REVIEW OF RECENT EPIDEMIOLOGICAL DATA ON HEALTH EFFECTS OF PARTICLES, OZONE AND NITROGEN DIOXIDE

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INTRODUCTION

Observational epidemiology has been an important research tool in assessing health effects of exposures to air pollution. Even though epidemiologic studies have certain limitations, they have a high degree of relevance to population-based health effects investigations. Consequently, air quality control strategies and health-based standards that have been adopted in most countries rely heavily on the results of environmental epidemiologic investigations.

Historically, ambient air pollution levels were much greater than currently experienced and frequently produced severe pollution episodes resulting in readily observable illness and death. London pollution episodes in the 1950's, pollution episodes in Donora, Pennsylvania in 1948, and in Meuse Valley, Belgium in 1930 were among the well documented of these cases. Analysis of health and pollution data for conditions that existed before the 1970's were conducted using limited pollution measurements and simple statistical techniques. Only over the last decade, the study of the relationships between different toxic components of air pollutants and alternative human health end points began receiving serious attention. By employing sophisticated sampling and analysis techniques, researchers can now collect pollutant-specific concentration information, as well as data on physical and chemical composition of atmospheric aerosols and gases. Using the results from refined field studies, epidemiologists have been able to better quantify the extent of the relationship between pollutant concentrations and human health effects.

This paper examines the recent epidemiologic evidence on the statistical associations between mortality and morbidity effects of particles, ozone and nitrogen dioxide. Not all of the health-end points are reviewed here. Emphasis is placed on total mortality (excluding suicides and accidents) and hospital admissions or emergency visits. Also, this review focuses on the findings from most recent studies published over the last three to five years, while building upon the knowledge derived from earlier investigations.

HEALTH EFFECTS OF PARTICLES

Atmospheric particles typically occur in two distinct size modes: fine and coarse aerosol mode. Particles in the fine mode (fine particles or $PM_{2.5}$) are usually smaller than 2.5μm in aerodynamic diameter (d_a) and constitute the most respirable fraction of urban aerosols. They include sulfates, organics, ammonium, nitrates, carbon, lead and trace elements, whereas particles in the coarse mode (PM_{10}) are often found in the size range $2.5\ \mu m < d_a < 10\mu m$. These particles are also inhalable and are mostly composed of earth crustal materials, iron, aluminium, sea salt and biological material. A wide variety of sources influence the concentration and chemical composition of the particles found in the atmosphere. Both natural sources of particles, such as windblown dust, airborne sea salt, smoke and forest fires, and man-made emissions from industrial, commercial and urban activities contribute to the mass loadings of particles measured in the ambient air. In industrial areas and in some metropolitan areas, a significant fraction of the respirable particles is due to emissions from fossil fuel combustion used for energy or domestic heat generation

Upon release into the atmosphere through condensation, evaporation, and chemical transformations gases may become particles. Sulfate (SO_4) is a primary example of this phenomenon. These (secondary) particles have been found to vary in size, shape, concentration, and composition, both spatially and temporally. Because different gases and types of particles are known to have varying toxicity or biological activity, characterization of gases and airborne particles for health studies becomes difficult. A number of other issues further complicate this assessment. Therefore, developing quantitative relationships between particles and human health effects requires consideration of a number of factors. In almost all of the available observational studies of air pollution epidemiology, population exposures were derived from monitoring data gathered by fixed-site ambient monitors. These ambient measurement were then used to represent, uniformly, the community-wide concentrations of all the individuals living in the study area. Thus, variations among personal exposure could not be characterized.

Most of the historic particle measurements used surrogates for toxic components of airborne aerosols rather than direct measurements of size-fractionated (e.g., PM_{10} or $PM_{2.5}$) aerosols by chemical composition. To the extent that the crude measures of exposures -- represented, for example, by outdoor Coefficient of Haze (COH), British Smoke (BS), Total Suspended Particulate matter (TSP) and sulfate (SO_4^{2-}) levels -- are surrogates for the harmful agents of airborne particles, the detailed characterization of aerosols may be unimportant, as long as the principal compositions of aerosols remains unchanged over time. However, emission controls, relocation of facilities, and changes in the available fuel has, in fact, reduced TSP levels and decreased the sootiness of the aerosols in most urban areas in the US and other countries.

Thus, predictions regarding the extent of association between air pollution and human mortality or morbidity are hampered

by data base limitations as well as methodological difficulties. In principle, only after carefully considering all relevant sources of error and utilizing improved exposure estimates in epidemiologic assessments, can one expect to develop reliable health risk coefficients for airborne particles and gases. In order to quantify air pollution health effects researchers have turned to observational studies as well as studies utilizing vital statistics data.

In the following, recent epidemiologic data on mortality and morbidity effect of particles are briefly summarized.

