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ACUTE RESPIRATORY EFFECTS OF PARTICULATE AIR POLLUTION

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INTRODUCTION

In the 1930s, 40s, and 50s, several episodes of extreme air pollution focused attention on the potential for adverse health effects of air pollution. These included an episode in the Meuse Valley, Belgium, in December 1930 (15), an episode in Donora, Pennsylvania in 1948 (36), and several episodes in London, England (23, 44). The sudden large increases in sickness and death that accompanied such episodes demonstrated that air pollution can adversely affect human health. The increased mortality associated with such episodes provided the first quantitative measure of the adverse effects of air pollution.

By the 1970s, a link had been well established between respiratory disease and particulate and/or sulfur-oxide air pollution, but still there remained disagreement as to the level of pollution that would significantly affect human health. In reviewing research published between 1968 and 1977, Holland and several other prominent British scientists (19) concluded that particulate and related air pollution at high levels pose hazards to human health, but that health effects of particulate pollution at lower concentrations could not be "disentangled" from health effects of other factors. Shy (45) responded by asserting that the review by Holland et al systematically discounted evidence of pollution-related health effects at contemporary pollution levels. Shy, and other reviewers (1, 12, 45, 54), contended that the cumulative weight of evidence provided sound reasons to believe that

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human health may be adversely affected by particulate pollution, even at relatively low concentrations.

Epidemiologic studies since the 1970s have provided more quantification of the health effects associated with particulate pollution at levels common in contemporary urban areas of the developed world. Recent epidemiological research has been based on more specific definitions and more precise measures both of pollution exposures and health endpoints. Advances in biostatistical and econometric analytic techniques for time-series data have expanded the opportunities to evaluate the acute health effects of particulate pollution and have increased the analytical rigor of these studies. In particular, advances in autoregressive Poisson and logistic regression analysis have permitted the evaluation of pollution associations in panels of patients or other small populations, which would not have been possible in the early 1970s. Most notable has been a series of studies showing that daily mortality is associated with particulate pollution at concentrations much lower than those experienced in the extreme episodes of the first half of this century.

Bates (3) has recently pointed out that the observation of increased mortality associated with air pollution exposures implies that measures of morbidity also must necessarily be increased—for example, hospital admissions, hospital emergency room visits, and outpatient or doctor's visits. Among potentially responsive subjects such as asthma patients, we expect to observe increased symptoms, lower lung function, increased medication use, and, ultimately, higher use of hospital services. A similar cascade of associations also may be detected among less sensitive individuals, i.e. among members of the general population. Bates (3) has described this as *coherence* of effects, i.e. the adverse effects of air pollution should be observable across a range of related health outcomes. Adverse effects of air pollution also should be reproducibly observed by different investigators in different settings, i.e. there should be *consistency* of effects across independent analytic studies.

This review presents a comparison of such recent studies of the acute effects of particulate air pollution and shows evidence for increased mortality and morbidity associated with particulate pollution, even at moderate concentrations. We evaluate both the coherency and consistency of recent epidemiologic data regarding adverse health effects of particulate air pollution. Our purpose is to stimulate a new look at these studies rather than to provide a comprehensive, detailed, or complete review.

SOURCES AND EXPOSURES

Particulate air pollution refers to an air-suspended mixture of solid and liquid particles that vary in size, composition, origin, and effects. The term

'aerosols' refers to a stable mixture of suspended particles and gases and therefore implies smaller-sized particles. Particulate air pollution is formed by condensation of gases or vapors, or by direct generation through mechanical processes. The different processes of formation lead to characteristic differences in size and composition of particles.

Particle Size and Chemical Characteristics

Particle size is expressed in terms of its aerodynamic diameter, defined as the diameter of a unit-density sphere that has the same settling velocity as the particle in question. The size distribution of suspended particles in the atmosphere is bimodal. Large particles (sometimes called "the coarse mode") are 2.5 to 30 μm aerodynamic diameter and most often have a basic pH. These large particles are derived from uncontrolled combustion and mechanical breakup of soil and other crustal materials. Biological particles such as pollens and spores are also found in this large-particle range. Smaller particles ("the fine mode") are < 2.5 μm aerodynamic diameter and are often acidic. These fine particles include soot and acid-condensates derived from vehicle emissions, manufacturing, power generation, and agricultural burning. Sulfate and nitrate aerosols generally make up the largest fraction of small particles by mass.

Deposition, Clearance, and Toxicity

Particle size is the most important characteristic influencing deposition in the respiratory system (2). Models of inhaled particle deposition relate aerodynamic particle diameter to the site of deposition. Most inhaled particles of greater than 5μm aerodynamic diameter deposit in the upper airways or larger lower airways. Particles smaller than 5μm aerodynamic diameter are more likely to deposit in the smaller airways, e.g. the bronchioles and the alveoli.

Particle clearance is achieved by several mechanisms. Particles deposited in the trachea and bronchioles rise on the mucociliary ladder to be expelled by coughing or to be swallowed. Particles deposited beyond the terminal bronchioles are cleared largely by lung macrophages that, in turn, transport the ingested particles onto the mucociliary ladder or into the lymphatic system. A small fraction of these distally deposited particles migrate through alveolar tissue directly into the lymphatic circulation.

Biologic effects of a particle are determined by the physical and chemical nature of the particle itself (particularly its solubility), the physics of deposition and distribution in the respiratory tract, and the physiologic events that occur in response to the particle's presence. Controlled human studies have focused on airway effects of single agents or simple mixtures. Toxicological studies have generally focused on chronic effects and single agents

(e.g. silica, asbestos) (55), and on the effects on sites of deposition or distribution (airways, alveoli).

Measures of in vitro macrophage cytotoxicity demonstrate the high toxicity of certain urban particle complexes relative to the classic toxic dusts, e.g. silica and asbestos. Toxicity of urban particles and diesel particulate emissions depend in part on the type of metal compounds they contain, as well as their combustion-derived organic content (16).

