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8. EPIDEMIOLOGY OF HUMAN HEALTH EFFECTS ASSOCIATED WITH AMBIENT PARTICULATE MATTER

8.1 INTRODUCTION

Epidemiologic studies linking community ambient PM concentrations to health effects played an important role in the 1996 PM Air Quality Criteria Document (PM AQCD; U.S. Environmental Protection Agency, 1996a). Many of those studies reported that measurable excesses in pulmonary function decrements, respiratory symptoms, hospital and emergency department admissions, and mortality in human populations are associated with ambient levels of various indicators of PM exposure, including most notably PM_{10} as well as other indicators of fine-fraction particles (e.g., $PM_{2.5}$). Numerous more recent epidemiologic studies discussed in this chapter have also evaluated ambient PM relationships to morbidity and mortality, using various PM indicators, with greater emphasis on $PM_{2.5}$ and other indicators of fine-fraction particles and, to much less extent, $PM_{10-2.5}$. The more recent studies provide an expanded basis for assessment of health effects associated with exposures to airborne PM at concentrations currently encountered in the United States.

The epidemiology studies assessed here are best considered in combination with information on ambient PM concentrations presented in Chapter 3, studies of human PM exposure (Chapter 5), and PM dosimetry and toxicology (Chapters 6 and 7). The epidemiology studies contribute important information on associations between health effects and exposures of human populations to “real-world” ambient PM and also help to identify susceptible subgroups and associated risk factors. Chapter 9 provides an interpretive synthesis of information drawn from this and other chapters.

This chapter opens with brief discussion of approaches used for identifying, presenting, and assessing studies; general features of the different types of epidemiologic studies assessed and key methodological issues that arise in analyzing and interpreting study results; and salient aspects of epidemiological evidence that are considered in their critical assessment. Section 8.2 and 8.3 present and assess epidemiologic studies of PM effects on mortality and morbidity, respectively. Section 8.4 then provides an interpretive assessment of the overall PM epidemiologic data base reviewed in Sections 8.2 and 8.3 in relation to various key issues and aspects of the evidence. The overall key findings and conclusions for this chapter are then summarized in Section 8.5.

8.1.1 Approaches for Identifying, Presenting and Assessing Studies

Numerous PM epidemiologic papers have been published since completion of the 1996 PM AQCD, and U.S. EPA (NCEA-RTP) has used a systematic approach to identifying pertinent epidemiologic studies for consideration in this chapter. In general, an ongoing continuous Medline search has been employed in conjunction with other strategies to identify PM literature pertinent to developing criteria for PM NAAQS. The literature search method is similar to those used by others (e.g., Basu and Samet, 1999). A publication base was first established by using Medline and other data bases and a set of key words (particles, air pollution, mortality, morbidity, cause of death, PM, etc.) in a search strategy which was later reexamined and modified to enhance identification of pertinent published papers. Since literature searches encounter not a static but a changing, growing stream of information, searches are not run just for the most recent calendar quarter but are backdated in an attempt to capture references added to that time period since the previous search was conducted. Papers were also added to the publication base by EPA staff (a) through review of advance tables of contents of thirty journals in which relevant papers are published and (b) by requesting scientists known to be active in the field to identify papers recently accepted for publication.

While the above search regime builds a certain degree of redundancy into the system, which ensures good coverage of the relevant literature and lessens the possibility of important papers being missed, additional approaches have augmented traditional search methods. First, at the beginning of the process, a Federal Register Notice was issued, requesting information and published papers from the public at large. Next, non-EPA chapter authors are expert in this field; and, while EPA provides them with the outcomes of searches, the authors are also charged with identifying the literature on their own. Finally, a keystone in the literature identification process is that, at several review stages in the process, both the public and CASAC offer comments which may identify additional potentially relevant publications; and the combination of these approaches is believed to produce a comprehensive collection of pertinent studies appropriate for review and assessment here. This collection of studies includes pertinent new studies accepted for publication through April, 2002, as well as some published since then (if such recent new papers provide particularly important information helpful in addressing key scientific issues).

Those epidemiologic studies that relate measures of ambient air PM to human health outcomes are assessed in this chapter, whereas studies of (typically much higher) occupational exposures are generally not considered here. Criteria used for selecting literature for the present assessment include mainly whether a given study includes information on: (1) ambient PM indices (e.g., PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, etc.) of short- and long-term exposures as a key element; (2) analyses of health effects of specific PM chemical or physical constituents (e.g., metals, sulfates, nitrates or ultrafine particles, etc.) or indicators related to PM sources (e.g., motor vehicle emissions, combustion-related particles, crusted particles); (3) evaluation of health endpoints and populations not previously extensively researched; (4) multiple pollutant analyses and other approaches to addressing issues related to potential confounding of effects and effects modification; and/or (5)studies addressing important methodological issues (e.g., lag structure model specification, thresholds, mortality displacement) related to long-term PM exposure effects.

In presenting the evidence, the authors first concisely highlight key points derived from the 1996 PM AQCD assessment of the available information. Then, key new information is presented in succinct text summary tables for important new studies that have become available since the 1996 PM AQCD. More detailed information on various methods and results for these and other newly available studies is summarized in tabular form in Appendices 8A and 8B. These appendix tables are generally organized to include: information about (1) study location and ambient PM levels; (2) description of study methods employed; (3) results and comments; and (4) quantitative outcomes for PM measures. In the main body of the chapter, greater emphasis is placed on integrating and interpreting findings from the array of evidence provided by the more important newer studies than on detailed evaluation of each of the numerous newly available studies. In presenting quantitative effects estimates in tables in the chapter and appendices, study results were normalized to standard PM increments, as was done in the 1996 PM AQCD. In selecting PM increments for use in this review, more recent air quality data were considered, resulting in no changes to the increments previously used for short-term exposure studies, but smaller increments than those used in the 1996 PM AQCD for long-term exposure studies. More specifically, the pollutant concentration increments used here to report relative risks (RR's) or odds ratios for various health effects are as follow for short term (≤ 24 h) exposure studies: 50 μg/m^3 for PM_{10}; 25 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$; 155 nmoles/m^3 (15 μg/m^3 for SO_4^{-2}; and 75 nmoles/m3 (3.6 μg/m^3, if as H_2SO_4) for H^+. For long-term exposure studies, the increments used here are 20 μg/m^3 for PM_{10} and 10 μg/m^3 for $PM_{2.5}$ and $PM_{10-2.5}$.

Particular emphasis is focused in the text on those studies and analyses thought to provide information most directly applicable for U.S. standard setting purposes. Specifically, North American studies conducted in the U.S. or Canada are generally accorded more text discussion than those from other geographic regions; and analyses using gravimetric (mass) measurements are generally accorded more text attention than those using non-gravimetric ambient PM measures, e.g., black smoke (BS) or coefficient of haze (CoH). In addition, emphasis is placed on text discussion of (a) new multi-city studies that employ standardized methodological analyses for evaluating PM effects across several or numerous cities and often provide overall effects estimates based on combined analyses of information pooled across multiple cities; (b) other studies providing quantitative PM effect-size estimates for populations of interest; and (c) studies that consider PM as a component of a complex mixture of air pollutants, including in particular the gaseous criteria pollutants (O_3, CO, NO_2, SO_2).

In assessing the relative scientific quality of epidemiologic studies reviewed here and to assist in interpreting their findings, the following types of questions were considered, as was done in the 1996 PM AQCD:

(1) Was the quality of the aerometric data used sufficient to allow for meaningful characterization of geographic or temporal differences in study population pollutant exposures in the range(s) of pollutant concentrations evaluated?

(2) Were the study populations well defined and adequately selected so as to allow for meaningful comparisons between study groups or meaningful temporal analyses of health effects results?

(3) Were the health endpoint measurements meaningful and reliable, including clear definition of diagnostic criteria utilized and consistency in obtaining dependent variable measurements?

(4) Were the statistical analyses used appropriate and properly performed and interpreted, including accurate data handling and transfer during analyses?

(5) Were likely important confounding or covarying factors adequately controlled for or taken into account in the study design and statistical analyses?

(6) Were the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

These guidelines provide benchmarks for judging the relative quality of various studies and for focusing on the highest quality studies in assessing the body of epidemiologic evidence. Detailed critical analysis of all epidemiologic studies on PM health effects, especially in relation to all of the above questions, is beyond the scope of this document. Of most importance for present purposes are those studies which provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for health effects associated with ambient air levels of PM currently likely to be encountered in the United States.

8.1.2 Types of Epidemiologic Studies Reviewed

Definitions of various types of epidemiologic studies assessed here were provided in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) and are briefly summarized here. Briefly, the epidemiologic studies are divided into *mortality* studies and *morbidity* studies. *Mortality* studies evaluating PM effects on total (non-accidental) mortality and cause-specific mortality provide the most unambiguous evidence related to a clearly adverse endpoint. The *morbidity* studies further evaluate PM effects on a wide range of health endpoints, such as: cardiovascular and respiratory-related hospital admissions, medical visits, reports of respiratory symptoms, self-medication in asthmatics, changes in pulmonary function; changes in cardiovascular physiology/functions, and blood coagulation; low birthweight infants, etc.

