symptoms, peak expiratory flow (PEF), and particulate air pollution

Location (reference)	Population	Health Effects	Association	Comment
Tucson, AZ (*24*)	Asthmatics	Daily symptoms and PEF	Gas stoves, humidity, temperature, pollen, ozone	TSP was significant only for productive cough among asthmatics in late winter and early spring
	Airway obstruction symptoms		Pollen, temperature	
	Allergies		Pollen, temperature	
	Normal		No association	
Utah Valley, UT (*25*)	34 symptomatic children	ΔPEF % and URT/LRT symptoms (high vs. low tertile)	ΔPEF% –4.1 vs. +0.7	PM_{10} range = 11–195 μg/m^3. Statistically significant association between reduction in PEF and PM_{10}
	21 asthmatic patients (8–72 years of age)		ΔPEF% –1.4 vs. +0.6	for both groups and between symptoms and PM_{10} for school children
Utah Valley, UT (*26*)	39 symptomatic students, grades 5, 6	Daily ΔPEF, cough, and LRS/URS (high vs. low tertile)	ΔPEF% –0.8 vs. +1.2	Authors conclude strongest asssociations with symptomatic children using 5-day moving
	40 asymptomatic students, grades 4,5		ΔPEF% –0.9 vs. +1.4	Exposure response suggests no trend for URT and LRT for the asymptomatic group and no biologically significant reduction in PEF for either group
Southern California (*27*)	321 nonsmokers >18 years with ≥1 child in school	Daily URT and LRT symptoms; eye irritation; risk ratio= estimate of risk for COH	LRT 1.11 (0.97–1.3) URT 1.05 (0.96–1.16)	Significant association between LRT symptoms, O_3, sulfate, and gas stove in home; no significant association with COH
The Netherlands (*28*)	112 children, 7–12 years of age	URT/LRT symptoms; risk ratio=estimate of effect for log PM_{10}	Cough 0.81 URT 0.76 LRT 0.85	No apparent association of symptoms with PM_{10}, log BS, or log SO_2

BS,black smoke; COH, coefficient of haze; LRS, lower respiratory symptoms; LRT, lower respiratory tract; pphm, parts per hundred million; ΔPEF, change in peak expiratory flow; URS, upper respiratory symptoms; URT, upper respiratory tract.

summarized below, show dissimilar and inconsistent results by different authors, indicating the results are dependent on the model used.

Steubenville, Ohio. Schwartz and Dockery (*33*) reported that in Steubenville a 100 μg/m^3 increase in TSP was associated with a 4% increase in mortality the next day. SO_2 was also associated with increased mortality when SO_2 was the only exposure variable in the model. Only the association with TSP remained when both TSP and SO_2 were in the model. Moolgavkar et al. (*34*) attempted to replicate these results and found that TSP was not significant when SO_2 was included in the regression model. In addition, the results were not robust, showing variable findings from small perturbations in the data and when different statistical models were used.

Philadelphia, Pennsylvania. A similar situation of conflicting results were observed from five studies conducted in Philadelphia, Pennsylvania. Schwartz and Dockery (*8*) reported an increased risk of death between 1973 and 1980 associated with a 50 μg/m^3 increase in TSP for COPD (9%), followed by total mortality (6.8%), pneumonia (5.2%), CVD (4.7%), and total mortality among persons 65 years of age or older. Li and Roth (*10*) added 10 more years of data to the Schwartz and Dockery (*8*) dataset, and used a wide variety of statistical models, air pollutants (TSP, SO_2, O_3), and weather factors (temperature, relative humidity, barometric pressure, precipitation). Unlike the earlier results (*8*), TSP was not significantly associated with any cause-specific mortality, and some estimated risks were less than 1.0, even with only TSP in the model. They concluded that the pollution/mortality association is dependent on the statistical model and varies across age groups, causes of death, and season. For nearly every positive result, there is a negative or nonsignificant result pointing in the opposite direction.

Moolgavkar et al. (*35*) also analyzed data from Philadelphia for the years 1973–1988 [8 more years than Schwartz and Dockery (*8*) and 2 less years than Li and Roth (*10*)] and found that mortality was associated with the highest temperature quintiles in the summer and the lowest temperature quintiles in the other three seasons. Moolgavkar et al. (*35*) concluded that, because the copollutants were so highly correlated, it was not possible to single out any specific pollutant effect. Wyzga and Lipfert (*36*) reported on 18 years of data for Philadelphia. The mortality associations with ozone and TSP were greater when O_3 and TSP concentrations were lowest, leading them to suggest that time–series "analyses of daily mortality provide no direct information on changes but might occur as a result of imposition of further pollution controls." Li and Roth (*7*) reported mixed results. There was a significant association between PM_{10} and noncardiovascular deaths, but only when no other pollutants were in the model. There was no PM_{10} association with CVD.

In commenting on the first three of the Philadelphia analyses and their divergent results (and after replication in the Health Effects Institute analysis), Samet (*37*) concurs with the interpretation of Moolgavkar et al. (*35*) and concludes that "assessment of the causality of associations should not rest solely on model results."

London, England. At least 21 analyses of weather/pollution and mortality in London have been tabulated. Although significant health effects were reported, the role attributed to British smoke (BS) versus SO_2 depended on the statistical model. For the winters 1958–1972, various interpretations of BS and SO_2 effects include the following (*38*): 1) association is with BS but not with SO_2; 2) BS and SO_2 predict mortality equally well and appear to act identically; 3) BS is more strongly associated with mortality than SO_2, but both are significant when considered alone; and 4) high correlations (0.79–0.96) between BS and SO_2 make it impossible to distinguish their separate effects.

Ito et al. (*38*) did their own analysis and added acid aerosols to the pollutant mixture

of BS and SO_2 as summarized above; they found that temperature was the strongest influence in all seasons and that all three pollutants were significant. However, no particular pollutant effect could be determined because of pollutant collinearity and lack of quantitative information about measurement error (both analytical error and errors in spatial representatives of the samplers in relation to the exposure of population).