REVIEW METHODS

Definition of Exposure

In 1987, the US Environmental Protection Agency redefined the National Ambient Air Quality Standard (NAAQS) for particles based on particulate matter smaller than 10μm aerodynamic diameter (PM_{10}) (13). This 10μm-size cutoff focused monitoring and regulatory efforts on particles of a size that would be deposited in, and damaging to, the lower airways and the gas-exchanging portions of the lung. Recent epidemiologic studies have used PM_{10} measurements as the basis of exposure estimation. Earlier studies, however, used a variety of measures of particle concentration to define exposure. These alternative measures are discussed below to compare results with PM_{10}-based measures.

The EPA's initial standard reference measure for particles was Total Suspended Particulates (TSP), measured by high-volume samplers. This sampling method has an ill-defined upper size limit between 25μm and 45μm that is dependent on wind speed and direction (22). In addition, TSP measurements are subject to artifactual conversion of SO_2 to sulfate on the filters or to volatilization of nitrate aerosols from sampler filters. Many epidemiologic studies of air pollution in the 1960s and 1970s in the United States used TSP measurements as the indicator of particle exposures. The EPA (26) determined that the PM_{10}-to-TSP ratio was generally between 50% and 60% for US sampling sites.

In the late 1970s and early 1980s, the EPA established a network of particulate matter samplers with an upper-size cutoff of 15μm aerodynamic diameter (PM_{15}) to measure "inhalable particulates." This cutoff was recommended to define the fraction of particles that would deposit primarily in the conducting airways and the gas-exchange areas of the respiratory system during mouth breathing (24). Only very limited data are available comparing the PM_{15} to PM_{10} concentrations, but concentrations measured by these two methods appear to be similar.

In addition to the total inhalable particle concentration, particles smaller than 2.5μm aerodynamic diameter ($PM_{2.5}$) were measured based on consideration of their characteristic chemical composition and the predominant

penetration into the gas-exchange regions of the respiratory tract (24). Spengler & Thurston (47) have presented data for $PM_{2.5}$ and PM_{10} from six US cities. The mean $PM_{2.5}$-to-mean PM_{10} ratio was approximately 60%.

In most parts of the United States, fine particle ($PM_{2.5}$) concentrations are highly correlated with sulfate (SO_4) concentrations. For example, in the Six Cities Study (47), city-specific correlations were all greater than 0.70, and in four cities, greater than 0.84. In these data, the mean ratio of SO_4 to PM_{10} was approximately 25%.

Studies from Great Britain and other European countries have often used a pseudomeasure of particle mass called British Smoke (BS). This is a measure of the darkness of particles collected on a filter and determined by reflectance. Mass concentration is estimated based on the reflectance of a standard particle mass. Calibration of reflectance depends on the specific chemical composition of the particles (22). The upper size limit of the sampler is nominally 4.5μm aerodynamic diameter, although the penetration of particles through the sampler inlet does not define a sharp size cut-point (22). Generally, particles in the fine mode tend to be dark while those in the coarse mode tend to be lighter in color (11). British Smoke, therefore, is thought of as a measure of fine particle mass concentrations. The EPA (26) concluded that British Smoke was equal to PM_{10} as a lower bound and equal to TSP as an upper bound.

In the United States, a similar method was used in which particles were deposited on a filter tape and the concentration was estimated by light transmission through the sample, measured in Coefficient of Haze (CoH) units. A comparison of CoH and PM_{10} measurements in Santa Clara County, California, indicated that the CoH-to-PM_{10} ratio equals 55% (14).

Thus for this discussion we will use the following guidelines for estimating PM_{10} exposures in epidemiologic studies where other measures of particle concentration were reported:

$$PM_{10} \approx PM_{15} \qquad PM_{10} \approx PM_{2.5}/0.60$$

$$PM_{10} \approx TSP * 0.55 \qquad PM_{10} \approx BS$$

$$PM_{10} \approx CoH/0.55 \qquad PM_{10} \approx SO_4 * 4$$

Criteria of Study Selection

In this review, we have included studies that provide the following information: (*a*) exposure to particulates reported as PM_{10} concentrations or a

measure that allowed conversion to PM_{10}; (*b*) health effects measured as change in mortality or indicators of respiratory disease with time scales of days up to weeks or months; and (*c*) reported measures of association and their variance, which would allow calculation of the relative increase in effect compared to particle exposures and the confidence that can be ascribed to the effect estimate.

We have separated epidemiologic studies by comparable health endpoints (for example, mortality or exacerbation of asthma). Within each of these health endpoints, we have expressed reported results as the estimated relative percent change in the health measure associated with a 10 $\mu g/m^3$ increase in daily mean PM_{10} concentrations. For many recent studies that used logistic or Poisson regression and PM_{10}, this is a simple calculation based on reported regression coefficients and their standard errors. Many earlier studies, in which particle concentrations were not measured as PM_{10}, required converting from the reported measure of particle concentrations to PM_{10} concentrations, conversions based on relationships described above.

In some studies, particularly those with continuous health endpoints such as pulmonary function, associations are reported as a linear rather than a proportional (or logarithmic) change associated with particulate pollution. For these studies, we re-estimated the effect as percent change from the mean response associated with 10 $\mu g/m^3$ increase in PM_{10} above the mean exposure. This is a reasonable assumption for estimates close to the mean but will break down far from the mean.

For a few studies, particle concentrations had been transformed before including them in the analysis, e.g. effects reported as a function of the logarithm of the particle mass concentrations. For these studies, we estimated the effect of a 10 $\mu g/m^3$ increase in PM_{10} above the mean exposure. Again, this is appropriate close to the mean but should not be extrapolated to concentrations far from the mean.