The epidemiologic strategies most commonly used in PM health studies are of four types: (1) *ecologic studies;* (2) *time-series semi-ecologic studies;* (3) *prospective cohort and longitudinal panel studies;* and (4) *case-control and crossover studies*. In addition, time-series analyses or other analytic approaches have been used in so-called intervention studies or “natural experiments.” All of these are observational studies rather than experimental studies. In general, the exposure of the participant is not directly observed; and the concentration of airborne particles and other air pollutants at one or more stationary air monitors is used as a proxy for individual exposure to ambient air pollution.

In *ecologic studies*, the responses are at a community level (for example, annual mortality rates), as are the exposure indices (for example, annual average PM concentrations) and covariates (for example, the percentage of the population greater than 65 years of age). No individual data are used in the analysis; therefore, the relationship between health effect and exposure calculated across different communities may not reflect individual-level associations between health outcome and exposure. The use of proxy measures for individual exposure and covariates or effect modifiers may also bias the results, and within-city or within-unit confounding may be overlooked.

Time-series studies are more informative because they allow the study of associations between *changes* in a health outcome and *changes* in exposure indicators preceding or simultaneous with the outcome. The temporal relationship supports a conclusion of a causal relation, even when both the outcome (for example, the number of non-accidental deaths in a city during a day) and the exposure (for example, daily air pollution concentration) are community indices.

Prospective cohort (or panel) studies use data from individuals, including health status (where available), individual exposure (not usually available), and individual covariates or risk factors, observed over time. The participants in a prospective cohort study are ideally recruited (using a simple or stratified random sample) so as to represent a target population for which individual or community exposure of the participants is known before and during the interval up to the time the health endpoint occurs. The use of individual-level data is believed to give prospective cohort studies greater inferential strength than other epidemiologic strategies. The use of community-level or estimated exposure data, if necessary, may weaken this advantage, as it does in time-series studies.

Case-control studies are retrospective studies in that exposure is determined after the health endpoint occurs (as is common in occupational health studies). As Rothman and Greenland (1998) describe it, "Case-control studies are best understood by defining a source population, which represents a hypothetical study population in which a cohort study might have been conducted . . . In a case-control study, the cases are identified and their exposure status is determined just as in a cohort study . . . [and] a control group of study subjects is sampled from the entire source population that gives rise to the cases . . . the cardinal requirement of control selection is that the controls must be sampled independently of their exposure status."

The *case-crossover design* is suited to the study of a transient effect of an intermittent exposure on the subsequent risk of an acute-onset health effect thought to occur short after exposure. In the original development of the method, effect estimates were based on within-subject comparisons of exposures associated with incident disease events with exposures at times before the occurrence of disease, using matched case-control methods or methods for stratified follow-up studies with spare data within each stratum. The principle of the analysis is that the exposures of cases just before the event are compared with the distribution of exposure estimated from some separate time period, the former being assumed to be representative of the distribution of exposures for those individuals while they were at risk for the outcome of interest.

When measurements of exposure or potential effect modifiers are available on an individual level, it is possible to incorporate this information into a case-crossover study (unlike a time-series analysis). A disadvantage of the case-crossover design, however, is the potential for bias due to time trends in the exposure time-series. Because case-crossover comparisons are made between different points in time, the case-crossover analysis implicitly depends on an assumption that the exposure distribution is stable over time (stationary). If the exposure time-series is non-stationary and case exposures are compared with referent exposures systematically selected from a different period in time, a bias may be introduced into estimates of the measure of association for the exposure and disease. These biases are particularly important when examining the small associations that appear to exist between PM and health outcomes.

Intervention studies (often involving features of time-series or other above types of analyses) provide a particularly powerful additional approach for evaluating possible causal relationships between ambient air pollution variables (e.g., PM) and health effects in human populations. In such studies, the effects of active interventions that result in reductions of one or another or several air pollutants (constituting essentially a "found experiment") are evaluated in relation to changes in mortality or morbidity outcomes among population groups affected by the reduction in air pollution exposure. To date, only a few epidemiological studies have evaluated the consequences of interventions that allow for comparison of PM-health outcome associations before and after certain relatively discrete events resulting in notable changes in ambient PM concentrations. Given that etiology of health outcomes related to PM or other air pollutants are typically also affected by other risk factors, it is important in intervention studies not only to measure air pollution exposure and health status before and after air pollution reductions but also to identify and evaluate potential effects of other risk factors before and after the air pollution reductions. The proposition that intervention studies can provide strong support for causal inferences was emphasized by Hill (1965), as discussed further in Section 8.1.4. In his classic monograph (The Environment and Disease: Association or Causation?), Hill (1965) addressed the topic of preventive action and its consequences under Aspect 8, stating:

> "Experiment: Occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent? The dust in the workshop is reduced, lubricating oils are changed, persons stop smoking cigarettes. Is the frequency of the associated events affected? Here the strongest support for the causation hypothesis may be revealed."

8.1.3 Overview of Key Methodological Issues

There are a number of methodological issues that arise in analyzing and interpreting epidemiologic studies that are fully discussed in Section 8.4 below. The following brief overview of two such key issues is intended to orient the reader to these issues so as to provide context for the presentation and assessment of the epidemiologic studies on mortality and morbidity effects in Sections 8.2 and 8.3.

8.1.3.1 Issues Related to Use of General Additive Models (GAM) in PM Epidemiology

In the spring of 2002, the original investigators of a key newly available multi-city study (the National Mortality and Morbidity Air Pollution Study; NMMAPS) cosponsored by the Health Effects Institute (HEI) reported that use of the default convergence criteria setting used in the GAM routine of certain widely-used statistical software (Splus) could result in biased estimates of air pollution effects when at least two non-parametric smoothers are included in the model (Health Effects Institute letter, May 2002). The NMMAPS investigators also reported (Dominici et al., 2002), as determined through simulation, that such bias was larger when the size of risk estimate was smaller and when the correlation between the PM and the covariates (i.e., smooth terms for temporal trend and weather) was higher. While the NMMAPS investigators reported that reanalysis of the 90 cities air pollution-mortality data (using stringent convergence criteria) did not qualitatively change their original findings (i.e., the positive association between PM_{10} and mortality; lack of confounding by gaseous pollutants; regional heterogeneity of PM, etc.), the reduction in the PM_{10} risk estimate was apparently not negligible (dropping, upon reanalysis, from 2.1% to 1.4% excess deaths per 50 $\mu g/m^3$ increase in PM_{10}).

Issues surrounding potential bias in PM risk estimates from time-series studies using GAM analyses and default convergence criteria were raised by EPA and discussed in July 2002 at the CASAC review of the Third External Review Draft of this PM AQCD. In keeping with a follow up consultation with CASAC in August 2002, EPA encouraged investigators for a number of important published studies to reanalyze their data by using GAM with more stringent convergence criteria, as well as by using Generalized Linear Model (GLM) analyses with parametric smoothers that approximated the original GAM model. EPA, working closely with HEI, also arranged for (a) the resulting reanalyses first to be discussed at an EPA-sponsored Workshop on GAM-Related Statistical Issues in PM Epidemiology held in November 2002; (b) then for any revamping of the preliminary analyses in light of the workshop discussions; before (c) submittal by the investigators of short communications describing the reanalyses approaches and results to EPA and HEI for peer-review by a special panel assembled by HEI; and (d) the publication of the short communications on the reanalyses, along with commentary by the HEI peer-review panel, in an HEI Special Report (2003a). Some of the short-communications included in the HEI Special Report (2003a) included discussion of reanalyses of data from more than one original publication because the same data were used to examine different issues of PM-mortality associations (e.g., concentration/response function, harvesting, etc.). In total, reanalyses were reported for more than 35 originally published studies.

8.1.3.2 Confounding and Effect Modification

A pervasive problem in the analysis of epidemiologic data, no matter what design or strategy, is the unique attribution of a given health outcome to a nominal causal agent (e.g., to airborne particles in this document). The health outcomes attributed to particles are not specific; and, as such, they may also be attributable to high or low temperatures, influenza and other diseases, and/or exposure to other air pollutants. Some of these co-variables may be *confounders* and others *effect modifiers*. The distinctions are important.

Confounding is " . . . a confusion of effects. Specifically, the apparent effect of the exposure of interest is distorted because the effect of an extraneous factor is mistaken for or mixed with the actual exposure effect (which may be null)" (Rothman and Greenland, 1998, p. 120).

Causal events occur prior to some initial bodily response. A causal association may usually be defined as an association in which alteration in the frequency or quality of one category (e.g., level of PM in ambient air) is followed by a change in the other (e.g, increased mortality). The concept of the chain mechanism is that many variables may be related to a single effect through a direct-indirect mechanism. In fact, events are not dependent on single causes. A given chain of causation may represent only a fraction of a web (MacMahon and Pugh, 1970). A causal pathway refers to the network of relationships among factors in one or more causal chains in which the members of the population are exposed to causal agents that produce the observed health effect. The primary cause may be mediated by secondary causes (possibly proximal to exposure) and may have either a direct effect on exposure or an indirect effect through the secondary causes, or both, as illustrated below. A non-causal pathway may involve factors not actually associated or correlated with population exposure to the pollutant of interest, but are coincidentally (spuriously) also associated with health outcome.