Mortality Effects of Particles

Cross-sectional mortality analysis

Cross-sectional mortality analysis refers to the study of the relationships between air pollution and health by analysing statistically the geographic differences in (annual) mortality and the corresponding pollution level. Many investigators have adopted this type of epidemiologic analysis of vital statistics data, perhaps most notable Lave and Seskin[1]. Their analysis of data for 117 Standard Metropolitan Areas (SMAs) from 1960 produced results that showed significant, positive association between mortality and TSP and TSP-sulfates. A review of the relevant cross-sectional mortality literature and the re-analysis of Lave and Seskin's 1960 data in Evans *et al.*[2] and in Özkaynak and Thurston[3] confirmed the positive associations that Lave and Seskin described. Özkaynak and Thurston[4] analyzed the 1980 US vital statistics and available ambient air pollution data bases for sulfates and fine, inhalable, and total suspended particles. Using multiple regression analyses, they conducted a cross-sectional analysis of the association between various particle measures and total mortality. Results from the various analyses indicated the importance of considering particle size, composition, and source information in modeling of particle pollution health effects. Of the independent mortality predictors considered, particle exposure measures related to the respirable and/or toxic fraction for the aerosols, such as fine particles and sulfates, were most consistently and significantly associated with the reported SMA-specific total annual mortality rates. On the other hand, particle mass measures that included coarse particles (e.g., total suspended particles and inhalable particles) were often found to be nonsignificant predictors of total mortality. Sulfate concentration was consistently found to be a significant predictor of mortality in the models considered. Often fine particle (FP) mass coefficients were also found to be statistically significant in the mortality regressions. The ranges of estimated total mortality effects of air pollution, using the following pollution surrogates reported in Özkaynak and Thurston[3], were: SO_4: 4-9%; FP: 3-8% and TSP: 0-6%.

Time-series mortality studies

In the absence of long-term studies designed specifically to detect the mortality effects resulting from exposures to air pollution, attempts have been made to utilize available mortality and pollution index data to search for a possible cause-effect relationship. Time-series analysis provides one means by which to test for such a relationship. Using many years of daily observations, the time-series approach utilizes statistical methods to estimate the influence of daily air pollution on daily mortality. There are, however, several issues which preclude direct estimation of effects and cloud the interpretation of the results obtained. One issue is the of "temporal confounding" i.e., the potential existence of variables which are correlated in time with air pollution and exert influence on mortality independently of air pollution. Temporal confounding has been considered as: low frequency (seasonal cycles or trends) and high frequency (day to day variations). For this reason most time-series investigations have included weather variables (after appropriate filtering) in their regressions.

Another issue limiting the interpretation of time-series results is the expression of coefficients for particle air pollution effects in terms of COH or BS, rather than, for example, TSP or FP concentrations. The latter set of units (or other particle-size-classified mass concentrations) would be of more direct use to policy analysts and might also be physiologically interpretable. However, soiling data are almost always used in time-series studies because they are the only historic data generally available on a daily basis for extended periods in large cities.

Recently Schwartz and Dockery[5,6] and Pope *et al.*[7] analyzed the associations between daily pollution and mortality in various cities in the US. These analyses showed that increased daily mortality was associated with increased particle concentrations, even after adjusting for sulfur dioxide exposures. A quantitatively similar association was reported for Utah Valley, UT for the period 1985-1989[7]. This study was especially important since the demonstrated associations with particle exposures were observed in the absence of sulfur dioxide or ozone pollution. In analysis of data from St. Louis, MO and Kingston, TN[8] daily mortality was associated with several measures of particle exposure. Associations, however, were not found with aerosol acidity, sulfur dioxide, ozone or nitrogen dioxide concentrations. Table 1 summarizes the results from these and other recent studies in terms of estimated percent increase in mortality for a 10$\mu g/m^3$ increase in daily PM_{10}.

Several studies have reported associations between daily mortality and various measures of airborne particulate levels, including TSP, PM_{10}, BS, and COH. However, very few such studies have also considered phot chemical oxidant data in the analyses conducted. Most recently, three major time-series investigations were conducted by Özkaynak, Kinney and their colleagues examining the associations between daily mortality and both particle and ozone pollution in major urban areas in the US and Canada.

TABLE 1. RECENT TIME-SERIES STUDIES OF EFFECTS OF PARTICULATES ON DAILY MORTALITY

Reference	Particulate Measure Used in the Study*	Percent Increase in Mortality for a 10μm/m³ Increase in Daily NM_{10} **	StudyLocation
Schwartz and Dockery[4]	Total Suspended Particulates	1.2% ± 0.2	Phiadelphia, PA
Schwartz[9]	Total Suspended Particulates	1.0% ± 0.3	Detroit, MI
Schwartz and Dockery[5]	Total Suspended Particulates	0.7% ± 0.2	Steubenville. OH
Schwartz[10]	PM_{10}	1.0% ± 0.4	Bir mingham, AL
Dockery *et al.*[7]	PM_{10}	1.5% ± 0.7	St. Louis, MO
Pope *et al.*[6]	PM_{10}	1.5% ± 0.3	Utah Valley, UT
Fairley[11]	Coefficient of Haze	0.8% ± 0.4	Santa Clara County, CA
Özkaynak and Kinney[12]	Coefficient of Haze ***	0.8% ± 0.3	New York City, NY
Kinney ond Özkaynak[8]	KM	0.4% ± 0.1	Los Angeles, CA
Özakaynak et al.(13)	Total Suspended Particulates	0.6% ± 0.2	Toronto, Canada