Ninety-five-percent confidence intervals were calculated for each exposure estimate. In most cases, reports included standard errors of the estimates or confidence intervals. In a few early studies, however, only p-values were given. In these studies we estimated the standard error, assuming a normal distribution. When p-values were reported as less than some arbitrary cut-off (e.g. $p<0.05$), the standard errors were calculated, based on the upper limit of the cut-off probability (e.g. $z = 1.96$ for $p<0.05$).

To provide a combined estimate of the effect of 10 $\mu g/m^3$ increase in PM_{10} concentration for each health endpoint, a weighted average effect estimate was calculated where the study-specific effect was weighted by its inverse variance (one over the standard error squared).

HEALTH EFFECT STUDIES

Mortality

In the past few years, a series of papers has been published describing the association between daily mortality and suspended particulate concentrations in various communities across the United States. In 1990, an association between particle concentrations and daily mortality was reported for residents of Santa Clara County, California, for the period 1980–1986 (14). Associations were observed at relatively low concentrations of particles and sulfur dioxide.

This report was followed by analyses of similar data for Steubenville, Ohio (40) and for Philadelphia, Pennsylvania, (39). Both analyses suggested increased daily mortality associated with increased particle concentrations, even after adjusting for sulfur dioxide exposures. A quantitatively similar association was reported for Utah Valley, Utah, for the period 1985–89 (33). This study was notable because these associations with particle exposures are observed in the absence of substantial sulfur dioxide or ozone pollution. In analysis of data from St. Louis, Missouri, and Kingston, Tennessee (9), daily mortality was associated with several measures of particle exposures, but not with aerosol acidity, sulfur dioxide, ozone, or nitrogen dioxide concentrations.

In large communities (with a population of several million), the mean number of deaths/day is far enough from zero that the distribution is reasonably symmetric and Gaussian statistics can be applied. In most communities, however, the mean number of deaths/day is small and the distribution is skewed towards higher values. In both cases, because daily death counts can be modeled as following a Poisson process, regression analysis using the Poisson rather than the Gaussian distribution is appropriate. Associations are typically fitted to the logarithm (ln) of the number of deaths/day, that is, on a proportional rather than a linear scale. Specifically, the Poisson regression estimates the (ln) relative risk of mortality associated with a given exposure, which can be re-expressed as a percent increase in risk. All of the recent analyses of daily mortality and air pollution have used Poisson regression methods.

Use of the same endpoint (nonaccidental daily mortality), particulate exposure measures, which can be converted into a common metric (PM_{10}), and common analytic methods (Poisson regression) make it possible to tabulate approximately comparable effect estimates: the percent increase in daily mortality for each 10 $\mu g/m^3$ increase in PM_{10} concentrations (see Table 1).

Table 1 Studies of acute effects of particles on daily mortality

Location and period	Particulate measure	Mean PM_{10} ($\mu g/m^3$)	% Change in daily mortality for each 10 $\mu g/m^3$ increase in PM_{10} (95% CI)	Reference
Total mortality				
St. Louis, MO 1985–86	PM_{10} (previous day)	28	1.5% (0.1%, 2.9%)	9
Kingston, TN 1985–86	PM_{10} (Previous day)	30	1.6% (−1.3%, 4.6%)	
Santa Clara, CA 1980–82, 84–86	Coefficient of haze	35	0.8% (0.2%, 1.5%)	14
Philadelphia, PA 1973–80	TSP (2-Day mean)	40	1.2% (0.7%, 1.7%)	39
Birmingham, AL 1985–88	PM_{10} (3-Day mean)	48	1.0% (0.2%, 1.9%)	38
Utah Valley, UT 1985–89	PM_{10} (5-Day mean)	47	1.5% (0.9%, 2.1%)	33
Detriot, MI 1973–82	TSP	48	1.0% (0.5%, 1.6%)	37
Steubenville, OH 1974–84	TSP (previous day)	61	0.7% (0.4%, 1.0%)	40
Combined			1.0%	
Respiratory				
Santa Clara, CA 1980–82, 84–86	Coefficient of haze	35	3.5% (1.5%, 5.6%)	14
Philadelphia, PA 1973–80	TSP (2-Day mean)	40	3.3% (0.1%, 6.6%)	39
Utah Valley, UT 1985–89	PM_{10} (5-Day mean)	47	3.7% (0.7%, 6.7%)	33
Birmingham, AL 1985–88	PM_{10} (3-Day mean)	48	1.5% (−5.8%, 9.4%)	38
Combined			3.4%	
Cardiovascular				
Santa Clara, CA 1980–82, 84–86	Coefficient of haze	35	0.8% (0.1%, 1.6%)	14
Philadelphia, PA 1973–80	TSP (2-Day mean)	40	1.7% (1.0%, 2.4%)	39
Utah Valley, UT 1985–89	PM_{10} (5-day mean)	47	1.8% (0.4%, 3.3%)	33
Birmingham, AL 1985–88	PM_{10} (3-Day mean)	48	1.6% (−0.5%, 3.7%)	38
Combined			1.4%	

There is good consistency in the estimated effect of PM_{10} across these studies. Effect estimates range between 0.7% and 1.6% increase in daily mortality for each 10 $\mu g/m^3$ increase in PM_{10} concentration with a weighted mean of 1.0%. Ostro (26a) has recently estimated a similar combined effect (0.96% per 10μ/m^3 PM_{10}) in a review of time-series and cross-sectional mortality studies.

Four of the daily mortality studies (14, 33, 38, 39) also provided a breakdown of mortality by broad cause-of-death categories. Cardiovascular deaths, which were about 45% of all deaths in these three studies, had effect estimates between 0.8% and 1.8% (weighted mean, 1.4%) increase for each 10$\mu g/m^3$ PM_{10}. Respiratory deaths, which were 2% to 8% of the total, had effect estimates between 1.5% and 3.7% (weighted mean, 3.5%) increase for each 10 $\mu g/m^3$ PM_{10}. In all four studies, no associations were found with cancer mortality or with other causes.