The determination of whether a potential confounder is an actual confounder may be elucidated from biological or physical knowledge about its exposure and health effects. Patterns of association in epidemiology may be helpful in suggesting where to look for this knowledge, but do not replace it. Gaseous criteria pollutants (CO, NO_2, SO_2, O_3) are candidates for confounders because all of these have at least some adverse health effects also associated with particles (CO more often being associated with cardiovascular effects and the others with respiratory effects, including symptoms and hospital admissions). In addition, the gaseous criteria pollutants may be associated with particles for several reasons, including common sources and correlated changes in response to wind and weather. Lastly, SO_2 and NO_2 may be precursors to sulfate and nitrate components of ambient particle mixes, while NO_2 contributes also to the formation of organic aerosols during photochemical transformations.

The problem of disentangling the effects of other pollutants is especially difficult when high correlation exists between ambient PM measurements and one or more of them. For example, both CO and particles are emitted from motor vehicles. These and other fossil fuel combustion sources also often emit SO_2 and/or NO, which converts to NO_2 upon emission. SO_2 and NO_2, in turn, are precursors to sulfates and nitrates as two widely common contributors to secondary ambient PM aerosol components. Ozone (O_3) also contributes to ambient PM via (a) hydroxyl radicals which oxidize SO_2 to H_2SO_4 and NO_2 to HNO_3 and (b) participation in chemical reactions underlying the formation of ultrafine particles from naturally occurring terpenes, isoprene, and other hydrocarbons. A common source, such as combustion of gasoline in motor vehicles emitting CO, NO_2, and primary particles (and often resulting in high correlations), may play an important role in confounding among these pollutants, as do weather and seasonal effects. Even though O_3 is a secondary pollutant also associated with emission of NO_2, it is often more variably correlated with ambient PM concentrations, depending on location, season, etc. Levels of SO_2 in the western U.S. are often quite low, so that secondary formation of particle sulfates plays a much smaller role there, resulting in usually relatively little confounding of SO_2 with PM mass concentration in the West. On the other hand, in the industrial Midwest and northeastern states, SO_2 and sulfate levels during many of the epidemiology studies were relatively high and highly correlated with fine particle mass concentrations. If the correlation between PM and SO_2 is not too high, it may be possible to estimate some part of their independent effects, which depend on the assumption of independence under the particular model analyzed. If there is a causal pathway, then it may be difficult to determine whether the observed relationship of exposure to health effect is a direct effect of the exposure (to sulfate or fine PM as an example), an indirect effect mediated by the potential confounder (e.g., exposure to SO_2), or a mixture of these. Consideration of additional (e.g., exposure, dosimetric, toxicologic) information beyond narrow reliance on observed correlations among the PM measure(s), other pollutants, and health outcome indicators is often useful in helping to elucidate the plausibility of PM or other pollutants being causally related to statistically-associated health effects.

Some variables fall into the category of *effect modifiers*. "Effect-measure modification differs from confounding in several ways. The main difference is that, whereas confounding is a bias that the investigator hopes to prevent or remove from the effect estimate, effect-measure modification is a property of the effect under study . . . In epidemiologic analysis one tries to eliminate confounding but one tries to detect and estimate effect-measure modification" (Rothman and Greenland, 1998, p. 254). Examples of effect modifiers in some of the studies evaluated in this chapter include environmental variables (such as temperature or humidity in time-series studies), individual risk factors (such as education, cigarette smoking status, age in a prospective cohort study), and community factors (such as percent of population > 65 years old). It is often possible to stratify the relationship between health outcome and exposure by one or more of these risk factor variables. Effect modifiers may be encountered (a) within single-city time-series studies or (b) across cities in a two-stage hierarchical model or meta-analysis.

Potential confounding is usually much more difficult to identify; and several statistical methods are available, none of them being completely satisfactory. The usual methods include the following:

Within a city:

(A) Fit both a single-pollutant model and then several multi-pollutant models, and determine if including the co-pollutants greatly changes the estimated effect and inflates its estimated standard error;

(B) If the PM index and its co-pollutants are nearly multi-collinear, carry out a factor analysis, and determine which gaseous pollutants are most closely associated with PM in one or more common factors;

Using data from several cities:

(C) Proceed as in Method A and pool the effect size estimates across cities for single- and multi-pollutant models;

(D) Carry out a hierarchical regression of the PM effects versus the mean co-pollutant concentration and determine if there is a relationship; and

(E) First carry out a regression of PM versus the co-pollutant concentration within each city and the regression coefficient of PM versus health effect for each city. Then fit a second-stage model regressing the PM-health effect coefficient versus the PM-co-pollutant coefficient, concluding that the co-pollutant is a confounder if there is an association at the second stage.

Each of the above methods (A through E) are subject to one or more disadvantages. The multi-pollutant regression coefficients in method A, for example, may be unstable and have greatly inflated standard errors, weakening their interpretation. In method B, the factors may be sensitive to the choice of co-pollutants and the analysis method, and may be difficult to relate to real-world entities. In method C, as with any meta-analysis, it is necessary to consider the heterogeneity of the within-city effects before pooling them. Some large multi-city studies have revealed unexpected heterogeneity, not fully explained at present. While method D is sometimes interpreted as showing confounding if the regression coefficient is non-zero, this is an argument for effect modification, not confounding. Method E is sensitive to the assumptions being made; for instance, if PM is the primary cause and the co-pollutant the secondary cause, then the two-stage approach may be valid. However, if the model is mis-specified and there are two or more secondary causes, some of which may not be identified, then the method may give misleading results.

Given the wide array of considerations and possibilities discussed above, it is extremely important to recognize that there is no single "correct" approach to modeling ambient PM-health effects associations that will thereby provide the "right" answer with regard to precise quantification of PM effect sizes for different health outcomes. Rather, it is clear that emphasis needs to be placed here on (a) looking for convergence of evidence derived from various acceptable analyses of PM effects on a particular type of health endpoint (e.g., total mortality, respiratory hospital admissions, etc.); (b) according more weight to those well-conducted analyses having greater power to detect effects and yielding narrower confidence intervals; and (c) evaluating the coherence of findings across pertinent health endpoints and effect sizes for different health outcomes.

The issue of what PM effect sizes should be the main focus of presentation and discussion in ensuing text – i.e., those derived from single-pollutant models including only PM or effect sizes derived from multi-pollutant models that include one or more other copollutants along with the PM indicator(s) – is an important one. Again, there is not necessarily any single "correct" answer on this point. Implicit in arguments asserting that multi-pollutant model results must be reported and accorded equal or more weight than single-pollutant model PM results is a functional construct that has generally been used in epidemiologic modeling of health effects of air pollution, a functional construct that considers the various air pollutants mainly independently of one another in terms of their health effects, which may not necessarily be the case. This may be causing either over- or under-estimation of PM health effects, depending on the modeling choices made by the investigator and the study situation. For example, ozone and $PM_{2.5}$ can share some similar oxidative formation and effect pathways in exerting adverse health effects on the lung, yet are often modeled as independent pollutants or are placed in models simultaneously, even though they may sometimes have high correlations over space and time and in their health effects on the human body. Another complication is that other pollutants can be derived from like sources and may serve less as a measure of direct effects than as a marker of pollution from a specific source. As an example noted earlier, SO_2 and $PM_{2.5}$ are often predominantly derived from the same sources in a locale (e.g., coal-fired power plants in the mid-western U.S.), so that putting these two pollutants in a model simultaneously may cause a diminution of the $PM_{2.5}$ coefficient that may be misleading.

One approach that has been taken is to look at pollutant interactions (either multiplicative or additive, depending on the model assumed), but until we understand (and appropriately model) the biological mechanisms, such models are assumptions on the part of the researcher. Present modeling practices represent the best methods now available and provide useful assessments of PM health effects. However, ultimately, more biological-plausibility based models are needed that more accurately model pollutant interactions and allow more biologically-based interpretations of modeling results.

Until more is known about multiple pollutant interactions, it is important to avoid over-interpreting model results regarding the relative sizes and significance of specific pollutant effects, but instead to use biological plausibility in interpreting model results. For example, as discussed later, Krewski et al (2000) found significant associations for both PM and SO_2 in their reanalysis for the Health Effects Institute of the ACS data set published by Pope et al. (1995). Regarding these pollutant associations, they concluded that: “The absence of a plausible toxicological mechanism by which sulfur dioxide could lead to increased mortality further suggests that it might be acting as a marker for other mortality-associated pollutants.” (Note: Annual mean SO_2 averaged < 10 ppb across ca. 125 cities in the ACS data set.) Rather than letting statistical significance be the sole determinant of the “most important” pollutant, the authors utilized biological plausibility to conclude which association was most likely driving the pollution-health effects association in question. Such biological plausibility/mechanistic considerations need to be taken into account more broadly in the future in modeling and assessing possible pollutant interactions in contributing to health effects attributed to PM. In the meantime, the results from single-pollutant models of PM effects are emphasized here, as being those most likely reflecting overall effects exerted by ambient PM either acting alone and/or in combination with other ambient air pollutants.