* Conversions used: 0.55 * TSP = PM_{10}, Sulfates/0.25 = PM_{10}, 2.2 * KM = PM_{10}, COH/0.55 = PM_{10}

** (± one standard error)

*** 40 * COH = PM_{10}

Kinney and Özakaynak[8] reported the findings from the investigation of the relationship between daily mortality and air pollution in Los Angeles county using records for the 10 year period: 1970 - 1979. Pollution and meteorological data were obtained from eight air monitoring stations in Los Angels run by SCAQMD. Analysis variables include daily: KM, CO, NO_2, SO_2, BEXT, TEMP, RH, and M (total mortality, cardiovascular mortality, and respiratory mortality). The pollution and mortality series were filtered or detrended using a filter developed by Shumway[14]. Results showed that temperature and one day lagged ozone were most significantly associated with daily excess mortality but particles, measured in terms of KM, which is a measure of optical reflectance on tape samplers, were also significantly associated with daily mortality (β_{KM} = 0.13 deaths/KM and excess mortality due to average particle pollution ~2%).

More recently a similar analysis was applied to data for the period 1971-1976 in New York City. The available data included total and cause-specific daily mortality, daily concentrations of SO_2, COH, and ozone (O_3) as well as measurements of three meteorological variables: temperature (T) relative humidity (RH), and visibility. Ozone data, as a daily one-hour maximum, were available for the months April - September. Özkaynak and Kinney[12] performed multiple regression analyses of mortality on the pollution and meteorological variables from New York City, after controlling for seasonal variations. A model which included T, RH, COH, and previous day (lag 1) O_3 explained approximately 10% of the variation in total mortality. The regression slope for particles measured in terms of COH, form an optical soiling index, was β_{COH} = 5.6 deaths/COH with estimated (COH) contribution to daily excess mortality around 2%.

Recently a time-series mortality analyses was performed by Özakaynak *et al*[13] using an extensive aerometric particulate database from Toronto, Canada covering the 19 year period, from 1972-1990. Data on total and cause-specific daily mortality counts for multiple age groups were available through a health data base maintained by Statistics Canada. The daily aerometric time-series records included pollution data on TSP, SO_2, COH, O_3, SO_4, CO and NO_2, and were

obtained from sixteen air monitoring stations from five boroughs of Toronto. Meteorological and visibility data were obtained from Pearson airport in Toronto. Multiple regression analyses of mortality on the pollution and meteorological variables were conducted after detrending the mortality and pollution series in order to control for seasonal variations in the data. A model which included temperature, relative humidity, same day maximum 1-hr O_3, and, either same day TSP or estimated PM_{10}, explained approximately 2% of the variation in the detrended daily mortality. Regression slopes (β) for TSP and PM_{10}, were: $\beta_{TSP}=0.011$ deaths/$\mu g/m^3$ ($p<0.001$), $\mu_{PM10}=0.022$ deaths/$\mu g/m_3$ ($p<0.001$), respectively. The estimated contribution of each pollutant to daily mortality at the mean pollution levels were: 2.3% for either PM_{10} or TSP. The total estimated contribution of particles and ozone to daily mortality was about 4%. This analysis, however, could not distinguish the estimated mortality effects of TSP from those associated with exposures to PM_{10}. The findings from this analysis are consistent with results from previous epidemiologic investigations conducted for other US metropolitan areas.

Overall, the effects of particles on daily mortality as shown in Table 1 across all studies seems to be about 1% for a 10 $\mu g/m^3$ increase in daily PM_{10}.

Morbidity effects of particles measured by increases in hospital admissions.

Researchers in the US, Canada and elsewhere have recently begun examining the acute effects of particles on hospital admissions and particulate (sulfate, acid aerosol and fine particle-$PM_{2.5}$) pollution. Recently this analysis has been conducted in New York (Buffalo and New York City), Southern Ontario, Toronto and Massachusetts. The findings from these epidemiologic analyses are summarized in Table 2. In general, these studies indicate an increase in asthma or total respiratory admissions or emergency room visits when particle levels are elevated. Typically, an increase around 2% in admissions for a10 $\mu g/m3$ increase in daily PM10 has been reported. Data from Boston and three other communities in Massachusetts suggested a higher rate of pneumonia and influenza admissions (about 15%) for children under 15 years old associated with an increase of daily PM_{10} levels by 10 $\mu g/m^3$.

A recent review of the acute respiratory effects of particulate air pollution by Dockery and Pope[15] report the following change in effects corresponding to 10 $\mu g/m^3$ increase in PM_{10}: asthmatic attacks: 3%; Bronchodilator use: 12.2%; Increase in respiratory systems reports: 1-3%; decrease in forced expired volume: 0.15%; decrease in peak expiratory flow: 0.08%.