Epidemiologic studies suffer from the weakness that observed associations with a specific exposure may result from an unmeasured association with an unknown or uncontrolled factor correlated with *both* exposure and disease, i.e. from a confounder. These time-series studies have the advantage that many major causes of increased mortality (such as smoking, hypertension, or even age) cannot confound the observed associations with particulate air pollution because these factors do not vary with daily pollution exposures. This is not to say that response may not differ by these factors. Indeed, the mortality effects of particulate air pollution are most strongly seen in the elderly in all those studies in which age is considered as an effect modifier.

Other factors such as weather conditions, which can vary with daily pollution exposures, are potential confounders in these analyses. All of the recent studies have attempted to control for weather factors (such as temperature) in the analysis. Residual confounding due to inadequate modeling or an unmeasured weather factor is removed by modeling the covariance of the residuals as autoregressive in these analyses. Similar associations are observed in areas with high winter particulate concentrations, characterized by trapping of direct industrial emissions—Utah Valley (33) and Steubenville (40)—and in areas of high summer particulate concentrations characterized by photochemical production of secondary particles such as sulfates and nitrates—Philadelphia (39) and Birmingham (38). The consistency of the effect estimate across different communities—in warm versus cold climates, in dry versus moist climates—suggests that climatic factors are in fact not important confounders.

If we accept the association between daily mortality and particulate air pollution shown in these studies, the possibility still remains that the true association is with some other pollutant correlated with PM_{10} or with a

specific component of the mixture of particles that makes up PM_{10}. The study of St. Louis and Kingston (9) considered a variety of pollutants and found the strongest associations with PM_{15} concentrations. Several studies (9, 39) evaluated sulfur dioxide as a possible confounder; no such confounding was shown. More importantly, associations between daily mortality and particulate air pollution in communities with low sulfur dioxide concentrations—Santa Clara (14) and Utah Valley (33)—were comparable to associations in communities with high sulfur dioxide concentrations—Steubenville (40). Kinney & Özkaynak (20) reported associations between daily mortality and ozone in Los Angeles. They emphasize the association with ozone, but strong associations were also observed with KM, a measure of light scattering by particles similar to Coefficient of Haze. The consistency of results across communities suggests an important if not dominant role of particle mass concentration in producing the observed associations with daily mortality.

Another interesting feature of these studies is the consistent finding of lagged associations between particle exposure and increased mortality. Most of the results presented have reported associations of increased mortality with particle concentrations on the previous day. It would violate a basic tenet of causality if the observed effect were not either concurrent with or lagged behind the exposure. In their analysis of Utah Valley deaths, Pope et al (33) considered longer lag structures up to seven days and found the strongest associations with the five-day moving average, i.e. with the mean PM_{10} of the current day and the four previous days. Thus, these data suggest that mortality effects of particulate air pollution may be lagged by several days.

In summary, a series of time-series analyses of the associations of daily mortality with particulate air pollution has shown a ~1.0% increase in total deaths/day associated with each 10 $\mu g/m^3$ increase in PM_{10} concentration. Stronger associations were observed with cardiovascular disease (1.4% per 10 $\mu g/m^3$ PM_{10}) and respiratory disease (3.4% per 10 $\mu g/m^3$ PM_{10}). The consistency of these estimates across communities suggests that these results are not due to confounding with an unknown or uncontrolled factor and that the mass concentration of the particle mix common to many urban areas, rather than specific chemical species within the mix, may be responsible for the observed associations.

Hospital Usage

If daily mortality is associated with daily particulate pollution levels, then associations with increased hospital admissions and emergency department visits should also be expected. In a unique natural experiment, Pope (28,

29) observed hospital admissions of children for respiratory disease in Utah Valley dropped by over 50 percent during the winter of 1986–87 compared to adjacent years. During this winter, a strike at the local steel mill led to much lower PM_{10} concentrations—a mean of 51 $\mu g/m^3$ and maximum of 113 $\mu g/m^3$ compared to a mean of 90 $\mu g/m^3$ and a maximum of 365 $\mu g/m^3$ in the previous year. Regression analyses estimated a 4.2% decrease in asthma and bronchitis admissions of children and a 7.1% decrease in all respiratory admissions of children associated with a 10 $\mu g/m^3$ decrease in the two-month mean PM_{10} concentration.

Increased rates of respiratory admissions, including asthma, for the years 1974 to 1983 in Southern Ontario have been associated with increased sulfate and ozone concentrations (4). A more recent analysis of hospital admissions for respiratory disorders in Southern Ontario for the summers of 1983 to 1988 (7) found an association with increased sulfate concentrations that was independent of associations with ozone exposures. Both studies have been interpreted as suggesting an association between hospital respiratory admissions and an unmeasured air pollutant correlated with sulfates and ozone. Specifically, the authors have suggested a link to acid aerosol concentrations. Alternatively, these associations may be attributable to particle mass concentrations, another air pollutant not considered in the analyses.

Recently, Thurston and colleagues have reported analyses of hospital admissions for respiratory complaints for Toronto, Ontario (50) and for several cities in New York state (51). Although the focus of these studies is the effects of acid aerosols, effect estimates are reported for various measures of particle exposure (Table 2). Taken together, these studies found an increase in hospital admissions for all respiratory diagnoses ranging from 0.8% to 3.4% (weighted mean, 0.8%) for each 10 $\mu g/m^3$ increase in daily mean PM_{10}. A slightly greater effect was seen in hospital admissions for asthma, ranging from 1.9% to 2.1% (weighted mean, 1.9%) for each 10 $\mu g/m^3$ increase in daily mean PM_{10}.