Lippmann and Ito (*39*) reanalyzed the London mortality data (1965–1972) using a new approach and attempted to separate the confounding effects of temperature, season, and ambient pollution levels. They did this by separating days into one or two naturally occurring temperature ranges in each season. Within each season there was minimal confounding from temperature. The strongest correlations were with SO_2 and H^+ (not BS) depending on season. BS was least significant in winter (H^+ was most significant) and summer (SO_2 most significant). In this analysis, a new pollutant (H^+) has been added to the list of potential confounders, and PM was the least important pollutant.

Utah. Three studies were conducted in Utah, with different results for each. Styer et al. (*3*) found no evidence that PM_{10} contributed to excess mortality among the elderly (relative risk [RR] = 0.99) in Salt Lake County, Utah. In contrast, Pope et al. (*5*) reported that for nearby Utah County there was an excess of predicted deaths of 20%, 9%, and 7.6% per 50 μg/m^3 increase in PM_{10} for respiratory disease, CVD, and total mortality, respectively. Lyon et al. (*4*) added 2 more years of data from Utah County and attempted to test the PM_{10}/mortality hypothesis more rigorously than previous studies. They found no apparent association between increased morality and PM_{10} ambient concentrations when stratified by year or season. When an association with PM_{10} was observed, it was often in seasons or years when PM_{10} concentrations were low rather than high. Further, the RR was highest among the least susceptible age group (15–59). They concluded the associations are not causal but are related to an uncontrolled confounder.

The reasons for the differences in findings between counties in Utah are unclear. The differences do not seem to be due to differences in exposure between study areas because PM levels in the two counties were similar (average of 47 μg/m^3 for Utah County versus a median of 48 μg/m^3 for Salt Lake County). The difference is also not related to increased statistical power from greater numbers of deaths in Utah versus Salt Lake County because average mortality was higher for a 16-month-longer time period in Salt Lake County than in Utah County (*3*).

Birmingham, Alabama. There are three different analyses of data from Birmingham: the original study by Schwartz (*6*), the replication by Samet et al. (*32*) using similar methods, and the third by Li and Roth (*7*) using different methods. For the years 1985–1988, Schwartz (*6*) found a significant association between PM_{10} and total mortality and cardiovascular disease (RRs per 100 μg/m^3 increase in PM_{10} exposure were 1.11 and 1.16, respectively). There were statistically nonsignificant increases with chronic lung disease and all causes other than respiratory or cardiovascular (RR of 1.16 and 1.06, respectively). The exposure–response (E-R) trend was monotonic with no evidence of a threshold down to 20 μg/m^3.

Li and Roth (*7*) analyzed Birmingham data for the years 1988–1993 and found virtually no association of PM_{10} and mortality, except when maximum temperature was used to control for weather. When a more appropriate variable for temperature (deviation from threshold) was used, the association disappeared. Because the association of temperature with mortality is not linear (e.g., a U-shaped relationship), maximum temperature or mean temperature as a linear term is incorrect according to Li and Roth (*7*). The only significant associations with PM_{10} were not for cardiovascular disease, but noncardiovascular and nonrespiratory deaths. They also found that the results were not robust, but sensitive to lag times, models, and temperature variables used in the analyses.

Other negative studies. Several studies have not found an association between 24-hr ambient PM levels and mortality. Derriennic et al. (*40*) evaluated the association of SO_2 and suspended particulates on mortality in two French cities, Marseilles and Lyon, and found no apparent association of suspended particulate with any cause of death. In Beijing, China, SO_2 and particulate concentrations are commonly much higher than those found in industrialized countries (*41*). SO_2 showed a stronger association with mortality than did TSP, and the association with TSP was not present in the winter season. These data are contrary to the PM/acute mortality hypothesis.

Are Results Consistent When Using Different Study Designs?

An often overlooked point about consistency is that results should be supported by studies using different study designs and having different potential biases. Because of inherent biases in ecologic risk estimates from group exposure data (*42–46*), risk must be independently checked using individual-level study designs having personal exposure measurements. For the PM/mortality hypothesis, experimental or chamber studies provide almost the only available data that meet this requirement. As discussed elsewhere, under the coherence criterion, the experimental studies do not show the risk from PM_{10} exposure suggested by the time–series studies of mortality and hospital admissions.

Strength of Association and Exposure-Response (E-R)

Is the magnitude of the association large? Is an E-R trend observed? Evaluating cause-effect based on weak associations (small differences in risk ratios between high and low exposures) is problematic because bias and confounding can more easily account for a weak association than a strong one (*47*). PM_{10} effects are weak, as risk ratios between high and low exposures (even differences of 100 μg/m^3) are generally less than 1.20. Wynder (*48*) has defined risk ratios <1.5–2 as weak. Higher mortality at higher exposure levels is evidence that there is an E-R trend. The greater the regression coefficient estimating the trend, the stronger the association.

For. The RRs for total mortality are likely to underestimate the true risk for the susceptible populations. For example, Schwartz and Dockery (*8*) showed total mortality was estimated to increase 7% for each 100 μg/m^3 increase in TSP in Philadelphia. However, the comparative RRs for susceptible cause-specific deaths were higher: COPD = 19%, pneumonia = 11%, CVD = 10%, and the RRs were stronger for those 65 years of age or older (10% increase) compared with those less than 65 years of age (3% increase).

Relative risks for the study population may also be underestimated due to certain biases. Typical biases known to occur in time–series correlation studies are errors in measurement of ambient concentrations and misclassification of personal exposure of those dying based on ambient air concentrations from a few samplers. These biases, when present in studies where personal rather than group exposure estimates are available, are commonly thought to reduce the magnitude of the true relative risk.

Time–series studies have consistently demonstrated E-R trends, with mortality increasing as ambient PM concentrations increase; this increase generally appears to be linear and with no threshold.

Against. Bias due to ambient concentrations that do not accurately reflect personal exposure does not always reduce the magnitude of the RR when present. In fact, Brenner et al. (*43*) and Styer et al. (*3*) have shown that for time–series correlation studies, bias produces an overestimate of the E-R gradient and sometimes even a reversal of the trend.

With regard to the consistent E-R trend observed, statistical significance of the pol-

lutant variable (or the coefficient in the regression model) indicates a statistically significant E-R trend. The significance level associated with the coefficient refers to the term being statistically significantly different from zero, and the significance level is related to the number of observations. With enough data, almost any coefficient in a model can be shown to be statistically significant. The very narrow confidence intervals around the risk estimates indicate the very large statistical power in these studies (see Table 1). But when confidence intervals around percentiles are available, as they are in the Health Effects Institiute reanalyses (*32*), the lower 95% confidence intervals are mostly below 1 and the E-R trend is not obvious (see Fig. 1).