TABLE 2. RECENT STUDIES OF ACUTE EFFECTS OF PARTICLES ON HOSPITAL ADMISSIONS

Study	Particulate Measure Used in the Study*	Percent Increase in Admissions for a 10 $\mu g/m^3$ Increase in Daily PM_{10}**			Study Location
Thurston *et al.*[16]	Sulfates	Asthma:	2.1% ±	1.4	Buffalo, NY
		Total Respiratory:	2.2% ±	0.4	
Thurston *et al.*[16]	Sulfates	Asthma:	1.9 ±	0.7	New York
		Total Respiratory:	1.0% ±	0.4	City, NY
Özkaynak *et al.*[17]	Total Suspended Particulates	Pneumonia and Influenza for < 15 year olds:	15% ±	0.4	Boston, MA
Burnett *et al.*[18]	Sulfates	Total Respiratory:	1.0% ±	0.2	Southern Ontario, Canada
Thurston *et al.*[19]	$PM_{2.5}$	Asthma:	2.2% ±	1.6	Toronto,
		Total Respiratory:	3.6% ±	1.6	Canada

* Conversions used: Sulfates/0.25 = PM_{10} 0.55*TSP = PM_{10}, $PM_{2.5}/0.60 = PM_{10}$

** (± one standard error)

HEALTH EFFECTS OF OZONE

Ozone is a photochemical oxidant formed in the urban atmosphere as a result of a series of complex chemical reactions. The pollutants most responsible for the formation of ozone are nitrogen oxides, hydrocarbons, aldehydes and carbon monoxide. Motor vehicles are a major source of emissions for these primary precursor pollutants, although stationary sources burning fossil fuel, such as electric power plants, contribute to nitrogen oxide emission as well. The amount of ozone formed in the atmosphere has a strong dependence on time of day, meteorologic conditions and the concentrations of the primary pollutants involved in ozone formation. Typically, the higher the amount of solar insulation and primary pollutant loading, the higher the levels of ozone in the atmosphere. For example, in Los Angeles, CA, ozone and photochemical smog formation rapidly rises during the daylight hours of 8:00 am to 1:00 pm with peak ozone levels reached around 10:00 am.

As discussed by Spengler[20] ozone exposure to humans cause irritation to the airways, leading to inflammation, increased permeability in lung tissue, and destruction of pulmonary macrophages. Prolonged exposure and perhaps chronic intermittent exposures can lead to thickening of airways and alveoli membranes with eventual loss of function. Intermittent acute exposures to ambient ozone results in reversible changes in lung function and respiratory symptoms. Elevated levels of daily ozone (peak hour) are associated with restricted activity, asthma symptoms, and respiratory admissions to hospitals. Long-term exposures may result in permanent loss of lung function and an increase in associated disease, but the evidence is not will established. The EPA document "Air Quality Criteria for Ozone and Other Photochemical Oxidants"[21] as will as review publications by Lippmann[22]and Dockery and Kriebel[23] provide more detailed discussion of ozone health effects. The focus here will be on a few studies that illustrate the range of mortality and morbidity effects observed in large populations.

Mortality effects of ozone

Epidemiologic studies linking acute or chronic effects of ozone exposures especially mortality effects are very few. One of the main reasons is that reliable historic ozone measurements are sparse. Ozone data in the US is mostly available after 1970. Time-series analysis of the association of daily mortality and air pollution has been the subject of three recent investigations conducted by Kinney and Özkaynak[8] for Los Angeles, Özkaynak and Kinney[12] for New York City and Özkaynak *et al.*[13] for Toronto, Canada. In a previous section, the basic design and data base content of these investigations were described. In the analysis of the Los Angeles data, a highly significant previous day max. 1-hour ozone effect on daily mortality was reported[8]. The regression slope for O_3, was 0.036 deaths/ppb ($p<0.01$). In the Los Angeles data, this represents about a 2% average effect of ozone on daily mortality. In the New York City analysis, a highly significant previous day ozone effect was also found(12). The estimated ozone coefficient was 0.055 deaths/ppb ($p<0.001$). Again, the average contribution of mean levels of ozone in New York City was about 2% of the daily total mortality. It is possible that the estimated ozone coefficient is higher in New York City than in Los Angeles due to higher levels of aerosol acidity in New York City which enhances or adds to the respiratory potency of ozone.

Recent analysis of the Toronto pollution and mortality series by Özkaynak *et al.*[13] showed a significant same day effect of ozone on total mortality with a regression slope 0.017 death/ppb ($p<01$) with an average contribution of 1.5% to daily mortality. These three studies have shown consistently significant association between daily peak ozone and mortality with an average contribution of ozone to daily mortality about 2%. Table 3 summarizes these results in terms of estimated percent increase in daily mortality corresponding to a 50 ppb increase in daily max. 1-hour ozone.

TABEL 3. RECENT TIME-SERIES STUDIES OF EFFECTS OF OZONE ON DAILY TOTAL MORTALITY

Study	Percent Increase in Daily Mortality for a 50 ppb Increase in Daily Max. 1-hr. Ozone*			Study Location
Kinney and Özkaynak(8)	1.2%	±	0.3	Los Angeles, CA
Özkaynak and Kinney(12)	1.5%	±	0.5	New York City, NY
Özkaynak et al.(13)	2.2	±	0.8	Toronto, Canada

• (± one standared error)

Acute effects of ozone on hospital admissions

Past studies have suggested an association between air pollution and increased hospital visits or admissions[24,25,26]. Recent investigations utilized multi-year hospital data and more specific measures of particle, sulfate, acidity or ozone measurements with refined statistical methods to quantify the strength of associations between ambient pollutant levels and hospital admissions rates.