8.1.4 Approach to Assessing Epidemiologic Evidence

The critical assessment of epidemiologic evidence presented in this chapter is conceptually based upon consideration of salient aspects of the evidence of associations so as to reach fundamental judgments as to the likely causal significance of the observed associations. In so doing, it is appropriate to draw from those aspects initially presented in Hill's classic monograph (Hill, 1965) and widely used by the scientific community in conducting such evidence-based reviews. A number of these aspects are judged to be particularly salient in evaluating the body of evidence available in this review, including the aspects described by Hill as strength, experiment, consistency, plausibility, and coherence. Other aspects identified by Hill, including temporality and biological gradient, are also relevant and considered here (e.g., in characterizing lag structures and concentration-response relationships), but are more directly addressed in the design and analyses of the individual epidemiologic studies included in this assessment. (As noted below, Hill's remaining aspects of specificity and analogy are not considered to be particularly salient in this assessment.) As discussed below, these salient aspects are inter-related and considered throughout the evaluation of the epidemiologic evidence presented in this chapter, and are more generally reflected in the integrative synthesis presented in Chapter 9.

In the following sections, the general evaluation of the strength of the epidemiological evidence reflects consideration not only of the magnitude of reported PM effects estimates and their statistical significance, but also of the precision of the effects estimates and the robustness of the effects associations. Consideration of the robustness of the associations takes into account a number of factors, including in particular the impact of alternative models and model specifications and potential confounding by co-pollutants, as well issues related to the consequences of measurement error. Another aspect that is related to the strength of the evidence in this assessment is the availability of evidence from "found experiments", or so-called intervention studies, which have the potential to provide particularly strong support for making causal inferences.

Consideration of the consistency of the effects associations as discussed in the following sections involves looking across the results of multi- and single-city studies conducted by different investigators in different places and times. In this assessment of ambient PM associations, it is important to consider the aspect of consistency in the context of understanding that ambient PM in different locations and at different times originates from different sources, such that its composition and physical characteristics can vary appreciably across studies using the same indicator for size-differentiated PM mass. Other relevant factors are also known to exhibit a great deal of variation across studies, including, for example, the presence and levels of co-pollutants, the relationships between central measures of PM and exposure-related factors, relevant demographic factors related to sensitive subpopulations, and climate and meteorological conditions. Thus, in this case, consideration of consistency, and the related issue of heterogeneity of effects, is appropriately understood as an evaluation of the similarity or general concordance of results, rather than an expectation of finding quantitative results within a relatively narrow range. Particular weight is given in this assessment, consistent with Hill's views, to the presence of "similar results reached in quite different ways, e.g., prospectively and retrospectively" (Hill, 1965). On the other hand, in light of these complexities in the chemical and physical properties of the mix of ambient PM, and its spatial and temporal variations, Hill's aspects of specificity of effects and analogy are not considered to be particularly salient in this review.

Looking beyond just the epidemiological evidence, consideration of the biological plausibility of the PM-effects associations observed in epidemiologic studies reflects consideration of both exposure-related factors and dosimetry and toxicologic evidence relevant to the identification of potential biological mechanisms. Similarly, consideration of the coherence of effects associations reported in the epidemiologic literature reflects broad consideration of information related to the nature of the various respiratory- and cardiac-related mortality and morbidity effects and biological markers evaluated in toxicologic and epidemiologic studies. These broader aspects of the assessment are addressed in this chapter and integrated into the discussion presented in Chapter 9.

In identifying these aspects as being particularly salient in this assessment, it is also important to recognize that no one aspect is either necessary or sufficient for drawing inferences of causality. As Hill (1965) emphasized:

> None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater

> or less strength, is to help us to make up our minds on the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?

Thus, while these aspects frame considerations weighed in assessing the epidemiologic evidence, they do not lend themselves to being considered in terms of simple formulas or hard-and-fast rules of evidence leading to answers about causality (Hill, 1965). One, for example, cannot simply count up the numbers of studies reporting statistically significant results for the various PM indicator and health endpoints evaluated in this assessment and reach conclusions about the relative strength of the evidence and the likelihood of causality. Rather, these salient considerations are discussed throughout this assessment with the goal of producing an objective appraisal of the evidence, informed by peer and public comment and advice, including weighing of alternative views on controversial issues, leading to conclusions and inferences that reflect the best judgements of the scientists engaged in this review.

8.2 MORTALITY EFFECTS ASSOCIATED WITH AIRBORNE PARTICULATE MATTER EXPOSURE

8.2.1 Introduction

The relationship of PM and other air pollutants to excess mortality has been studied extensively and represents an important issue addressed in previous PM criteria assessments (U.S. Environmental Protection Agency, 1986, 1996a). Recent findings are evaluated here mainly for the two most important epidemiology designs by which mortality is studied: time-series mortality studies (Section 8.2.2) and prospective cohort studies (Section 8.2.3). The time-series studies mostly assess acute responses to short-term PM exposure, although some recent work suggests that time-series data sets can also be useful in evaluating responses to exposures over a longer time scale. Time-series studies use community-level air pollution measurements to index exposure and community-level response (i.e., the total number of deaths each day by age and/or by cause of death). Prospective cohort studies usefully complement time-series studies; they typically evaluate human health effects of long-term PM exposures indexed by community-level measurements, using individual health records with survival lifetimes or hazard rates adjusted for individual risk factors.

8.2.2 Mortality Effects of Short-Term Particulate Matter Exposure

8.2.2.1 Summary of 1996 Particulate Matter Criteria Document Findings and Key Issues

The time-series mortality studies reviewed in the 1996 and other past PM AQCD's provided much evidence that ambient PM air pollution is associated with increases in daily mortality. The 1996 PM AQCD assessed about 35 PM-mortality time-series studies published between 1988 and 1996. Of these studies, only five studies used GAM with default convergence criteria. Recent reanalyses (Schwartz, 2003a; Klemm and Mason, 2003) using GAM with stringent convergence criteria and other non-GAM approaches for one of these five studies, i.e., the Harvard Six cities time-series analysis (the only multi-city study among the five studies), essentially confirmed the original findings. Thus, information provided in the 1996 PM AQCD can be summarized without major concern with regard to the GAM convergence issue. Information derived from those studies was generally consistent with the hypothesis that PM is a causal agent in contributing to short-term air pollution exposure effects on mortality.

The PM_{10} relative risk estimates derived from short-term PM_{10} exposure studies reviewed in the 1996 PM AQCD suggested that an increase of 50 $\mu g/m^3$ in the 24-h average of PM_{10} is most clearly associated with an increased risk of premature total non-accidental mortality (total deaths minus those from accident/injury) on the order of relative risk (RR) = 1.025 to 1.05 in the general population or, in other words, 2.5 to 5.0% excess deaths per 50 $\mu g/m^3$ PM_{10} increase. Higher relative risks were indicated for the elderly and for those with pre-existing cardiopulmonary conditions. Also, based on the Schwartz et al. (1996a) analysis of Harvard Six City data (as later confirmed in the reanalysis by Schwartz [2003a] and Klemm and Mason [2003]), the 1996 PM AQCD found the RR (combined across the six cities) for excess total mortality in relation to 24-h fine particle concentrations to be about 3% excess risk per 25 $\mu g/m^3$ $PM_{2.5}$ increment.

While numerous studies reported PM-mortality associations, important issues needed to be addressed in interpreting their findings. The 1996 PM AQCD evaluated in considerable detail several critical issues, including: (1) seasonal confounding and effect modification; (2) confounding by weather; (3) confounding by co-pollutants; (4) measurement error; (5) functional form and threshold; (6) harvesting and life shortening; and (7) the role of PM components. As important issues related to model specification became further clarified, more studies began to address the most critical issues, some of which were at least partially resolved, whereas others required still further investigation. The next several paragraphs summarize the status of these issues at the time of the 1996 PM AQCD publication.

One of the most important components in time-series model specification is adjustment for seasonal cycles and other longer-term temporal trends. Residual over-dispersion and autocorrelation result from inadequate control for these temporal trends, and not adequately adjusting for them could result in biased RRs. Modern smoothing methods allow efficient fits of temporal trends and reduce such statistical problems (it did introduce additional issues as discussed in later sections). Most recent studies controlled for seasonal and other temporal trends, and it was considered unlikely that inadequate control for such trends seriously biased estimated PM coefficients. Effect modification by season was examined in several studies. Season-specific analyses are often not feasible in small-sized studies (due to marginally significant PM effect size), but some studies (e.g., Samet et al., 1996; Moolgavkar and Luebeck, 1996) suggested that estimated PM coefficients varied from season to season. It was not fully resolved, however, whether these results represent real seasonal effect modifications or are due to varying extent of correlation between PM and co-pollutants or weather variables by season.

While most available studies included control for weather variables, some reported sensitivity of PM coefficients to weather model specification, leading some investigators to speculate that inadequate weather model specifications may still have erroneously ascribed residual weather effects to PM. Two PM studies (Samet et al., 1996; Pope and Kalkstein, 1996) involved collaboration with a meteorologist and utilized more elaborate weather modeling, e.g., use of synoptic weather categories. These studies found that estimated PM effects were essentially unaffected by the synoptic weather variables and also indicated that the synoptic weather model did not provide better model fits in predicting mortality when compared to other weather model specifications used in previous PM-mortality studies. Thus, these results suggested that the reported PM effects were not explained by more sophisticated synoptic weather models. However, both of these studies used GAM, presumably with default convergence criteria, and therefore need to be interpreted with caution, especially in light of their not having been reanalyzed with more stringent GAM convergence criteria and/or by GLM or other types of modeling specifications.