Emergency department visits also have been analyzed by many investigators, and three studies provided quantitative effect estimates of the effects of particles (see Table 2). An analysis of emergency department visits for asthma in Seattle (42) found an increase of 3.4% associated with a 10 $\mu g/m^3$ increase in PM_{10}. Emergency department visits for chronic obstructive pulmonary disease in Barcelona (48, 49) increased by 1.7% associated with a 10 $\mu g/m^3$ increase in PM_{10}. Emergency department visits in Steubenville (35) increased by 0.5% associated with a 10 $\mu g/m^3$ increase in PM_{10}. The weighted mean of these combined effect estimates was a 1.0% increase in emergency department visits associated with each 10 $\mu g/m^3$ increase in PM_{10}.

Table 2 Acute effects of particles on hospital usage

Measure of hospital usage	Location and period	Particulate measure	% Change in hospital usage for each 10 $\mu g/m^3$ increase in PM_{10}	Reference
Hospital Admissions				
Asthma	New York City	Daily mean SO_4	1.9% (0.4%, 3.4%)	51
	Buffalo, NY		2.1% (−0.6%, 5.0%)	
	Toronto, ONT Summer 86–88	Daily mean $PM_{2.5}$	2.1% (−0.8%, 5.1%)	50
	Combined		1.9%	
All respiratory	New York City	Daily mean SO_4	1.0% (0.2%, 1.8%)	51
	Buffalo, NY		2.2% (0.6%, 3.8%)	
	Toronto, ONT Summer 86–88	Daily mean $PM_{2.5}$	3.4% (0.4%, 6.4%)	50
	Southern Ontario Summer 83–88	Daily mean SO_4	0.8% (0.4%, 1.1%)	7
	Combined		0.8%	
Emergency Department Visits				
Asthma (<65 yr)	Seattle, WA 1989–90	Daily mean PM_{10}	3.4% (0.9%, 6.0%)	42
Respiratory disease	Steubenville, OH	Daily mean TSP	0.5% (0.0%, 1.0%)	35
Chronic obstructive pulmonary disease	Barcelona, Spain Winter 85–89	British Smoke	2.3% (1.4%, 3.2%)	49
	Combined		1.0%	

Asthma

Evidence from hospital admissions and emergency department visits presented above suggests that particle exposures may be directly associated with asthma attacks. Several investigators have considered less severe asthmatic attacks reported by panels of asthma patients. Winter studies of asthmatic children with chronic respiratory symptoms in The Netherlands (34) and of asthmatic adults in Denver, Colorado, (27) both found substantial increases in reported asthmatic attacks associated with particle exposures. An earlier study of sixteen asthma panels in the Los Angeles area (56) reported increased attacks associated with particle exposures but the effect

was much lower than in the more recent studies (see Table 3). In part this lower effect estimate may reflect over-control of lagged effects of particles by including the previous day's asthma status in the model. The weighted mean of these three studies, however, gives an effect estimate of 3% increase in asthmatic attacks associated with 10 $\mu g/m^3$ PM_{10}.

The use of bronchodilators also has been evaluated as a measure of exacerbation of asthma in a panel of asthmatics in The Netherlands (34) and in panels of symptomatic children and asthmatic patients in the Utah Valley (31; see Table 3). The weighted mean of these studies gives an estimated effect of a 2.9% increase in bronchodilator use associated with 10 $\mu g/m^3$ PM_{10}.

Lung Function

Lung function is a sensitive indicator of acute response to ozone in controlled exposure and chamber studies (21). Repeated measures of lung function in panels of children also have been used to evaluate the effect of particulate air pollution episodes on children.

Panels of elementary school children in Steubenville had their lung function measured weekly before, during, and after particulate and sulfur dioxide episodes during four periods in 1978 through 1980 (10). Forced Expired Volume in three-quarters of a second ($FEV_{.75}$) was reported to decline following these episodes. There was a suggestion that $FEV_{.75}$ remained depressed for up to two weeks following the episode. A study of weekly lung function measurement of school children in The Netherlands (7a) following a sulfur dioxide and particulate episode in January 1985 reported decreases in Forced Expired Volume in one second (FEV_1), which were similar in magnitude and in lag structure to those observed in Steubenville. Subsequent studies of panels of school children with weekly lung function measurements (17, 18) have also shown decreased FEV_1 associated with daily PM_{10} concentrations.

Analysis of longer lags in The Netherlands panel (17) found a significant association between decreased FEV_1 and mean PM_{10} over the previous seven days. Similarly, in a re-analysis of the Steubenville data, Brunekreef (6) found the strongest association with the mean TSP over the previous five days.

Recently, Pope & Kanner (32) analyzed repeated FEV_1 measurements in a panel of chronic obstructive pulmonary disease patients participating in the Lung Health Study. Measurements were taken 10 to 90 days apart. FEV_1 level was reported to be associated with a 0.2% decrease in FEV_1 for each 10 $\mu g/m^3$ increase in daily PM_{10}.

Taken together, these studies found a decrease of between 0.05% and

Table 3 STudies of acute effects of particles on exacerbation of asthma

Measure of asthmatic response	Location and period	Particulate measure	Subjects	% Change in daily asthma response for each 10 $\mu g/M^3$ increase in PM_{10}	Reference
Bronchodilator use	Utah Valley, UT Winter 1989–90	Daily mean PM_{10}	School panel Asthma panel	11.2% (2.4%, 20.7%) 12.0% (4.7%, 19.7%)	31
	2 Dutch Cities Winter 1990–91	Daily mean PM_{10}	School panel	2.3% (0.7%, 3.8%)	34
	Combined			2.9%	
Asthmatic attacks	2 Dutch Cities Winter 1990–91	Daily mean PM_{10}	School panel	1.1% (−3.5%, 5.9%)	34
	Los Angeles, CA 1972–75	TSP	Asthma panels	1.4% (0.3%, 2.6%)	56
	Denver, CO 1987–88	$PM_{2.5}$	Asthma panel	11.5% (8.9%, 14.3%)	27
	Combined			3.0%	

0.35% or a weighted average of 0.15% decrease in FEV_1 associated with each 10 $\mu g/m^3$ increase in daily mean PM_{10} (see Table 4).