Özkaynak *et al.*[17] reported on the results of analyses of two years of hospital admissions and pollution data from Massachusetts. Seasonal, weekly and daily variations in the data were controlled utilizing data filtering approaches used by Bates and Sizto[25]. Multivariate regression analyses showed a positive and significant ozone effect on pneumonia and influenza admissions only when summer data were used. This result was consistent with animal toxicology data which show increased susceptibility of ozone-exposed animals to bacterial pneumonias. The association found was only significant for the age group 15 years or older. Sample size limitations for the younger age group may have adversely effected the ability of the study to detect a significant effect in the younger age group.

Thurston *et al.*[16] collected and analyzed air pollution and respiratory hospital admissions data in the Buffalo, Albany, and New York City, NY, metropolitan areas. Pollutant samples were collected daily at suburban air monitoring sites and analyzed for their content of particulate phase aerosol strong acidity (i.e., hydrogen ion, H^+) and sulfate ($SO_4^=$). In addition, daily hospital admissions for respiratory causes, other community air pollutant measurements (e.g., ozone, O_3), and meteorological data (e.g., temperature) were also obtained for these metropolitan areas. The summer months (June-August) were selected for analysis because that is when the highest H^+ (and O_3) are usually experienced at these sites, and because these months are rarely complicated by other major influences (e.g., high pollen counts). Regression analyses in Thurston *et al.*[19] indicated that the pollution-admissions associated remained significant ($p<0.05$) even after the simultaneous inclusion of lagged daily maximum temperature. Ozone consistently had the highest mean effects estimates. Relative risk (RR) calculations indicated that the risk of admission for asthma was increased by a factor of 1.19 to 1.43 in these cities on maximum 1988 summertime pollution day, with H^+ consistently having the highest RR estimates. However, associations were weaker in the less urbanized Albany metropolitan area and in the New York City (NYC) suburbs, even though the NYC suburban O_3 exposures were similar to (and the H^+ concentrations may even be somewhat higher than) those in the centre city.

Daily hospital admissions data for July and August 1987 and 1988 were obtained from Health and Welfare Canada for the Toronto metropolitan area and analyzed by Thurton *et al.*[19] Aerosol acidity and sulfate ion were measured. Also, during all three summers, 24 hr average inhalable particle (IP) mass samples (both for the fine, $d_a < 2.5$ mm, and the coarse, $2.5\ \text{mm} \leq d_a \leq 15\ \mu\text{m}$, mass) were collected daily at the Breadalbane St. site and analyzed for trace elements and mass. Daily TSP, hourly observations of ozone, nitrogen dioxide (NO_2), and sulfur dioxide data for the Breadalbane site were also gathered. Thurston *et al.*[19] reported significant associations for both O_3 and $SO_4^=$ with total respiratory and asthma admissions to acute care hospitals in Toronto, Ontario. In contrast to the strong H^+ and O_3 associations with summertime respiratory and asthma admissions in this city, the particle mass measures considered were weaker or not at all associated with hospital admissions in this investigation.

Most recently Burnett *et al.*[18] reported on an extensive analysis of daily Ontario hospital admissions and air pollution data for the period 1983-1988. To investigate the acute respiratory health effects of ambient air pollution, the number of emergency or urgent daily respiratory admissions to 168 acute care hospital in Ontario were related to estimates of exposure to oxone and sulphates in the vicinity of each hospital. Ozone levels were obtained from 22 monitoring stations maintained by the Ontario Ministry of the Environment. In the Burnett *et al.*[18] analysis positive and statistically significant associations were found between both ozone and sulphates recorded on the day of admission and up to three days previous to that date. According to Burnett *et al.*[18], five percent of daily respiratory admissions in the months of May to August were estimated to be attributable to ozone, with sulphates accounting for an additional 1% of these admissions. Ozone was a stronger predictor of admissions than sulphates. Positive and statistically significant ($p < 0.05$) associations were observed between the ozone-sulphate pollution mix and admissions for asthma, COPD and infections. Positive associations were also found in all age groups, with the largest impact on infants (15% of admissions attributable to the ozone-sulphate pollution mix) and the least effects on the elderly (4%).

Table 4 summarizes the findings from recent studies of acute effects of ozone on hospital admissions in terms of predicted increase in admissions for a 50 ppb increase in daily max. 1-hour ozone.