Many earlier PM studies considered at least one co-pollutant in the mortality regression, and some also examined several co-pollutants. In most cases, when PM indices were significant in single pollutant models, addition of a co-pollutant diminished the PM effect size somewhat, but did not eliminate the PM associations. When multiple pollutant models were performed by season, the PM coefficients became less stable, again, possibly due to PM's varying correlation with co-pollutants among season and/or smaller sample sizes. However, in many studies, PM indices showed the highest significance (versus gaseous co-pollutants) in single and multiple pollutant models. Thus, it was concluded that PM-mortality associations were not seriously distorted by co-pollutants, but interpretation of the relative significance of each pollutant in mortality regression as relative causal strength was difficult because of limited quantitative information on relative exposure measurement/characterization errors among air pollutants.

Measurement error can influence the size and significance of air pollution coefficients in time-series regression analyses and is also important in assessing confounding among multiple pollutants, as varying the extent of such error among the pollutants could also influence the corresponding relative significance. The 1996 PM AQCD discussed several types of such exposure measurement or characterization errors, including site-to-site variability and site-to-person variability — errors thought to bias the estimated PM coefficients downward in most cases. However, there was not sufficient quantitative information available to estimate such bias.

The 1996 PM AQCD also reviewed evidence for threshold and various other functional forms of short-term PM mortality associations. Several studies indicated that associations were seen monotonically below the existing PM standards. It was considered difficult, however, to statistically identify a threshold from available data because of low data density at lower ambient PM concentrations, potential influence of measurement error, and adjustments for other covariates. Thus, the use of relative risk (rate ratio) derived from the log-linear Poisson models was considered adequate and appropriate.

The extent of prematurity of death (i.e., mortality displacement or "harvesting") in observed PM-mortality associations has important public-health-policy implications. At the time of the1996 PM AQCD review, only a few studies had investigated this issue. While one of the studies suggested that the extent of such prematurity might be only a few days, this may not be generalizable because this estimate was obtained for identifiable PM episodes. There was not sufficient evidence to suggest the extent of prematurity for non-episodic periods from which most of the recent PM relative risks were derived. The 1996 PM AQCD concluded:

In summary, most available epidemiologic evidence suggests that increased mortality results from both short-term and long-term ambient PM exposure. Limitations of available evidence prevent quantification of years of life lost to such mortality in the population.
Life shortening, lag time, and latent period of PM-mediated mortality are almost certainly distributed over long time periods, although these temporal distributions have not been characterized. (p. 13-45)

Only a limited number of PM-mortality studies analyzed fine particles and chemically specific components of PM. The Harvard Six Cities Study (Schwartz et al., 1996a) analyzed size-fractionated PM ($PM_{2.5}$, $PM_{10/15}$, and $PM_{10/15-2.5}$) and PM chemical components (sulfates and H^+). The results suggested that, among the components of PM, $PM_{2.5}$ was most significantly associated with mortality. Because the original study was conducted using GAM with default convergence criteria, the data were recently reanalyzed by Schwartz (2003a), who reanalyzed only $PM_{2.5}$ and by Klemm and Mason (2003), who analyzed $PM_{2.5}$, $PM_{10/15}$, $PM_{10/15-2.5}$, and sulfate. Although the excess risk estimates were somewhat lower than those in the original study, Klemm and Mason's reanalysis confirmed the original findings with regard to the relative importance of fine versus coarse particles. While H^+ was not significantly associated with mortality in the original and an earlier analysis (Dockery et al., 1992), the smaller sample size for H^+ than for other PM components made a direct comparison difficult. The 1996 PM AQCD also noted that mortality associations with BS or CoH reported in earlier studies in Europe and the U.S. during the 1950s to 1970s most likely reflected contributions from fine particles, as those PM indices had low 50% cut-points ($\leq$ 4.5 µm). Furthermore, certain respiratory morbidity studies showed associations between hospital admissions/visits with components of PM in the fine particle range. Thus, the U.S. EPA 1996 PM AQCD concluded that there was adequate evidence to suggest that fine particles play especially important roles in observed PM mortality effects.

Overall, then, the status of key issues as addressed in the 1996 PM AQCD can be summarized as follows: (1) the observed PM effects are unlikely to be seriously biased by inadequate statistical modeling (e.g., control for seasonality); (2) the observed PM effects are unlikely to be seriously confounded by weather (at least by synoptic weather models); (3) the observed PM effects may be to some extent confounded or modified by co-pollutants, and such extent may vary from season to season; (4) determining the extent of confounding and effect modification by co-pollutants requires knowledge of relative exposure measurement characterization error among pollutants (there was not sufficient information on this); (5) no clear evidence for any threshold for PM-mortality associations was reported (statistically identifying a threshold from existing data was also considered difficult, if not impossible); (6) some limited evidence for harvesting, a few days of life-shortening, was reported for episodic periods (no study was conducted to investigate harvesting in non-episodic U.S. data); (7) only a relatively limited number of studies suggested a causal role of fine particles in PM-mortality associations, but in the light of historical data, biological plausibility, and the results from morbidity studies, a greater role for fine particles than coarse particles was suggested in the 1996 PM AQCD as being likely. The AQCD concluded:

> The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, mis-specification of concentration-effect models, biases in study design or implementation, measurement of errors in health endpoint, pollution exposure, weather, or other variables, nor confounding of PM effects with effects of other factors. While the results of the epidemiologic studies should be interpreted cautiously, they nonetheless provide ample reason to be concerned that there are detectable human health effects attributable to PM at levels below the current NAAQS. (p. 13-92)

8.2.2.2 Newly Available Information on Short-Term Mortality Effects

Since the 1996 PM AQCD, numerous new studies have examined short-term associations between PM indices and mortality. Of these studies (over 80 studies), nearly 70% used GAM (presumably with default convergence criteria). In the summer of 2002, U.S. EPA asked the original investigators of some of these studies to reanalyze the data using GAM with more stringent convergence criteria and GLM with parametric smoothers such as natural splines. Because the extent of possible bias caused by the default criteria setting in the GAM models is difficult to estimate for individual studies, the discussion here will focus only on those studies that did not use GAM Poisson models and those studies that have reanalyzed data using more stringent convergence criteria and/or alternative approaches. Newly available U.S. and Canadian studies on relationships between short-term PM exposure and daily mortality that meet these criteria are summarized in Table 8-1. More detailed summaries of all the short-term exposure PM-mortality studies, including other geographic areas (e.g., Europe, Asia, etc) are described in Appendix Table 8A-1. These include the studies that apparently used GAM with default convergence criteria, and these studies are noted as such. Information on study location and period, levels of PM, health outcomes, methods, results, and reported risk estimates and lags is provided in Table 8A-1. In addition to these summary tables, discussion in the text below highlights findings from several multi-city studies (Section 8.2.3) and single-city studies (Section 8.2.4). Discussion of implications of new study results for types of issues identified in foregoing text is mainly deferred to Section 8.4.

The summary of studies in Table 8-1 and 8A-1 (and in other tables) is not meant to imply that all listed studies should be accorded equal weight in the overall interpretive assessment of evidence regarding PM-associated health effects. In general, for those studies not clearly flawed and having adequate control for confounding increasing scientific weight should be accorded to in proportion to the precision of their estimate of a health effect. Small studies and studies with an inadequate exposure gradient generally produce less precise estimates than large studies with an adequate exposure gradient. Therefore, the range of exposures (e.g., as indicated by the IQR), the size of the study as indexed by the total number of observations (e.g., days) and total number of events (i.e., total deaths), and the inverse variance for the principal effect estimate are all important indices useful in determining the likely precision of health effects estimates and in according relative scientific weight to the findings of a given study. As can be seen in Tables 8-1 and 8A-1, nearly all of the newly reported analyses with a few exceptions continue to show statistically significant associations between short-term (24 h) PM exposures indexed by a variety of ambient PM measurements and increases in daily mortality in numerous U.S. and Canadian cities, as well as elsewhere around the world. Also, the effects estimates from the newly reported studies are generally consistent with those derived from the 1996 PM AQCD assessment, the newly reported PM risk estimates generally falling within the range of ca. 1 to 8% increase in excess deaths per 50 $\mu g/m^3$ PM_{10} and ca. 2 to 6% increase per 25 $\mu g/m^3$ $PM_{2.5}$. Several newly available PM epidemiologic studies that conducted time-series analyses in multiple cities are of particular interest, as discussed below. Multi-city studies, such as the