Peak flow measurements have been widely used as a simple, inexpensive indicator of acute changes in lung function among asthmatic patients. Weekly peak flow measurements were made in the spirometric studies of school children in The Netherlands (17, 18). In these two studies, peak flow declined approximately 0.16% for each 10 $\mu g/m^3$ increase in PM_{10}.

Daily peak flow measurements have been gathered in a series of recent

Table 4 Studies of acute effects of particles on lung function

Measure of lung function	Location and period	Particulate measure	% Decrease in daily lung function for each 10 $\mu g/m^3$ increase in PM_{10}	Reference
Forced Expired Volume				
$FEV_{.75}$	Steubenville, OH 1978–80	Daily Mean TSP	0.05% (0.00%, 0.10%)	10
FEV_1	4 Cities, NL Winter 1987–90	Daily Mean PM_{10}	0.06% (−0.01%, 0.14%)	18
	Wageningen, NL Winter 1990–91	Daily Mean PM_{10}	0.35% (0.23%, 0.48%)	17
	Salt Lake City, UT 1987–89	Daily Mean PM_{10}	0.21% (0.05%, 0.37%)	32
	Combined		0.15%	
Peak Expiratory Flow				
Daily (evening)	Utah Valley, UT 1989–90	Daily Mean PM_{10}	0.25% (0.10%, 0.39%)	31
	Utah Valley, UT 1990–91	Daily Mean PM_{10}	0.06% (−0.00%, 0.12%) 0.04% (−0.02%, 0.09%)	30
	Wageningen, NL 1990–91	Daily Mean PM_{10}	0.09% (−0.01%, 0.20%)	34
	Uniontown, PA Summer 1990	Daily Mean PM_{10}	0.19% (0.01%, 0.37%)	25
(> = weekly)	4 Cities, NL Winter 1987–90	Daily Mean PM_{10}	0.16% (0.05%, 0.28%)	18
	Wageningen, NL Winter 1990–91	Daily Mean PM_{10}	0.16% (−0.03%, 0.36%)	17
	Combined		0.08%	

studies. In two separate panel studies in the winters of 1989–90 and 1990–91 in Utah Valley (30, 31), panels of school children measured their peak flow daily before going to bed. In both cases, small but significant reductions in peak flow were found associated with mean PM_{10} concentrations that day. In both studies there appeared to be associations between lower peak flow and PM_{10} concentrations for up to five days prior, and stronger associations were found when these lag structures were included in the models. In the second study (30), the estimated effect was about twice as large with the five-day lagged mean compared to the one-day mean PM_{10}.

Similar winter panel studies of school children have been conducted in The Netherlands (34). Effects were observed between evening peak flow and daily mean PM_{10} concentrations, and seven-day mean PM_{10} concentration, which were similar to those observed in Utah.

A panel study of children was conducted in the summer of 1992 in Uniontown, Pennsylvania, (25) to evaluate peak flow changes in an area of high aerosol acidity. Although the strongest associations were found with aerosol acidity, there also was an association between evening peak flow and daily mean PM_{10} that was very consistent with the estimates from other studies.

Comparing the results from these studies of repeated peak flow measurements, there was a decrease of between 0.04% and 0.25% in peak flow (weighted mean of 0.08%) associated with each 10 $\mu g/m^3$ increase in daily mean PM_{10} concentration (Table 4).

In summary, studies of repeated measure of lung function consistently show a small decrement in FEV_1 (weighted mean 0.15%) and peak flow (weighted mean 0.08%) associated with each 10 $\mu g/m^3$ in PM_{10} daily mean concentration. There is a strong suggestion in these data that changes in lung function may reflect the cumulative exposure of several (5–7) days prior to the measurement.

Respiratory Symptoms

Daily diaries of respiratory symptoms, an inexpensive method of evaluating acute changes in respiratory health status, have been widely used in evaluating acute effects of particulate air pollution. In a commonly applied study design, panels of school children recorded the presence of specific respiratory symptoms daily on weekly or monthly calendars. These symptom reports are often aggregated into *upper respiratory symptoms* (including such symptoms as runny or stuffy nose, sinusitis, sore throat, wet cough, head cold, hayfever, and burning or red eyes) and *lower respiratory symptoms* (including wheezing, dry cough, phlegm, shortness of breath, and chest discomfort or pain). In addition, *cough,* the most frequently reported symptom, is often

analyzed separately. In this review, symptom reports are presented separately for each of these symptom groups.

The frequency of reported respiratory symptoms was generally taken as their prevalence on any given day, that is, the fraction of participating children reporting a symptom complex on each day. In some cases (41), however, incident cases were reported, where "incidence" required that the child be symptom-free for two days prior to the incident symptom report.

Studies of upper and lower respiratory symptoms have been conducted in Utah Valley (30, 31), The Netherlands (17, 18), in a study of six US cities (41), and Southern California (27a; Table 5).

The combined weighted average from these studies gives an estimated effect of 3.0% increase in lower respiratory symptoms with each 10 $\mu g/m^3$ increase in daily mean PM_{10} concentrations. For upper respiratory symptom reports, the weighted average effect estimate was only a 0.7% increase in upper respiratory symptoms with each 10 $\mu g/m^3$ increase in daily mean PM_{10} (Table 5).

Cough reports were analyzed in three of these studies as well as in a winter diary study in The Netherlands (34), a study of two Swiss cities (5), and the summer diary study in Uniontown (25; Table 5). The weighted mean effect estimate from these studies was a 1.2% increase in cough associated with each 10 $\mu g/m^3$ increase in daily mean PM_{10}.

SUMMARY

Evidence from the selected epidemiologic studies presented in this review suggests a *coherence* of effects across a range of related health outcomes and a *consistency* of effects across independent studies with different investigators in different settings. This compilation also provides insights into the relative magnitude of effects being observed in various studies (Table 6).