TABLE 4. RECENT STUDIES OF ACUTE EFFECTS OF OZONE ON HOSPITALADMISSIONS

Study	Precent Increase in Admissions for a 50 ppb Increase in Daily Max. 1-hr. Ozone*			Study Location
Thurston et al.(16)	Asthma:	16% ±	7.0	Buffalo, NY
	Total Respiratory:	12% ±	7.0	
Thurston et al.(16)	Asthma:	9% ±	3.5	New York City,
	Total Respiratory:	4% ±	1.5	NY
Özkaynak et al.(17)	Pneumonia and inluenza for >15 year olds:	20% ±	5.0	Boston, MA
Burnett et al.(18)	Total Respiratory:	6% ±	1.5	Southern Ontario Canada
Thurston et al.(19)	Asthma:	16% ±	7.0	Toronto, Canada
	Total Respiratory:	19% ±	7.0	

*(± one standard error)

HEALTH EFFECTS OF NITROGEN DIOXIDE

Nitrogen dioxide (NO_2) is a by-product of high temperature combustion. In outdoor air, motor vehicles and fossil fuel power plants are the primary sources of NO_2 emissions. In indoor air, particularly in residences, unvented gas cooking and heating appliances and kerosene space heaters are the principal sources of NO_2. Epidemiological studies examining the effects of NO_2 on childhood respiratory illness and symptom rates have not shown consistent associations. Most of these studies, however, suffered from imperfect characterization of personal exposures and accurately measuring or scoring multiple respiratory health end-points.

Earlier work done in England by Melia and her coworkers[27] suggested that a large cohort of primary school children living in homes with gas stoves had more respiratory symptoms or diseases than the children who lived in homes with electric stoves. However, a later study by the same researchers[28] failed to demonstrate a (significant) relationship between the prevalence of respiratory illness and levels of NO_2.

Research conducted by the Harvard Six Cities Study also resulted in findings that were equivocal. Speizer *et al.*[29] estimated a statistically significant effect of gas stoves (versus electric stoves) on the rates of serious respiratory illness before age two. Subsequently, Ware *et al.*[30] reported results from the same study group over a longer period but with different and reduced risks for children from homes with gas stoves. Dockery *et al.*[31] studied a different cohort of the Six Cities Study and during a different time period of data collection. Chronic cough, bronchitis, chest illness, persistent wheeze and non-respiratory illness variables were not significantly associated with gas stove use in the home. Doctor-diagnosed respiratory illness prior to age two, however, was marginally significant. Use of kerosene heaters in the homes was associated with increased respiratory illness.

Most recently, Neas *et al.*[32] examined the effect of NO_2 on the prevalence of respiratory symptoms and pulmonary function level in a Six City cohort of 1,567 white children aged 7 to 11 years: This analysis showed that NO_2 was significantly associated with an increased prevalence of a composite indicator of lower respiratory symptoms. The response variable used was based on reporting one or more of the following symptoms: attack of shortness of breath with wheeze, chronic wheeze, chronic cough, chronic phlegm, or bronchitis. However, analysis of pulmonary function measurements showed no consistent effect of NO_2[32].

Hasselblad *et al.*[33] applied meta-analysis techniques to combine the evidence of NO_2 effects on respiratory illness in children under 12 years old. They concluded that there is an increase in the odds of respiratory illness especially in elementary school age children exposed to long-term levels of NO_2 of 30$\mu g/m^3$. The distribution of estimates shown in Figure 1 is centred about an odds ratio of 1.2 (i.e. an increase of 20% in the odds of respiratory illness) with 95% confidence limits of 1.1 to 1.3.

This study was also relied upon in the recent version of the EPA NO_2 criteria document[34] in assessing health effects of NO_2. The Hasselblad *et al.*[33] meta-analysis combined many studies with different design and measurement protocols, building types and demographic attributes. It was an attempt to synthesize data with varied quality rather than propose a new or independent finding.

In contrast, recently researchers from the University of New Mexico and Harvard School of Public Health[35] conducted a prospective investigation of 1,205 healthy infants living in homes with gas or electric stoves in Albuquerque, NM. Nitrogen dioxide exposures were carefully estimated from repeated measurements in multiple locations in the subjects' homes up to an 18-month study period. Respiratory illnesses

were monitored prospectively using a surveillance system based on daily parental diaries of respiratory signs and symptoms. Parental reports of illness episodes were validated in a subset of the population by comparison with clinical diagnoses and microbiological testing. Potential confounding factors were minimized by selecting subjects whose parents did not smoke or intend to use day-care services outside the home. The results from this most recent and comprehensive NO_2 field investigation were quite clear and consistent. Samet *et al.*[35] found no association between nitrogen dioxide exposure and the incidence rates from any illness category (upper respiratory, lower respiratory illness, lower respiratory illness with wet cough, and lower respiratory illness with wheeze); nor was there any association between illness incidence and the presence of a gas stove. There was also no significant association found between nitrogen dioxide levels and the duration of illness for the first three illness categories listed above. However, at the highest nitrogen dioxide exposure category (greater then 40 ppb), there was a nonsignificant increase in the duration of illnesses classified as lower respiratory illness with wheezing. These findings apply to healthy infants, and cannot by generalized to populations who may be more susceptible to the effects of nitrogen dioxide exposure, such as premature babies, babies with low birth weight or respiratory problems, and infants living in homes with parents who smoke. Due to the study design, these findings, also, cannot be generalized to susceptible young children, older children or adults. Table 5 from Samet *et al.*[35] showing the estimated odds ratios for effects of NO_2 on incidence of all lower respiratory illness, overall and stratified by various factors. Again, as noted above, most of the odds ratios (calculated by contrasting rates between high and low NO_2 exposure groups) are near or below 1 and are not statistically significant. The Samet *et al.*[35] study point out the importance of accounting for other factors such as mother's education, ethnicity and seasonal factors in the study pertaining to NO2 health effects. The role of these and other community-specific factors potentially confounding or biasing previous NO2 health effects studies is presently difficult to assess.