TABLE 8-1. RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Multi- City Mortality Studies in the U.S. and Canada				
PM_{10} studies using NMMAPS data				
Samet et al. (2000a, b, c); Dominici et al. (2000a, b); Samet (2000); Dominici et al. (2003)	A	88 cities in the 48 contiguous U.S. states plus AK and HI, 1987-1994; mainly 20 largest.	PM_{10}, O_3, CO, NO_2, SO_2	Numerous models; range of PM_{10} values depending on city, region, co- pollutants. Pooled estimates for 88 cities, individual estimates for 20 largest with co- pollutant models.
Daniels et al. (2000); Dominici et al. (2003)	A	20 cities in the 48 contiguous U.S. states, 1987-1994	PM_{10} only	Smooth non- parametric spline model for concentration- response functions. Average response curve nearly linear.
Dominici et al. (2002) Dominici et al. (2003)	A	88 cities in the 48 contiguous U.S. states, 1987-1994	PM_{10} only	Smooth non-parametric spline models for PM_{10} concentration-response functions. Average response curves are nearly linear in the industrial Midwest, Northeast regions, and overall, but non-linear (usually concave) in the other regions. Possible thresholds in Southeast.
Studies using every day PM_{10} data				
Schwartz (2000a); Schwartz (2003b)	A	Ten U.S. cities: New Haven, CT; Pittsburgh, PA; Detroit, MI; Birmingham, AL; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA. 1986-1993.	PM_{10} , O_3, CO, NO_2, SO_2	Pooled PM_{10} (0 and 1 day lag average) mortality estimates for the ten cities were presented. Confounding and/or effect modification was examined for season, co-pollutants, in- versus out-of-hospital deaths.
Schwartz (2000b); Schwartz (2003b).	A	Same ten U.S. cities as in (Schwartz, 2000a)	PM_{10} only.	Several pooled estimates across cities evaluated for single day, moving average, and distributed lags.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Multi- City Mortality Studies in the U.S. and Canada (cont'd)				
Studies using every day PM_{10} data (cont'd)				
Braga et al. (2001); Schwartz (2003b)	A	Same ten U.S. cities as in (Schwartz, 2000a)	PM_{10} only.	Pooled estimates across cities evaluated for deaths due to pneumonia, COPD, cardiovascular, and myocardial infarction using distributed lags models.
Laden et al.. (2000); Schwartz (2003a)	A	Same six cities as in Harvard Six city study, with Harvard air monitors and community daily mortality time-series: Boston (Watertown), MA, Harriman-Kingston, TN; Portage- Madison, WI; St. Louis, MO; Steubenville, OH; Topeka, KS.	Chemically speciated $PM_{2.5}$ and factors aligned with putative sources for each city identified by specific chemical elements as tracers.	Different coefficients in different cities, depending on source type, chemical indicators, and principal factor method. The motor vehicle combustion component was significant, other factors occasionally, but not the crustal element component.
Klemm et al., (2000); Klemm and Mason (2003)	A	Same six cities as (Laden et al., 2000), 1979-1988.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates	Replicated Schwartz et al. (1996a) with additional sensitivity analyses.
Tsai et al. (1999, 2000)	B	Camden, Elizabeth, and Newark, NJ, 1981-1983.	$PM_{2.5}$, PM_{15}, sulfates, trace elements.	Significant effects of $PM_{2.5}$, PM_{10}, and sulfates in Newark, Camden at most lags, but not Elizabeth. Source-specific factors (oil burning, automobiles) were also associated with mortality.
Clyde et al. (2000)	B	Phoenix, AZ, May, 1995- March, 1998. Seattle, WA, 1990- 1995.	$PM_{2.5}$, $PM_{10-2.5}$ in Phoenix. PM_{10}, $PM_{2.5}$, nephelometer, SO_2 in Seattle.	$PM_{10-2.5}$ significant in most of the 25 "best" models for Phoenix, $PM_{2.5}$ in almost none. $PM_{2.5}$ and PM_{10} in some models for Seattle, none in the 5 best.
Burnett et al. (2000); Burnett and Goldberg (2003)	A	Eight Canadian cities: Montreal, Ottawa, Toronto, Windsor, Calgary, Edmonton, Winnipeg, Vancouver, 1986-1996.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, O_3, CO, NO_2, SO_2.	The results of reanalysis indicate no clear difference in association with mortality between $PM_{2.5}$ and $PM_{10-2.5}$.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Single-City Mortality Studies in the U.S. and Canada				
Moolgavkar (2000a); Moolgavkar (2003).	A	Three large U.S. counties (cities): Cook Co., IL; Los Angeles Co., CA; Maricopa Co., (Phoenix), AZ, 1987-1995 in the original analysis. In the reanalysis, Maricopa Co. was not analyzed.	PM_{10} in all three; $PM_{2.5}$ in Los Angeles. O_3, CO, NO_2, and SO_2 in some models. In the GAM reanalysis, O_3 was not analyzed.	Gaseous pollutants were at least as significantly associated as PM indices. In particular, CO was the best single index of air pollution association with mortality in Los Angeles.
Ostro et al. (1999a, 2000); Ostro et al. (2003)	A	Coachella Valley (Palm Springs), CA, 1989-1998.	PM_{10} in earlier study, $PM_{2.5}$ and $PM_{10-2.5}$ in later study; O_3, CO, NO_2. Reanalysis reported PM risk estimates only.	PM_{10} (~65% of which was coarse particles) and $PM_{10-2.5}$ (missing values predicted from PM_{10}) were associated with cardiovascular mortality. $PM_{2.5}$ was available for shorter period.
Fairley (1999); Fairley (2003)	A	Santa Clara County (San Jose), CA, 1989-1996.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, nitrates, O_3, CO, NO_2.	All significant in one- pollutant models, nitrates significant in all multi- pollutant models, $PM_{2.5}$ significant except with particle nitrates.
Schwartz et al. (1999)	B	Spokane, WA, 1989-1995.	PM_{10} only.	No association between mortality and high PM_{10} concentrations on dust storm days with high concentrations of crustal particles.
Lippmann et al. (2000); Ito (2003)	A	Detroit, MI, 1985-1990; 1992-1994 (separate analysis for two periods).	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, acidity, TSP, O_3, CO, NO_2, SO_2	PM mass indices were more strongly associated mortality than sulfate or acidity. The extent of association with health outcomes was similar for $PM_{2.5}$ and PM_{10-25}.
Chock et al. (2000)	B	Pittsburgh, PA, 1989-1991.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, CO, NO_2, SO_2	Fine and coarse particle data on about 1/3 of days with PM_{10}. Data split into ages < 75 and 75+, and seasons. Significant effects for PM_{10} but not for other size fractions, likely because of smaller sample size.

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Single-City Mortality Studies in the U.S. and Canada (cont'd)				
Klemm and Mason (2000)	B	Atlanta, GA, 1998-1999 (one year).	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, oxygenated hydrocarbons (HC), elemental carbon (EC), organic carbon (OC), sulfates, acidity	No significant effects likely due to short time-series (ca. one year).
Schwartz (2000c); Schwartz (2003a)	A	Boston, MA, 1979-1986.	$PM_{2.5}$	Larger effects with longer-term $PM_{2.5}$ and mortality moving averages (span 15 to 60 days) for total and cause-specific mortality.
Lipfert et al. (2000a)	B	Philadelphia, PA- Camden, NJ seven- county area, 1995-1997.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfates, acidity, metals, O_3, CO, NO_2, SO_2	Exploration of mortality in different areas relative to air monitor location. Peak O_3 very significant, greatly reduced PM coefficients.
Levy (1998)	B	King County (Seattle), WA, 1990-1994.	PM_1 (nephelometer), PM_{10}, CO, SO_2	PM_1 associated only with out- of- hospital ischemic heart disease deaths; total mortality with neither PM_{10} nor PM_1
Mar et al. (2000); Mar et a. (2003)	A	Phoenix, AZ, near the EPA platform monitor, 1995-1997.	PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, $PM_{2.5}$ metals, EC, OC, O_3, CO, NO_2, SO_2, and source-apportioned factor scores.	Only cardiovascular mortality was reanalyzed; it was significantly associated with PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, EC, OC, factors associated with motor vehicle, vegetative-burning, and regional sulfate.
Clyde et al. (2000)	B	Phoenix, AZ, 1995-1997.	$PM_{2.5}$ and $PM_{10-2.5}$	Effect on elderly mortality consistently higher for $PM_{10-2.5}$ among 25 "best" models. Estimates combined using Bayesian model averaging.
Smith et al. (2000)	B	Phoenix, AZ (within city and within county), 1995-1997.	$PM_{2.5}$ and $PM_{10-2.5}$	Significant linear relationship with $PM_{10-2.5}$, not $PM_{2.5}$ Piecewise linear models with possible $PM_{10-2.5}$ threshold for elderly mortality 20-25 µg/m^3.
Gamble (1998)	B	Dallas, TX, 1990-1994.	PM_{10}, O_3, CO, NO_2, SO_2	O_3, CO, NO_2 significantly associated with mortality, PM_{10} and NO_2 not associated

TABLE 8-1 (cont'd). RECENT U.S. AND CANADIAN TIME-SERIES STUDIES OF PM-RELATED DAILY MORTALITY*

Reference	Type**	Location(s)/period	Pollutants	Comments
Single-City Mortality Studies in the U.S. and Canada (cont'd)				
Ostro (1995)	B	San Bernardino and Riverside Counties, CA, 1980- 1986.	$PM_{2.5}$ estimated from visual range, O_3	Positive, significant $PM_{2.5}$ association only in summer.
Murray and Nelson (2000)	B	Philadelphia, PA, 1973- 1990	TSP only	Kalman filtering used to estimate hazard function in a state space model. Both TSP and the product of TSP and average temperature are significant, but not together. Includes estimate of risk population.
Neas et al. (1999)	B	Philadelphia, PA 1973- 1980	TSP only	Case- crossover study. Significant TSP mortality associations reported.
Goldberg et al. (2001a,b,c,d; 2003); Goldberg and Burnett (2003)	A	Montreal, PQ, Canada, 1984- 1995	CoH and extinction were available daily. $PM_{2.5}$ and PM_{10} every sixth day until 1992, daily through 1993.	Reanalysis indicated attenuation of PM risk estimates, especially sensitive to weather model specification. Congestive heart failure, as classified based on medical records from insurance plan, was associated with CoH, SO_2, and NO_2.
Ozkaynak et al. (1996)	B	Toronto, ON, Canada 1970- 1991	TSP, CoH, O_3, CO, NO_2, SO_2	Significant association with 0- day lag TSP. Factor analysis identified a factor with high loadings on CoH, CO, and NO_2 (traffic presumably) significantly associated with total most cause- specific deaths.