Another way to assess the strength of association is to examine R^2 values, which measure how much of the variability in the observed data (e.g., mortality) is explained by the statistical model. For example, a PM_{10} coefficient with a statistically significant p-value but an R^2 of 0.01 explains approximately 1% of the variability in mortality, which has no practical significance for prediction. Another way of saying this is that the signal to noise ratio (ratio of PM effect to the health endpoint) is so low, or the PM signal is so weak as to be close to unmeasurable. Few air pollution studies have reported R^2 values. Those that have are summarized in Table 4.

These limited data indicate PM is not of practical significance in explaining variability of mortality or morbidity. Doubt concerning the ability to measure reduced mortality and morbidity when PM levels are reduced has also been expressed by members of the Clean Air Scientific Advisory Committee (unpublished) and Samet (*37*). If one cannot measure the effect of a suspected risk factor, it is not logical to assert a cause–effect relationship.

The very low predictive power of PM (i.e., very low R^2) increases the possibility that incomplete adjustment for confounding variables (e.g., weather, co-pollutants), bias, or the seasonal nature of the data (Morris, personal communication) could result in a consistantly small but spurious risk ratio.

Specificity of the Association

Is PM associated with disease-specific mortality such as respiratory or CVD? (see Table 1).

For. Schwartz (*9*) examined this question particularly for Philadelphia. The RR of dying on high pollution days was highest for COPD (RR = 1.25) and pneumonia (RR = 1.13). The RR for CVD was 1.09, with respiratory factors contributing to the primary cause of death. Lung cancer mortality (a nonspecific effect) was also increased (RR = 1.19). Studies showing increased risks for respiratory deaths and CVD include Pope et al. (*5*) in Utah Valley and Schwartz (*6*) in Birmingham. Ostro (*14*) concludes that these studies provide ample evidence of specificity.

Against. Reanalyses of data from Philadelphia by Li and Roth (*10*) do not show the same specificity by cause of death, and there are many relative risks less than 1.0. For example, the association with COPD was positive (RR = 1.02) with two or more pollutants in the model but less than 1.0 with only TSP in the model. Moreover, there were no consistent associations with CVD (RRs less than 1.0) (*10*).

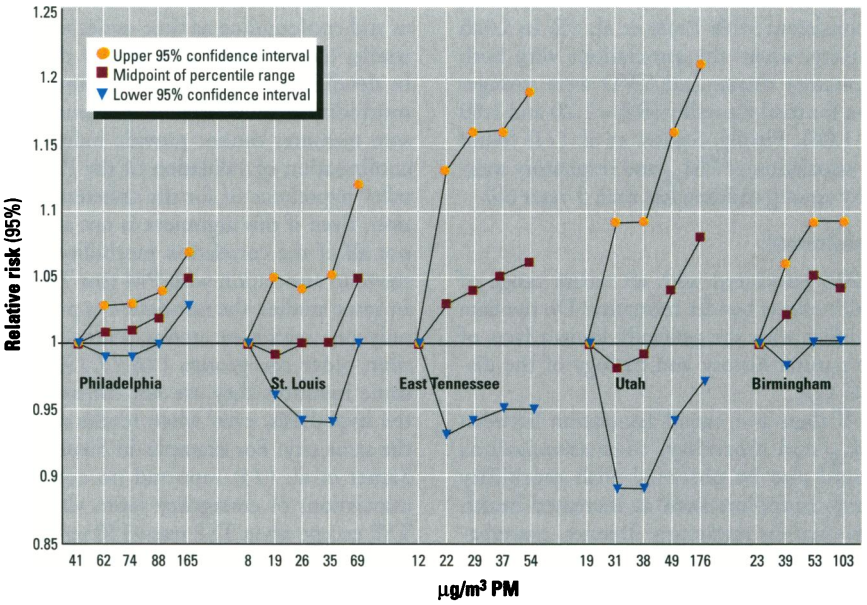

Figure 1. Relative risk and confidence intervals: total mortality for 5 U.S. locations.

Table 4. Summary R^2 values from time–series studies

Effects	Location (reference)	Air quality	R^2
Mortality	Santa Clara, CA (*49*)	COH alone	0.03
		COH + temperature + RH	0.07
		COH + temperature + RH + season	~0.13
	Philadelphia, PA (*10*)	2-days weather (temperature, dewpoint, RH)	<65 years, ~0.15; 65 years, ~0.117
		TSP, O_3, SO_2 alone	<65 years, 0.06; 65 years, 0.04
		TSP, O_3, SO_2 with nonpollutant variables also in the model	<65 years, <0.005; 65 years, <0.005
Morbidity (hospital admissions)	Steubenville, OH, 1947–1977 (*15*)	Respiratory disease admissions	
		Maximum temperature	0.006
		Unlagged TSP	0.011
		Unlagged SO_2	0.012
		All disease admissions	
		Maximum temperature	0.12
		Unlagged TSP	0.01
	Southern Ontario (*16*)	Summer: respiratory admissions	
		SO_2 + O_3 + temperature (COH not significant)	0.12
		Winter: admissions for children with asthma	
		Temperature + NO_2 (COH not significant)	0.063
	Southern Ontario (*50*)	Weather and pollutants (TSP, SO_2, NO_2, O_3, SO_4)	Typically 0.01–0.05

COH, coefficient of haze; RH, relative humidity; TSP, total suspended particulate.

Styer et al. (*3*) did not find any significant PM_{10}/mortality association in Salt Lake City, Utah, and the RR for mortality in people 65 years of age or older was less than 1.0 in summer and fall. Lyon et al. (*4*) found that in Utah County the association was strongest for CVD (RR = 1.13), while the PM_{10}/mortality association for respiratory disease was less than that for total mortality (RR = 1.03 vs. 1.04). These results are inconsistent with Pope et al. (*5*) in Utah County, where the associations with both respiratory disease and CVD were stronger than for total mortality (RR = 1.20 and 1.09 vs. 1.08). Finally, Saldiva et al. (*11*) found no association of PM_{10} and respiratory mortality among children less than 5 years old.