TABLE 5. ODDS RATIOS FOR EFFECTS OF NITROGEN DIOXIDE EXPOSURE VARIABLES ON INCIDENCE OF ALL LOWER RESPIRATORY ILLNESS, OVERALL AND STRATIFIED BY VARIOUS FACTORS[a][35]

		Unlagged NO_2[c]		Lagged NO_2[c]	
	Gas stove Homes[b]	20 - 40 ppb	> 40 ppb	20 - 40 ppb	> 40 ppb
Overall	0.95	0.97	0.91	0.96	0.89
Age					
0 - 6 Months	0.92	1.01	0.97	1.06	0.96
7 - 12 Months	0.94	0.85[d]	0.79	0.83[d]	0.78
13 - 18 Months	0.99	1.08	0.95	1.02	0.95
Atopy/asthma					
Parent history positive	0.96	1.02	0.94	1.01	1.08
No parent history	0.96	0.93	0.89	0.93	0.75
Ethnicity					
Hispanic	1.06	0.97	1.25	1.02	1.25
Non-Hispanic	0.92	0.98	0.63[d]	0.93	0.65[d]
Household income					
< $10.000	1.23	0.83	0.96	0.77	0.91
$10.000 - $39.000	0.89[d]	1.02	0.87	1.00	0.89
> $40.000	1/12	0.92	1.15	0.97	0.78
Maternal education					
< 12 Years	1.05	0.95	1.24	0.89	1.41[d]
13 - 15 Years	0.85[d]	0.84[d]	0.83	0.89	0.73
> 16 Years	1.00	1.21[d]	0.69	1.22[d]	0.62[d]
Season					
Fall/winter	1.00	1.01	0.99	1.03	1.00
Spring/summer	0.85[d]	0.99	0.78	0.90	0.75

[a] Logistic regression models include terms for age, parental atopy/asthma, ethnicity, income, mother's education, season, day care, breast feeding, other siblings, and maternal history of respiratory symptoms, as applicable.

[b] Compared with electric stove homes.

[c] Compared with 0 - 20 ppb NO_2.

[d] Odds ratio differ significantly from 1.0. $p < 0.05$.

CONCLUSIONS

Quantitative estimation of the relationships between current levels of ambient pollution and human morbidity or mortality is hampered by the limitations of the available data bases. An important sources of limitation in the epidemiologic analyses of air pollution health effects is the use of central-site pollution data as opposed to more accurate estimates of personal exposures. Furthermore, most of the past epidemiological data are based on high pollution levels and pollution mixes that are often different from the present composition of ambient aerosols. Because particles were not differentiated by size, chemical properties, metal composition, or acidity but by poor pollution measures (e.g., TSP, BS, COH) it is difficult to reliably predict pollutant-specific exposure-response relationships. In addition, biases due to exposures influence the outcome of most epidemiologic studies of air pollution. Finally, limitations of sample size in most observational analysis, and the lack of sufficient number of studies which provide morbidity data limit our ability to detect health effects of air pollution which may be small but significant.

While recognizing these and other limitations of most of the air pollution epidemiology studies, this paper reviewed the recent evidence on mortality and morbidity effects of particles and ozone and the evidence on effects of NO_2 on the respiratory illnesses in young children. A consistent pattern of effects was discerned for particle and ozone and the evidence on effects of NO2 on the respiratory illnesses in young children. A consistent pattern of effects was discerned for particle and ozone effects on daily mortality. Time-series investigations provided similar result to earlier cross-sectional studies on air pollution mortality effects.

Estimated total excess deaths due to either particulate pollution or ozone were about 2%. The overall effect of pollution on excess daily mortality was about 4% in the cities studied in the US and Canada. Particulate pollution effects on hospital admissions were about 2% for asthma and total respiratory admissions categories for a 10 $\mu g/m^3$ increase in daily PM_{10} level. Effects of ozone on asthma and total respiratory admissions for a 50 ppb increase in daily max. 10 hr ozone, however, ranged from 4% to 19% depending on the study location.

In contrast, the evidence on the respiratory health effects of NO_2 was found to be mixed. Even though a recent meta-analysis of the published results suggest a positive association, a well-designed and extensively reviewed recent study of infants living in Albuquerque, NM, failed to demonstrate a significant association between measured NO_2 and reported respiratory illness among this cohort. It is clear that for particles and ozone, different health effects are now detected at much lower levels than estimated earlier. The concept of threshold or acceptable levels for most criteria pollutants is becoming more questionable. More precise resolution of potential health effects of particles, ozone and NO2 will depend on our ability to improve our measurement and analysis techniques.