Total mortality is observed to increase by approximately 1% per 10 $\mu g/m^3$ increase in PM_{10}. Somewhat stronger associations are observed for cardiovascular mortality (approximately 1.4% per 10 $\mu g/m^3$ PM_{10}), and considerably stronger associations are observed for respiratory mortality (approximately 3.4% per 10 $\mu g/m^3$ PM_{10}). No acute effects are detected with cancer and other nonpulmonary and noncardiovascular causes of mortality. These relative differences in cause-specific mortality are plausible, given the respiratory route of particle exposures.

If respiratory mortality is associated with particulate pollution, then health care visits for respiratory illness would also be expected to be associated with particulate pollution. Respiratory hospital admissions and emergency department visits increase by approximately 0.8% and 1.0% per 10 $\mu g/m^3$

Table 5 Studies of acute effects of particles on respiratory symptom reports

Measure of respiratory symptoms	Location and period	Particulate measure	Sample	% Change in daily symptom reporting for each 10 $\mu g/m^3$ increase in PM_{10}	Reference
Lower respiratory	Utah Valley, UT Winter 1989–90	Daily mean PM_{10}	Children Asthmatics	5.1% (1.1%, 9.3%) 0.2% (−4.2%, 4.8%)	31
	Utah Valley, UT Winter 1990–91	Daily mean PM_{10}	Symptomatic children Asymptomatic children	4.8% (1.5%, 8.3%) 2.4% (−1.8%, 6.8%)	30
	6 US cities Summer 1984–88	Daily mean PM_{15}	School children	15.2% (6.3%, 24.9%)	41
	Wageningen, NL Winter 1990–91	Daily mean PM_{10}	School children	1.2% (−3.1%, 5.7%)	17
	4 Dutch cities Winters 87–90	Previous day PM_{10}	School children	1.5% (−1.1%, 4.2%)	18
	Southern CA Winter 1978–79	Daily mean CoH	Nonsmoking adults	5.9% (−1.9%, 14.3%)	27a
	Combined			3.0%	
Upper respiratory symptoms	Utah Valley, UT Winter 1989–90	Daily mean PM_{10}	Children Asthmatics	3.7% (0.7%, 6.8%) −0.2% (−4.2%, 4.0%)	31
	Utah Valley, UT Winter 1990–91	Daily mean PM_{10}	Symptomatic children Asymptomatic children	3.7% (0.6%, 6.9%) −0.2% (−4.9%, 4.7%)	30

	6 US cities Summer 1984–88	Daily mean PM_{15}	School children	6.9% (−0.7%, 15.0%)	41
	Wageningen, NL Winter 1990–91	Daily mean PM_{10}	School children	2.6% (0.1%, 5.3%)	17
	4 Dutch cities Winters 1987–90	Previous day PM_{10}	School children	−0.2% (−1.2%, 0.8%)	18
	Southern CA Winter 1978–79	Daily mean CoH	Nonsmoking adults	2.7% (−2.5%, 8.2%)	27a
	Combined			0.7%	
Cough symptoms	Utah Valley, UT Winter 1990–91	Daily mean PM_{10}	Symptomatic children Asymptomatic children	5.2% (2.3%, 8.2%) 3.4% (−0.1%, 7.0%)	30
	6 US cities Summer 1984–88	Daily mean PM_{15}	School children	8.6% (2.2%, 15.4%)	41
	2 Dutch cities Winter 1990–91	Previous day PM_{10}	Symptomatic children	0.1% (−0.8%, 1.1%)	34
	4 Dutch cities Winters 1987–90	Previous day $PM_{1)}$	School children	1.3% (−0.1%, 2.7%)	18
	2 Swiss cities	Previous day TSP	Children	8.6% (2.1%, 15.6%)	5
	Uniontown, PA Summer 1990	Daytime mean $PM_{2.5}$	Children	28.1% (4.5%, 57.1%)	25
	Combined			1.2%	

Table 6 Combined effect estimates of daily mean particulate pollution

	% Change in health indicator per each 10$\mu g/m^3$ increase in PM_{10}
Increase in daily mortality	
Total deaths	1.0
Respiratory deaths	3.4
Cardiovascular deaths	1.4
Increase in hospital usage (all respiratory)	
Admissions	0.8
Emergency department visits	1.0
Exacerbation of asthma	
Asthmatic attacks	3.0
Bronchodilator	2.9
Emergency department visits*	3.4
Hospital admissions	1.9
Increase in respiratory systems reports	
Lower respiratory	3.0
Upper respiratory	0.7
Cough	1.2
Decrease in lung function	
Forced expired volume	0.15
Peak expiratory flow	0.08

*One study only

PM_{10} respectively. Emergency department visits for asthmatics (3.4% increase per 10 $\mu g/m^3$ PM_{10}) and hospital admissions for asthmatic attacks (1.9% increase per 10 $\mu g/m^3$ PM_{10}) are more strongly associated. Asthmatic subjects also report substantial increases in asthma attacks (an approximate 3% increase per 10 $\mu g/m^3$ PM_{10}) and in bronchodilator use (an approximate 3% increase per 10 $\mu g/m^3$ PM_{10}).

Less severe measures of respiratory health also are associated with particle exposures. Lower respiratory symptom reporting increases by approximately 3.0% per 10 $\mu g/m^3$ PM_{10} and cough by 2.5% per 10 $\mu g/m^3$ PM_{10}. Weaker effects are observed with upper respiratory symptoms (approximately 0.7% per 10 $\mu g/m^3$ PM_{10}). While lung function provides accurate objective measures, the observed mean effects are fairly modest: approximately 0.15% decrease for FEV_1 or $FEV_{.75}$ and 0.08% decrease for peak flow per 10

mg/m^3 PM_{10}. Despite the relatively small size of these lung-function effect estimates, they consistently achieve statistical significance. Moreover, mean changes in lung function may not reflect substantial changes in sensitive individuals.