Coherence

Is PM associated with an entire range of health effects besides mortality? Do the data "conflict with the generally known facts of the natural history and biology of the disease" (*1*)?

If there is a causal association between PM_{10} and mortality, then associations should also be observed with morbidity health endpoints such as increased health care visits for respiratory illnesses, exacerbations of asthma, increased respiratory symptoms, and declines in lung function (*30*). Studies examining the relationship between PM exposures and hospital admissions are summarized in Table 2. Respiratory morbidity measured as symptoms and changes in lung function [primarily peak expiratory flow (PEF)] are summarized in Table 3.

A second guideline for coherence is whether the time–series morbidity data conflict with the known facts about asthmatic admission to hospitals, asthmatic response to PM measured in experimental studies, and response measured in time–series studies. The common measure of response in studies of morbidity is reduction in lung function, primarily FEV_1 (forced expiratory volume in 1 sec) and PEF. Airway obstruction is the primary abnormality during an asthmatic attack, and asthmatics constitute that portion of the population most sensitive to airway constriction. During an asthmatic attack resulting in hospital admission, asthmatics have shown mean reductions in FEV_1 of >30%–>56% (median of mean >50%) in various studies (*51–55*). Mean reductions in PEF were 38%–81% (*54,56*). The subjects in these studies are a subset of all respiratory admissions to hospitals in time–series studies. To validate the coherence criterion, mean reductions of FEV_1 among asthmatics should be at least greater than 30% at PM_{10} concentrations less than 150 $\mu g/m^3$ in experimental and time–series studies.

For. Bates (*31*) suggests that coherence within epidemiological data is "generally strong and therefore convincing" for the PM/mortality hypothesis. That is, time–series studies of hospital admissions and symptoms generally show an association with PM.

Against. The PM/morbidity studies are of the same design as PM/mortality studies and are, therefore, subject to the same biases and confounding as time–series mortality studies (confounding and bias are discussed in detail later). Consequently, time–series morbidity studies without personal exposure measures cannot provide independent confirmation or validation of the PM/mortality hypothesis or for the coherence criterion. Even if this argument is not accepted, not all of the correlation morbidity studies show an association with PM (see Table 2). In some studies, the association is present in only one season or among younger rather than older age groups (*16,17,19,20*). In some instances they are not coherent with the hypothesis, even when results are from the same city. For example, in Steubenville, Samet et al. (*15*) reported no consistent associations of emergency room visits with TSP except when TSP was >150 $\mu g/m^3$ and temperature was high. These results are more coherent with the negative mortality results of Moolgavkar et al. (*34*) than with Schwartz and Dockery (*33*).

Symptom data also do not show a consistent association with measures of PM air pollution. Studies measuring changes in PEF generally show a significant association with ambient PM; however, the actual reductions in PEF are quite small (<5%), they are not an adverse health effect, and they are less than diurnal variation (see Table 3).

Are individual-level study results coherent with the time–series ecologic study results of hospital admissions? Is mean FEV_1 reduced 30–60% among asthmatic volunteers exposed to ambient air or among asthmatics exposed to PM for several hours under experimental conditions?

The one time–series morbidity study with personal measures of PM exposure shows slight changes in FEV_1 that are much less than observed for patients admitted to hospitals. Silverman et al. (*57*) conducted a time–series study of pulmonary function and personal exposure to PM for 10 days in summer and 10 days in winter among asthmatics. When adjusted for medication use, a 50 $\mu g/m^3$ change in personal exposure to PM_{10} was estimated by regression to be associated with a 4.7% reduction in FEV_1 during summer and a 10.6% increase in winter. SO_2 and NO_2 were measured but, along with weather, were apparently not included in the analysis. The increase in FEV_1 during the winter was attributed to increased medication. This individual-level study is not coherent with the time–series ecologic studies of hospital admissions.

Chamber studies have used exposure mixtures of polluted air, acid aerosols, and environmental tobacco smoke (ETS), agents that are similar to portions of ambient PM. Acid aerosols, especially those with high acidity, have been implicated in time–series mortality studies in London at H_2SO_4 concentrations less than 10 $\mu g/m^3$ (*39*). Combustion is a major source of both indoor and outdoor PM. For example, motor vehicle exhaust constitutes up to 40% of average PM_{10} at many sampling sites, and ETS is the major source of PM_{10} in the homes of smokers. Pope (*58*) suggests that combustion-source particles have a greater toxicity than naturally occurring particles because of chemical composition, submicron size, or both.

Chamber studies of asthmatics exposed to mixtures of polluted air containing PM concentrations 30–100% higher than 150 $\mu g/m^3$ showed no reductions in lung function. These exposure mixtures also contained from 100–500 ppb SO_2 and NO_2 (*59,60*).

Bauer et al. (*61*) exposed 11 elderly patients with COPD to 75 $\mu g/m^3$ H_2SO_4 for 2 hr; these patients excercised for 40 min. No decrease in lung function (FEV_1, FVC) was observed. The lack of airway obstruction and shortness of breath on exertion in the presence of PM_{10} does not provide plausibility to the idea that this susceptible group of COPD patients is vulnerable to acute PM_{10} exposures as suggested by the correlation studies. Exercising asthmatics exposed to H_2SO_4 concentrations as high as 2000 $\mu g/m^3$ have shown either mild (5–10%) or moderate (10–20%) reductions in FEV_1 (*62–64*). Mean reductions were less than 10% after subtracting the effect of exercise. Despite concentrations of H_2SO_4 more than 10 times greater than the U.S. air quality standard for PM_{10} and increased airway sensitivity because of withholding asthma medication, the response among a subset of the susceptible population is well below the magnitude estimated to result in hospital admission.

There are several chamber studies of healthy and asthmatic volunteers exposed to ETS containing PM concentrations ranging from about 850 $\mu g/m^3$ to over 4000 $\mu g/m^3$ (Table 5). The most sensitive and susceptible subjects studied were atopic smoke-sensitive asthmatics (*65,66*). In these two studies, there was a total of 52 asthmatics 12–50 years of age. Because they were selected for sensitivity to ETS and their normal asthma medication was stopped, they may be a hypersusceptible population for airway reac-

tivity and probably should be included among the most sensitive and susceptible portion of the asthmatic population. When taken as a group, subjects in these two studies were exposed to several levels of ETS. In Stankus et al. (*65*), the number of reactors was determined at each level, and only nonreactors were administered higher exposures. A reactor was one who showed a 20% or greater increase in airway obstruction as measured by FEV_1. The lowest effect level was 852 μg/m^3 PM for 10% of the atopic smoke-sensitive asthmatics. Some asthmatics did not react to ETS containing $PM_{1.0}$ levels as high as ~2600 μg/m^3 for 2 hr or 1300 μg/m^3 for 4 hr. The reductions in FEV_1 were completely reversible and were not severe enough to result in hospital admission.