For future air pollution health effects studies, we need combinations of both improved personal exposure and health measures. Biomarkers of exposure and dose and pharmacokinetic based models of exposure would be very beneficial. We clearly need more prospective health studies to enable characterization of chronic and acute health effects of ambient pollutants and their mixtures. Also needed are better estimates of personal exposures to particles, acid aerosols, ozone, and nitrogen oxides, including information on indoor/outdoor particle exposures by source and chemical composition. However, since new data sets will take a decade or two to develop, existing retrospective population health data sets should continue to be re-analyzed with more representative exposure estimates by accounting for misclassification biases. Particular attention should also be paid to improving exposure estimation by incorporating available personal monitoring data and exposure modelling techniques. Finally, associations obtained between air pollution exposures and different measures of health effects should be studied and compared for different pollution groups to improve our understanding of many factors influencing human morbidity and mortality.

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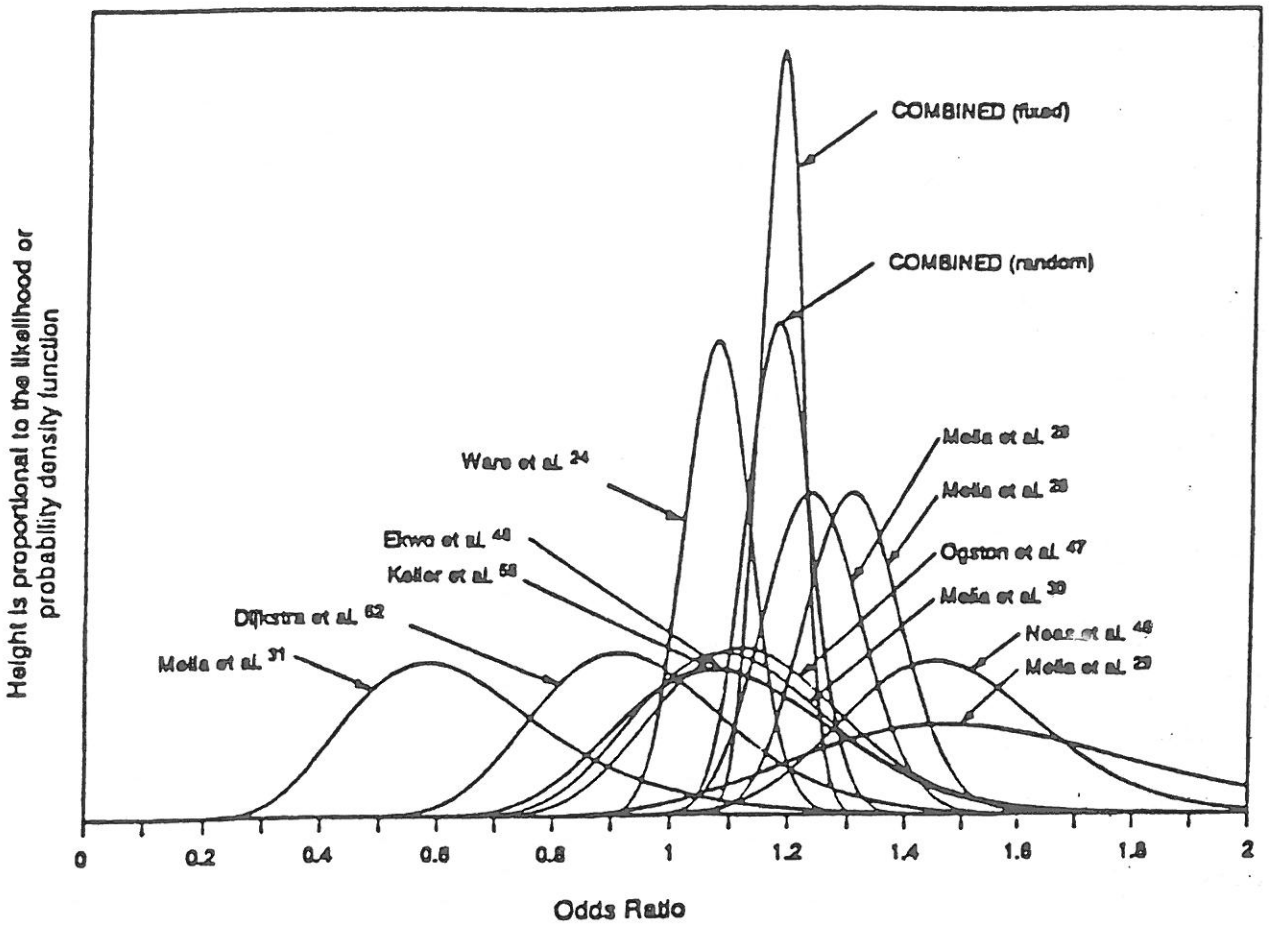

Figure 1. Meta-analysis of epidemiologic studies of 30 μg m³ nitrogen dioxide exposure increase on respiratory illness in children ≤ 12 years old.[33]