*Brief summary of new time-series studies on daily mortality since the 1996 Air Quality Criteria Document for Particulate Matter (U.S. Environmental Protection Agency, 1996a). More complete descriptive summaries are provided in Appendix Table 8A-1. The endpoint is total daily non- trauma mortality, unless noted otherwise. Due to the large number of models reported for sensitivity analyses for some of these papers, some evaluating various lags and co-pollutant models, some for individual cities, and others for estimates pooled across cities, quantitative risk estimates are not presented in this table.

**Type: Type of studies: (A) Original study used GAM model including non-parametric smoothing terms with default or other lax convergence criteria, but was reanalyzed using stringent convergence criteria and/or using parametric smoothers; (B) Original study used GLM with parametric smoothers or other approaches, or used GAM but with only one non-parametric smoother.

NMMAPS study, avoid potential publication bias, because the cities were selected on the basis of population size and the presence of PM monitoring data. In addition, because use of uniform statistical analytical methods, findings cannot be attributed to different analytical approaches.

8.2.2.3 New Multi-City Studies

The new multi-city studies are of particular interest here due to their evaluation of a wide range of PM exposures and large numbers of observations holding promise of providing more precise effects estimates than most smaller scale independent studies of single cities. Another major advantage of the multi-city studies, over meta-analyses for multiple "independent" studies, is the consistency in data handling and model specifications that eliminates variation due to study design. Further, unlike regular meta-analysis, they clearly do not suffer from potential omission of negative studies due to "publication bias." Furthermore, geographic patterns of air pollution effects can be systematically evaluated in multiple-city analyses. Thus, the results from multi-city studies can provide especially valuable evidence regarding the consistency and/or heterogeneity, if any, of PM-health effects relationships across geographic locations. Also, many of the cities included in these multi-city studies were ones for which no time-series analyses had been previously reported. Most of these new multi-city studies used GAM Poisson models, but the data sets have recently been reanalyzed using GAM models with more stringent convergence criteria, as well as by GLM with parametric smoothers.

8.2.2.3.1 U.S. Multi-City Studies

U.S. PM_{10} 90-Cities NMMAPS Analyses

The National Morbidity, Mortality, and Air Pollution Study (NMMAPS) focused on time-series analyses of PM_{10} effects on mortality during 1987-1994 in the 90 largest U.S. cities (Samet et al., 2000a,b), in the 20 largest U.S. cities in more detail (Dominici et al., 2000a), and PM_{10} effects on emergency hospital admissions in 14 U.S. cities (Samet et al., 2000a,b). These NMMAPS analyses are marked by extremely sophisticated statistical approaches addressing issues of measurement error biases, co-pollutant evaluations, regional spatial correlation, and synthesis of results from multiple cities by hierarchical Bayesian meta-regressions and meta-analyses. These analyses provide extensive new information of much importance and relevance to the setting of U.S. PM standards, because no other study has examined as many

U.S. cities in such a consistent manner. That is, NMMAPS used only one consistent PM index (PM_{10}) across all cities (noted PM_{10} samples were only collected every 6 days in most of the 90 cities); death records were collected in a uniform manner; and demographic variables were uniformly addressed. The 90-cities analyses studies employ multi-stage models (see Table 8-1) in which heterogeneity in individual city's coefficients in the first stage Poisson models were evaluated in the second stage models with city- or region-specific explanatory variables.

As noted earlier, the original investigators of the NMMAPS study reported in 2002 a potential problem with using the GAM Poisson models with default convergence criteria available in popular statistical software in estimating air pollution risks (Dominici et al., 2002). The default convergence criteria were too lax to attain convergence in the setting of air pollution, weather, and mortality/morbidity parameters where "small" PM regression coefficients were estimated and at least two covariates were modeled with non-parametric smoothers. Their simulation analysis also suggested that the extent of bias could be more serious when the magnitude of risk coefficient was smaller and when PM's correlation with covariates was stronger. The investigators since then reanalyzed the 90 cities data, using more stringent convergence criteria as well as using fully parametric smoothers, and reported revised results. The following description of the NMMAPS mortality study therefore focuses on the results of the reanalysis of the 90 cities study.

In the original and reanalyzed 90 cities studies, the combined estimates of PM_{10} coefficients were positively associated with mortality at all the lags examined (0, 1, and 2 day lags), although the 1-day lag PM_{10} resulted in the largest overall combined estimate. Figure 8-1 shows the reanalyzed results for the estimated percent excess total deaths per 10 $\mu g/m^3$ PM_{10} at lag 1 day in the 88 (90 minus Honolulu and Anchorage) largest cities, as well as (weighted average) combined estimates for U.S. geographic regions depicted in Figure 8-2. The majority of the coefficients were positive for the various cities listed along the left axis of Figure 8-1. The estimates for the individual cities were first made separately. The cities were then grouped into the 7 regions seen in Figure 8-2 (based on characteristics of the ambient PM mix typical of each region, as delineated in the 1996 PM AQCD). The bolded segments represent the posterior means and 95% posterior intervals of the pooled regional effects without borrowing information from other regions. The triangle and bolded segment at the bottom of Figure 8-1 display the combined estimate of overall nationwide effects of PM_{10} for all the cities.

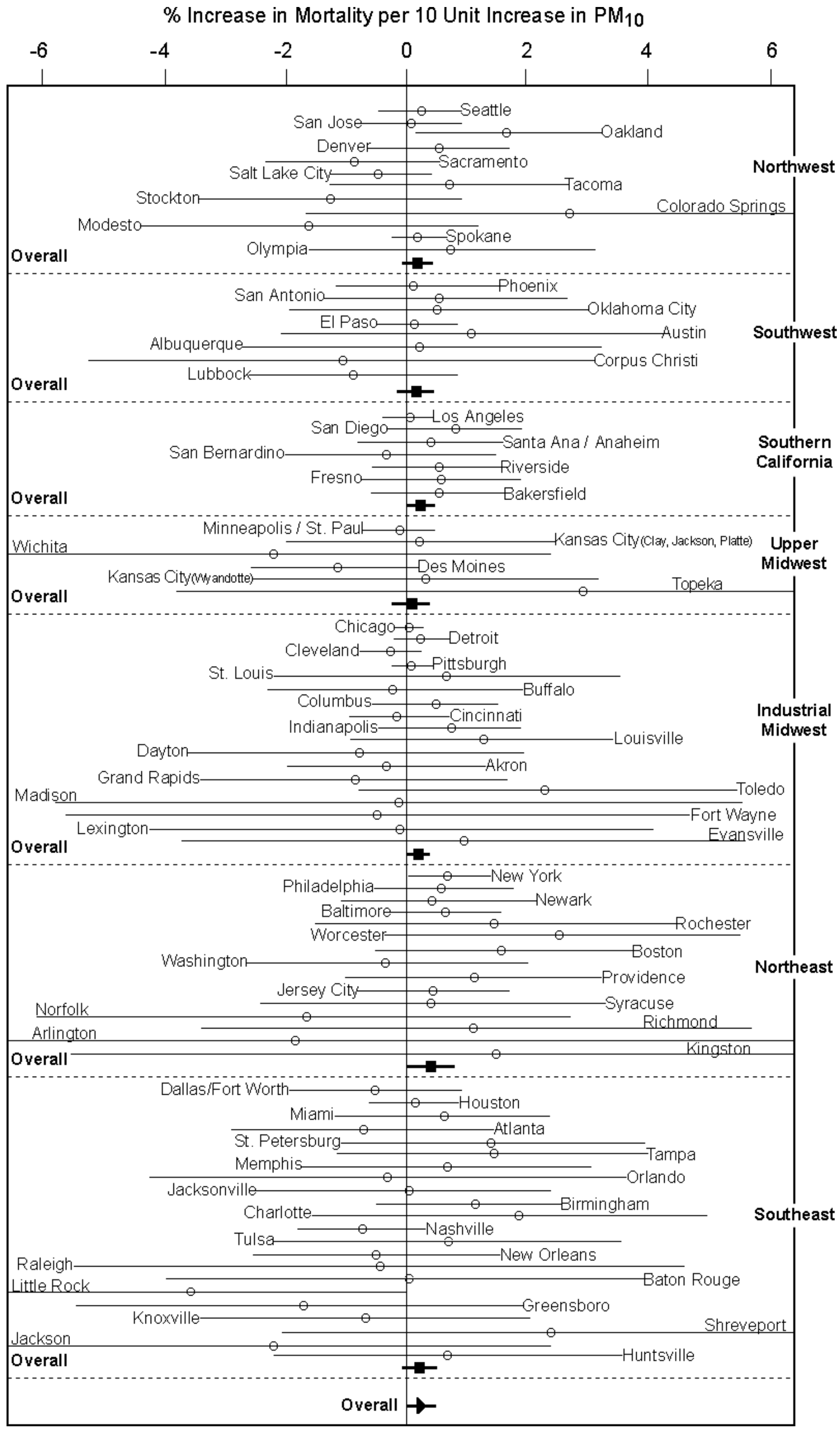

Figure 8-1. Estimated excess risks for PM mortality (1 day lag) for the 88 largest U.S. cities as shown in the revised NMMAPS analysis.