Biological Plausibility

Are the results biologically plausible and do they agree with current understanding of how organisms respond to low concentrations of PM?

For. Schlesinger (*67*) reviewed the question of whether PM health effects are consistent with toxicological knowledge. He concluded that responses consistent with morbidity findings in humans include increased airway hyperresponsiveness, altered mucociliary transport and secretory-cell hyperplasia from acid sulfates, and immunosuppression from acid sulfates and metals.

Oberdörster et al. (*68*) hypothesizes that ultrafine particles (<0.05 μm) might cause acute lung injury based on the highly toxic nature of freshly generated polytetrafluorethylene (PTFE, teflon) fumes. Seaton et al. (*69*) proposes that acidic ultrafine particles produced by combustion provoke inflammation of the lung alveoli, which in turn cause increased blood coagulability (increasing the susceptibility to acute episodes of CVD) and release of mediators able to provoke attacks of acute respiratory illness in susceptible persons.

Against. Schlesinger (*67*) also states that while PM exposures may induce effects similar to those observed in toxicology studies, the PM exposures at which these effects are observed are so high as to be irrelevant to human populations. Moreover, the time is too short for effects such as reduced transport, hyperplasia, and immunosuppression to produce acute mortality.

The relevance of PTFE fumes studied by Oberdörster et al. (*68*) needs to be determined, and these authors suggest that there is no known mechanism for low-level ambient particle concentrations to cause acute mortality/morbidity. The PTFE particles are unstable and coagulate with larger particles and other ultrafine particles. Oberdörster (*70*) suggests that it is in the freshly generated singlet (but not the aggregate) state that the ultrafine particles escape phagocytosis and promote inflammation.

The hypothesis of Seaton et al. (*69*) remains to be tested. A competing hypothesis proposes that effects attributed to PM_{10} (e.g., CVD, respiratory distress, etc.) are also caused by temperature extremes, as suggested by a consistent association between temperature and cardiovascular mortality in different countries and cities over time and in different age groups. Both clinical and laboratory data indicate that temperature can adversely affect hemostasis, blood viscosity, blood lipids, sympathetic nervous system function, vasoconstriction, and blood pressure, providing biological plausibility for temperature as a possible mechanism (*71*).

Bias

Bias, or systematic error, is of particular concern in epidemiology because of the observational nature of the science. Judgment as to the meaning of an association must consider the potential role of bias.

Three categories of bias are discussed below. The first category concerns the question: Can ecologic studies be used for hypothesis testing, or should they be limited only to hypothesis generating because of the unknown effects of measurement error bias, or the ecologic fallacy? There is a wide range of opinion on this question. Regardless of the answer, the hypothesis (and the data derived from ecologic studies) should be judged on its merits. That judgment includes how well causal criteria are met (as discussed above) and whether other major uncontrolled biases that invalidate statistically significant associations are unlikely.

The remaining biases are divided into 1) biases identified with time–series ecologic study design and/or the PM/mortality hypothesis, and 2) potential confounding biases from other pollutants and from weather.

Ecologic Study Design and the Ecologic Fallacy Bias.

The question of whether the time–series ecologic studies can be used for hypothesis testing has been virtually ignored. The need to validate risk estimates from time-series correlation studies with individual-level studies has not been recognized with regard to the PM/mortality hypothesis. Because of the unpredictable effect of bias on risk estimates from ecological studies, the answers to these questions are crucial. Richardson et al. (*42*) provide an illustration of the importance of validating findings from ecologic studies with findings from individual-level studies. They found that relative risks for esophageal cancer attributed to smoking and drinking and obtained from ecologic studies did not correctly define the role of either risk factor

Table 5. Summary of selected chamber studies of atopic smoke-sensitive asthmatics exposed to environmental tobacco smoke (ETS)

Subjects	% Reactors[a] (number reactors/total study size)	Exposure to ETS
Atopic smoke-sensitive asthmatics, 21–50 years of age (*65*)	10% (2/21)	2 hrs: 852 μg/m^3 PM_1; 8.7 ppm CO; 180 μg/m^3 nicotine
Atopic smoke-sensitive asthmatics, nonreactors from above	24% (5/21) (14/21 = nonreactors ΔFEV_1 <10%)	2 hrs: 852 μg/m^3 PM_1; 8.7 ppm CO; 180 μg/m^3 nicotine,+30 min rest plus 2 hrs: 1452 μg/m^3 PM_1; 13.3 ppm CO, 439 μg/m^3 nicotine
Asthmatics, 5 nonreactors from above	0% (0/5)	2 hrs: ~2600 μg/m^3 PM_1, 14 ppm CO
Atopic smoke-sensitive asthmatics, 12–50 years of age (*66*)	16% (5/31)	4 hrs: 1266 μg/m^3 PM_{10}; 226 μg/m^3 nicotine
Atopic smoke-sensitive nonasthmatics, 12–50 years of age (*66*)	0% (0/39)	4 hrs: 1266 μg/m^3 PM_{10}; 226 μg/m^3 nicotine

[a] Reactor defined as reduction in FEV_1 (forced expiratory volume in 1 sec) greater than or equal to 20%.
ΔFEV_1, change in FEV_1.

when tested using individual-level study results.

For. Dockery and Schwartz (*72*) indicate that the results of the Steubenville data (*33*) generated the hypothesis that PM rather than SO_2 was specifically associated with daily mortality. The hypothesis was then tested in Philadelphia (*8*) with similar associations in eight other U.S. communities (*5,6,49,73–76*).