In this review, changes in health measures are reported for only small changes in daily particulate pollution: 10 μg/m^3 increase in PM_{10} concentrations. Because daily concentrations of PM_{10} in some US cities average over 50 μg/m^3 and often exceed 100 or 150 μg/m^3, the effects of particulate pollution can be substantial for realistic acute exposures. For example, a 1% effect estimate per each 10 μg/m^3 increase would produce a 5% increase in the health measure for a 50 μg/m^3 increase in PM_{10} concentrations, and a 3% effect estimate would produce a 16% increase. Thus the estimated increase in attacks of asthma (3.0% per 10 μg/m^3 PM_{10}) would be 16% for a 50 μg/m^3 increase in PM_{10} concentrations.

LIMITATIONS

Mass concentration of inhalable particles is only one measure of a complex mixture of gaseous and particulate air pollution to which people are exposed. In this review the possible contribution of gaseous co-pollutants has been ignored. The mass concentration of PM_{10} includes a wide array of potentially toxic chemical species. It is, therefore, presumptuous to assign these observed health effects solely to the mass concentration of particulates. On the other hand, the consistency of these observed effects across so many communities suggests that, lacking an explicit hypothesis, these associations should be assigned to a nonspecific definition of inhalable or fine particle concentrations common to urban areas.

The physical and chemical characteristics of ambient particles are generally not known and so are impossible to duplicate in controlled animal- or human-exposure studies. Many health effects of particles are thought to reflect the combined action of the diverse components in the pollutant mix. Until controlled animal- and human-exposure studies identify the active component(s) of these complex mixtures and can characterize their underlying mechanisms of toxicity, it is prudent to ascribe health effects observed by epidemiologists to the undifferentiated particle mass rather than to any specific component.

Conversion of various measures of particle concentration to PM_{10} mass concentrations are approximations only, based on results presented in published reports. These conversions are certainly correct within a factor of two and are probably within 20% of the true relationship. Thus, while other reviewers may legitimately argue about specific relationships between the

particle measures used in the various studies, the estimated effects would remain remarkably comparable, even assuming other reasonable conversions to PM_{10} mass concentrations.

The results of epidemiologic studies of acute effects of particulate air pollution, particularly those describing associations with cardiovascular mortality, have been called into question because of the lack of a biologically plausible mechanism (52, 53). The linkage between air pollution exposure and acute cardiovascular mortality is not clear. Many authors have suggested that air pollution episodes, like episodes of extreme temperature, high or low, are an additional environmental stress that may cause death in otherwise-compromised patients. Bates (3) has suggested three additional mechanisms by which respiratory and cardiovascular mortality might increase in air pollution episodes: (*a*) acute bronchitis and bronchiolitis may be misdiagnosed as pulmonary edema; (*b*) air pollutants may increase lung permeability and precipitate pulmonary edema in people with myocardial damage and increased left atrial pressure; (*c*) bronchiolitis or pneumonia induced by air pollution, in the presence of pre-existing heart disease, might precipitate congestive heart failure. An alternative explanation is that respiratory causes of death, either primary or contributing, are erroneously reported as cardiovascular. In a summary of a workshop of chronic obstructive pulmonary disease mortality, Speizer (46) observed that chronic obstructive pulmonary disease is considerably underdiagnosed on death certificates. While the specific biologic mechanism for these acute increases in mortality is not clear, the internal consistency of the mortality studies and the external consistency with evidence of acute increases in morbidity measures suggest that these results are not artifacts.

RECOMMENDATIONS

Mortality has always been a key health endpoint in epidemiologic studies, i.e. it serves as a leading indicator for hypothesis generation. It is a well-defined health outcome and mortality data are routinely collected and are readily available for epidemiologic analysis. When the numerous time-series studies of the association of mortality with particulate air pollution are compiled, using comparable measures of effect (% increase) and exposure (PM_{10}) as in Table 1, the consistency of estimated effects becomes clear. When estimated effects of particulate air pollution are similarly combined for other health indicators, the consistency and coherence of results also becomes apparent. These findings highlight the importance of using equivalent exposure metrics and health endpoints in air pollution studies.

Thus, we recommend that researchers report results such that they can be readily compared with previous (and future) investigations. The groupings

of health endpoints considered here present some guidance. Likewise, the reporting of associations with PM_{10} concentrations is important. This recommendation should not be interpreted as a request for regimentation or an attempt to limit innovation. Rather, it is recommended that the associations with common endpoints and PM_{10} exposures be reported in addition to other, potentially more sensitive or specific, indicators of health effect or exposure.

A quantitative effect estimate and its estimated standard error should be reported in all cases. Reports of statistical significance without effect estimates are not very informative. Likewise, correlation coefficients and other unscaled measures of association fail to provide useful information.

Epidemiologic research regarding the health effects of particulate air pollution has been impeded by the lack of daily (or more frequent) particle measurements (8). In communities that are not likely to violate (or that clearly exceed) the NAAQS for particles, PM_{10} measurements are made only once every six days, as required by the EPA (13). Fortunately for epidemiologists, the EPA has required daily monitoring in communities likely to violate the NAAQS for particles. These regulations have had the unanticipated (but beneficial) effect of making feasible new epidemiologic studies of the acute effects of particles. Inasmuch as associations are being observed between daily particle exposures and adverse health effects down to the lowest measureable concentrations, it is recommended that daily PM_{10} concentrations be measured whenever possible. When alternative measures of particle concentrations are used, then a description of the relationship to PM_{10} concentrations should be provided.

Research into mechanisms of the adverse health effects of PM_{10} mass concentrations observed in recent epidemiologic studies needs to be undertaken in controlled exposure studies of humans and animals. It is only through integration of the complementary evidence from laboratory animal and controlled human exposure studies with the results from epidemiologic studies that the risk of particle exposures can be fully evaluated. Nevertheless, these recent epidemiologic studies implicate particulate air pollution as contributing to respiratory morbidity and mortality even at exposure levels below the current NAAQS in the United States.

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