Against. Epidemiology text books and articles in epidemiology literature consistently note that ecological studies are limited in their usefulness to hypothesis generation because of the fallacy inherent in estimating individual risk based on group data (*42,44–46*). Based on this judgment, hypothesis testing should be left to studies with individual-level exposure and response data. The logical fallacy in the time–series studies is that the concentration of PM collected from a sampler in a metropolitan area is not a reasonable proxy for personal exposure to PM.

The limited data available suggest that correlations of ambient concentrations with indoor and personal exposures are generally close to zero. For example, in the same area where a PM_{10} mortality study showed a RR of 1.08 per 50 $\mu g/m^3$ increase in PM_{10} (*74*), Spengler et al. (*77*) showed that ambient $PM_{3.5}$ explained less than 1% of variance in personal exposure for 225 nonsmokers. R^2 varied from 8% (smoke-exposed at work) to 0.1% (not exposed to smoke at work). Spengler et al. (*77*) conclude that ambient measurements were poor predictors of personal exposure and that ETS is the dominant source of indoor air pollution. Smoking a pack of cigarettes on average raised respirable particulate levels 20 $\mu g/m^3$ and in fully air conditioned buildings ~42 $\mu g/m^3$ (*78*). On average, persons spend ≤10% of time outdoors, and ambient PM composition is probably different than personal PM exposure (*77*). Further, actual PM exposures and measured exposures are likely to vary among individuals, with differences in exposure between the elderly; persons with CVD, asthma or COPD; children; smokers; etc. Thus, ambient concentrations are not good surrogate measures of personal exposure.

The range of opinion regarding ecologic studies can be quite wide. In contrast to the opinions noted in the "for" arguments, Piantadosi et al. (*45*) conclude there are no consistent guidelines for interpreting ecological correlations or regressions when only group data are available. Although virtually ignored in the PM/mortality hypothesis issue, there is a spirited debate in other areas regarding the usefulness of ecologic studies such as investigating the role in indoor radon and lung cancer (*79–81*). Cohen (*79*) defends the use of ecologic studies to estimate linear nonthreshold E-R relationships, while Greenland and Morgenstern (*80*) are doubtful of their validity and conclude there is no "ecological method available to identify or measure ecological bias."

The differences between actual and measured exposure are rarely determined. Therefore, the measurement error for all the independent variables in time–series correlation studies is largely unknown. In a multiple regression model with collinear independent variables having different magnitudes of measurement error, the results are complex and not always predictable.

Lipfert and Wyzga (*82*) performed data simulations and numerical experiments using mortality and pollutant data from Philadelphia to demonstrate some of this complexity. In a standard multiple regression procedure, a pollutant having a lower measurement error yields an inflated coefficient or risk estimate, while the coefficient of the pollutant with the higher measurement error is reduced. In Philadelphia, when seasonal and other variables were put into the model, inflation of the variance of SO_2 resulted in TSP being selected into the model first and achieving higher t values. Conversely, inflation of TSP variance only slowly decreased the significance of TSP, perhaps because there is less daily variation in TSP than SO_2. These data support the idea that measurement error is important in partitioning the effects of correlated pollutants and may provide a partial explanation of why SO_2 but not PM effects are often attenuated in regression analyses.

In summary, both the direction and magnitude of these biases are largely unknown. In both cases, one should be extremely cautious before accepting risk estimates from ecologic studies as being approximately true. Only after consideration of chemical constituents of PM, effects of other copollutants, and biases due to errors in measurement and spatial representativeness "can observational epidemiology do more than suggest causality for health-effects of PM_{10} exposures" (*83*).

PM/Mortality–Morbidity Related Biases

Measurement validity bias. Measurement validity bias is similar to measurement error bias in that the lower the analytic/instrument measurement error of one pollutant compared to other pollutants in the model the more inflated the regression coefficient. That is, pollutants should have similar analytical and instrument errors, similar spatial representativeness in the monitor network, similarity in number of samplers and amount of missing data, similarity in the response averaging time, and similar correlation of personal exposure and ambient concentrations. There appear to be many more measuring sites for PM_{10} than for other pollutants, suggesting inflated regression coefficients of PM relative to other pollutants in the model. For example, in the United States, 537 sites were reported with ambient levels of CO, 377 for NO_2, 925 for O_3, 692 for SO_2, and 1508 for PM_{10} from 1984 to 1993 (*84*). Thus, the pollutant with the lowest measurement error will have the spuriously highest regression coefficient. In contrast, the regression of correlated copollutant with higher measurement error will be lowered and may go to essentially zero unless these differences are minimized. All of these biases (but not necessarily their magnitude) are known to be present in air pollution studies (*82*).

Averaging time or lag bias. For a valid (unbiased) estimate of the regression coefficient in an air pollution model, the appropriate lag period must be used for the independent variables (*82*).

The appropriate lag period is different for each pollutant in the model, and the selection of inappropriate lag times may influence the effect attributed to each pollutant. Li and Roth (*10*) found that the mean of current and previous day pollutant levels for TSP, SO_2, and O_3, along with a lag time of 2 days for weather, gave the strongest association for pollutants in Philadelphia when testing lag times that varied between 2 and 4 days. Schwartz and Dockery (*8*) used a similar lag time for pollutants (Philadelphia), whereas the previous day was used in Detroit (*73*), current and the previous 2 days in Birmingham (*6*), and current and the previous 4 days in Utah (*5*). If SO_2 and O_3 effects are related to peak exposures (as they may be) rather than 24-hr or longer means, then the estimates for all pollutants in the model will be biased. The variable number of lag times used in various studies also raises concern about the lack of a rationale for a 24-hr averaging time for PM_{10}.

The lags for weather may also be biased, as lag time between weather and mortality in the summer is less than or equal to 1 day and is much longer in winter. Three-day lag times were common in a number of U.S. cities (*85*). As a minimum, the lag time for weather must be adjusted for season to avoid bias. This is one reason to do analysis by season and to use a lag time that varies by season. Often the lag time for weather is not reported or only one lag time is utilized that is wrong for both hot and cold weather.

Response function bias. Bias occurs unless the appropriate form of the expo-

sure–response pattern is used. Selection of the most important pollutant cannot be made without consideration of the form of the dose–response relationship. Lipfert and Wyzga (*82*) showed that, in a respiratory hospital admissions study in southern Ontario, linear was best for TSP, a square root transformation for SO_4, a natural log transformation for SO_2, and an exponential for O_3. In Philadelphia, SO_2 performed better with square root and log models and TSP with exponential and square functions. Most models use a linear form, even if more than one pollutant is in the model, and may therefore produce biased estimates.

Horse blinder or tunnel vision bias. Many of the studies have focused on PM only as the pollutant of choice, and have ignored other pollutants, although some studies have also included pollutants such as SO_2 or O_3. "Analyses focusing on only one routinely collected pollution metric, to the exclusion of other possibly more influential pollution components, can cause the effects of the overlooked pollutants to be ascribed to the studied pollutant" (*86*).

One-sided reference bias. The implications of negative studies and multiple studies with variable results at the same locations and the significance of individual-level studies as tests of ecologic study results have largely been ignored. Consideration of arguments and data contrary to a cause–effect relationship must be addressed to eliminate the one-sided reference bias and before accepting the PM/mortality hypothesis (*87*).

Confounding from Weather and Other Pollutants

For. Reviewers of the PM/mortality hypothesis have asserted that potential confounding from pollutants and weather cannot explain the observed associations because, 1) the associations are seen in locations where a non-PM pollutant is too low to have an effect, 2) some attempts to control for weather or seasonal effects were part of the analysis, and 3) the estimated pollution effects are reasonably consistent for areas with different climates, weather conditions, and pollutant levels (*88*).

Against. There are several reasons confounding from pollutants and weather may in part explain the observed associations. If confounding is not accounted for, PM coefficients must be regarded as including the effects of the omitted or uncontrolled risk factors (*82*).

The high R^2 values for weather in climate time–series studies and low R^2 values in air pollution studies indicate that there has not been adequate control for weather. Weather (and not necessarily mean temperature or relative humidity as commonly used in air pollution studies) shows relatively high R^2 values (see Table 6, which summarizes weather/mortality associations in selected cities). Kalkstein and Davis (*85*) reported that, in Philadelphia, five variables explained 34% of the variability in total mortality in summer and two variables explained 27% of variability in total mortality in winter. These values compare to *15–17%* for three variables (temperature, relative humidity, dewpoint) reported by Li and Roth (*10*). The R^2 for weather in the Li and Roth (*10*) analysis was three to nine times larger than for the copollutants TSP, O_3, and SO_2.

Kalkstein (*89*) suggests that people may respond to air masses rather than individual weather elements such as temperature. In a cursory evaluation of 10 U.S. cities, none showed a strong or moderate pollution effect, i.e., none of the synoptic climate categories with high pollution levels showed increased mortality. Results from St. Louis, Missouri, using this synoptic weather/pollution evaluation suggested fluctuations in daily mortality were much more sensitive to stressful weather than high pollution levels. The most stressful synoptic weather category was associated with highest mortality (R^2 = 0.56) and did not have high pollution concentrations. The same model without PM or visibility explained 51% of the variability in elderly mortality. PM was not significant in these analyses. These results are contrary to the analysis of St. Louis by Dockery et al. (*74*).

It seems reasonable to infer from these data by Kalkstein (*89*) that weather is a stronger risk factor than PM; temperature and relative humidity do not adequately adjust for weather and are correlated with PM; and weather is confounding the PM/mortality association.

With such low R^2 for PM and the probability that confounding is occurring, it is questionable that the E-R trends are valid; this suggests that lowering PM would not lower mortality or morbidity.

The lack of control is probably due to the use of improper metrics to measure weather and inappropriate lag times for temperature. Both hot and cold temperatures (and other aspects of weather) above and below temperature thresholds increase total mortality as well as specific causes of death including CVD, respiratory disease, coronary and stroke deaths, pneumonia, coronary artery disease, cerebral infarction, and ischemic heart disease (*90–95*). And the further away from threshold, the greater the risk. The appropriate lag peri-

Table 6. Statistically significant weather models with R^2 values for mortality in selected cities where air pollution studies have been conducted

	R^2 for total mortality (significant weather variables)		
	Summer		Winter
City	All ages	≥65 years	All ages
Birmingham, AL	0.24 (WNDPM, CDH)	0.25 (CDH)	0.11 (MINT)
Chicago, IL	0.36 (MAXT, MAXTD, WNDPM, VISPM, CLD, time)	0.35 (same as all ages)	0.18 (VISPM,WNDPM, WNDAM, HDH)
Cincinnati, OH	0.18 (MAXT, WNDPM VISPM)	0.20 (MAXT, WNDAM)	0.15 (WNDPM)
Detroit, MI	0.22 (MINTD, WNDPM, CLD)	0.24 (WNDPM, CLD)	0.14 (MAXT, MAXTD)
Los Angeles, CA	0.21 (MINT, VISPM, time)	0.31 (MINT, MAXTD, VISPM, time)	—
New York, NY	0.64 (MINT, MAXTD, CDH)	0.70 (MINT, WNDPM, CDH, time)	0.32 (MAXTD, VISAM, VISPM, HDH)
Philadelphia, PA	0.34 (WNDPM, VISAM, VISPM, CDH, time)	0.38 (MAXTD, VISAM, CDH)	0.27 (VISPM, WNDAM)
St. Louis, MO	0.38 (MINT, WNDAM, CDH)	0.43 (MAXT, MINT, MAXTD, time)	0.13 (MAXTD, WNDAM, WNDPM)

MAXT, maximum temperature; VISAM, 3 A.M. visibility; MINT, minimum temperature; VISPM, 3 P.M. visibility; MAXTD, maximum dewpoint; WNDAM, 3 A.M. windspeed; MINTD, minimum dewpoint; WNDPM, 3 P.M. windspeed; CDH, cooling degree hours (summer only); CLD, mean 10 A.M.–4 P.M. cloud cover; HDH, heating degree hours (winter only). Data from Kalkstein and Davis (*85*).

ods for hot temperature are 0–1 days; for cold temperatures, the lag periods are somewhat longer (one week or even longer). However, in many air pollution studies, mean temperatures are used and lagged 0–3 days without regard to whether they are above or below the threshold (*85*).

Kinney et al. (*96*) have the viewpoint that, because of collinearity of temperature and weather, both a lack of control and over control of temperature may yield biased estimates of pollution, though the bias is in different directions. Both the coefficient and statistical significance are affected if inappropriate lags are used (*7*).

Inappropriate control of confounding produces a spurious overestimate of the effect of PM. For example, Mackenbach et al. (*97*) showed that using mean temperatures produced an association between SO_2 and mortality that the authors interpreted to be causal. Where lag periods for temperature, humidity, precipitation, and wind were determined empirically rather than arbitrarily, no association with SO_2 was observed.

Copollutants (SO_2, NO_2, O_3, CO) have not been included in most air pollution studies, so the effect of excluded and collinear pollutants is falsely attributed to PM by default. This horse-blinder bias may result in spurious overestimate of the risk, as demonstrated by a reduction in the PM-attributed risk when co-pollutants are added to the model.

When pollutants are included in the model, measurement errors must be approximately equal or the pollutant with the lowest error will include the effects of the pollutant with higher error (see measurement validity bias). This error also occurs when concentration data (PM, SO_2, NO_2, O_3, and CO, for example) do not have a similar number of monitoring stations on all days (*82*). When co-pollutants are in the model, collinearity may make it impossible to assess the independent effects. Thus, it may not be possible to obtain reliable estimates of E-R relationships for individual pollutants in a time–series study.

Summary and Conclusion

The objective of this review is to evaluate the question: Is there a cause–effect relationship between short-term low-level ambient concentrations of PM_{10} (<150 $\mu g/m^3$) and increased acute mortality or morbidity? Causality is evaluated in terms of meeting criteria of temporality, consistency, coherence, strength of association, biological gradient, specificity, plausibility, and freedom from or control of confounding and bias. Since the hypothesis has been both generated and tested by studies using group exposure data, judgment must also be made whether estimates of risk from ecologic studies are reliable.

The major arguments favoring a causal association are consistency of the findings at different locations with different climatic and pollutant characteristics, and coherence of the findings, namely, increased morbidity (e.g., hospital admissions) associated with daily concentrations of ambient PM. Confounding from weather and co-pollutants is said to be adequately controlled.

It is important to realize that all of the PM mortality and morbidity epidemiology studies have one design: a time–series ecologic study with no personal measures of exposure. Results obtained from ecologic studies have the inherent problem that conclusions are subject to the ecologic fallacy. The validity of individual risk estimates based on group data is not known and cannot be reliably determined from an ecologic study design. The ecologic study is primarily designed for generating hypotheses. Testing the hypothesis, assessing the validity of the association, and obtaining reliable estimates of the exposure–response relationships require independent testing by individual-level study designs having personal exposure measures, as well as individual health data.

Regardless of the validity of using ecologic studies to perform hypothesis testing, a review of the evidence suggests that associations are statistical rather than cause-effect. Reasons that the available data do not meet criteria for causality are described below.

- Consistency. Reanalyses by different authors at different locations have produced contradictory results at all of the five locations where independent analyses have been performed. Thus, there is as yet no internal consistency from ecologic time–series studies. The most valid test of consistency requires results using a different study design and having measures of personal exposure. Experimental exposure of volunteers in chambers to known mixtures of PM provide the only available data that meet this criteria. The lung function responses from chamber studies are considerably less than those predicted by time–series studies, and at considerably higher PM concentration than observed in ambient air.
- Coherence. Time–series ecologic studies of morbidity can not provide independent support of time–series mortality studies because both are subject to the same biases. Utilizing them to support coherence employs circular reasoning. Chamber studies of asthmatics and COPD patients exposed to acid aerosols and ETS do not experience reductions in lung function of the magnitude that will cause hospital admission, even at PM concentrations much higher than 150 $\mu g/m^3$. Thus, results from individual-level studies of PM do not support the coherence or consistency criteria.
- Strength of association. The association is weak (RR <1.50 for as much as 100 $\mu g/m^3$ change in PM). It is problematic whether an observational study can reliably detect risks this low, especially in light of potential biases. The explanatory strength of the statistical models as measured by R^2 appears to be too low to measure with any certainty the role of low-level pollution. The low R^2 values also provide little assurance that lowering PM levels will reduce mortality/morbidity.
- Biological gradient (E-R). Linear relationships are often assumed, but the true shape of the E-R is not known. E-R relationships cannot be determined if collinearity of pollutants is too high. E-R based on PM-only models may not be reliable because effects of other pollutants may be falsely attributed to PM. Confounding (e.g., weather, copollutants) and biases (e.g., measurement error) make E-R estimates unreliable.
- Specificity. The PM association with cardiopulmonary disease may be confounded by weather, which has a similar but stronger effect on mortality and morbidity than PM.
- Temporality. Death-bed mortality may be the only cause of death that clearly meets the temporality requirement, and there are not enough of these deaths to explain the mortality attributed to PM.
- Plausibility. There is as yet no biological mechanism to explain how low-level ambient PM less than 150 $\mu g/m^3$ could cause the increased mortality and morbidity suggested by the time–series studies.
- Freedom of studies from bias. Confounding from other pollutants such as SO_2, CO, O_3, and NO_2 is likely and, where collinearity is high, it is not possible to separate individual pollutant effects. Confounding from weather has not been adequately controlled, as indicated by the low R^2 of air pollution/mortality–morbidity studies relative to climate/mortality–morbidity studies. It is not yet known how to adequately control for confounding from weather. A number of biases are present that can spuriously elevate the E-R relationship or spuriously bias it toward the null. Ecologic fallacy can occur during estimation of individual risk based on group data. The direction and magnitude of measurement error is problematic as the correlation between ambient and indoor air is poor, and

between ambient and personal exposure is largely unknown.

Another bias is lag bias. Lags for temperature vary by season. There is no consistent lag time for PM among time–series studies, and the lags used may be incorrect for both hot and cold temperatures.

In measurement validity bias, PM may have fewer errors (e.g., more sampling sites) than other pollutants, thereby inflating the regression coefficient. For response function bias, the form of the E-R relationship may not be linear and, if not, the regression coefficient is biased. Tunnel vision bias, caused by focusing primarily on PM to the exclusion of other pollutants, may bias results toward a positive PM finding.

A primary author in many of the PM studies concludes that the evidence seems to leave little room to doubt that particulate air pollution at commonly occurring levels is causally associated with a range of adverse outcomes, including early mortality (*13*). However, as outlined above, the causal criteria are not met and the weight of evidence does not support the PM/mortality hypothesis.

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