Source: Dominici et al. (2002; 2003).

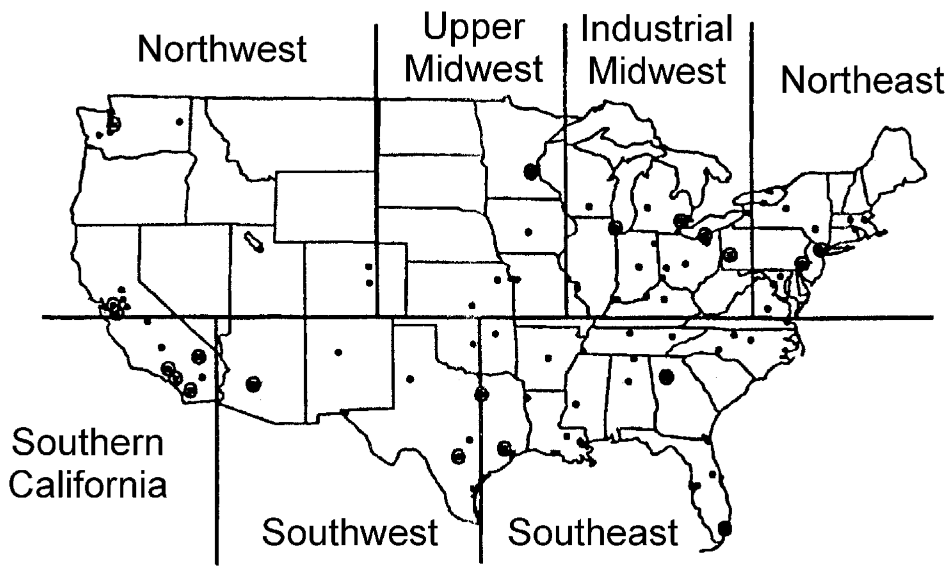

Figure 8-2. Map of the United States showing the 88 cities (the 20 cities are circled) and the seven U.S. regions considered in the NMMAPS geographic analyses.

Note that there appears to be some regional-specific variation in the overall combined estimates for all the cities in a given region. This can be discerned more readily in Figure 8-3, which depicts overall region-specific excess risk estimates for 0, 1, and 2 day lags. For example, the coefficients for the Northeast are generally higher than for other regions. The NMMAPS investigators noted that the extent of the regional heterogeneity in the reanalysis result was reduced slightly compared to the original finding (between-city standard deviation changed from 0.112 to 0.088 in the unit of percent excess deaths per 10 $\mu g/m^3$ PM_{10}), but the pattern of heterogeneity remained the same. The overall national combined estimate (i.e., at lag 1 day, 1.4% excess total deaths per 50 $\mu g/m^3$ increase in PM_{10} using GAM with stringent convergence criteria) for the 90 cities is somewhat lower than the range of estimates for the cities reported in the 1996 PM AQCD.

In the original 90 cities study, the weighted second-stage regression included five types of county- specific variables: (1) mean weather and pollution variables; (2) mortality rate (crude mortality rate); (3) sociodemographic variables (% not graduating from high school and median household income);(4) urbanization (public transportation); and (5) variables related to measurement error (median of all pair-wise correlations between monitors). Some of these

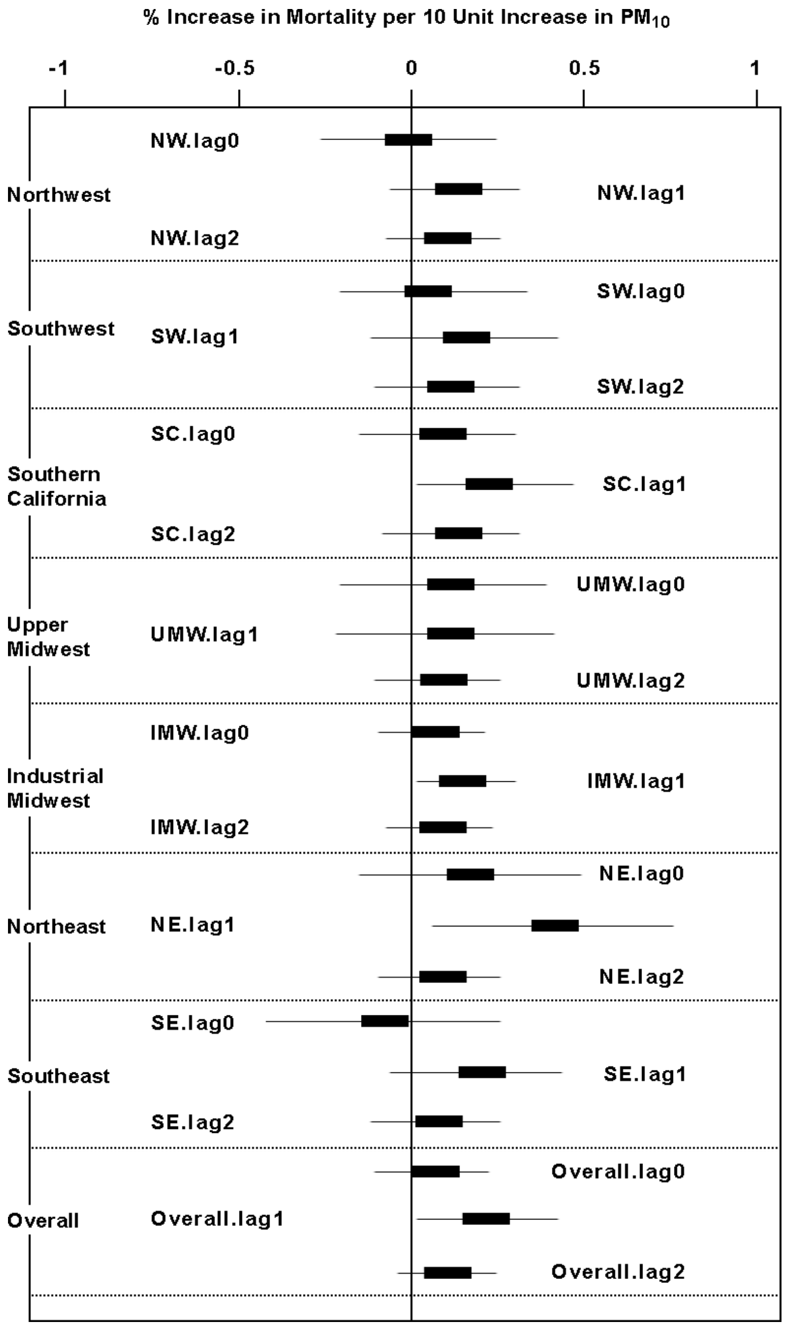

Figure 8-3. Percent excess mortality risk (lagged 0, 1, or 2 days) estimated in the NMMAPS 90-City Study to be associated with 10-µg/m^3 increases in PM_{10} concentrations in cities aggregated within U.S. regions shown in Figure 8-4.

Source: Dominici et al. (2002; 2003).

variables were apparently correlated (e.g., mean PM_{10} and NO_2, household income and education) so that the sign of coefficients in the regression changed when correlated variables were included in the model. Thus, while some of the county-specific variables were statistically significant (e.g., mean NO_2 levels), interpreting the role of these county-specific variables may require caution. Regarding the heterogeneity of PM_{10} coefficients, the investigators concluded that they "did not identify any factor or factors that might explain these differences."

Another important finding from Samet and coworkers' analyses was the weak influence of gaseous co-pollutants on the PM_{10} effect size estimates (see Figure 8-4). In the reanalysis of 90 cities data, PM_{10} coefficients slightly increased when O_3 was added to regression models. Additions of a third pollutant (i.e., PM_{10} + O_3 + another gaseous pollutant) hardly changed the posterior means of PM_{10} effect size estimates, but widened the distribution. However, the posterior probabilities that the overall PM_{10} effects are greater than zero remained at or above 0.96. The gaseous pollutants themselves in single-, two-, and three-pollutant models were less consistently associated with mortality than PM_{10}. Ozone was not associated with mortality using year-round data; but, in season-specific analyses, it was associated with mortality negatively in winter and positively in summer. SO_2, NO_2, and CO were weakly associated with mortality, but additions of PM_{10} and other gaseous pollutants did not always reduce their coefficients, possibly suggesting their independent effects. As noted in Section 8.1, CO and NO_2 from motor vehicles are likely confounders of $PM_{2.5}$ and, thus, of PM_{10} when it is not dominated by the coarse particle fraction. The investigators stated that the PM_{10} effect on mortality "was essentially unchanged with the inclusion of either O_3 alone or O_3 with additional pollutants."

The reanalyses of the 90 cities data by the original NMMAPS investigators also included a sensitivity analysis of lag 1day PM_{10} GLM results to the alternative degrees of freedom for adjustment of the confounding factors: season, temperature, and dewpoint. The degrees of freedom for each of these three smoothing terms was either doubled or halved, resulting in nine scenarios in addition to the degrees of freedom in the original GLM model. The PM_{10} effect posterior means were generally higher when the degrees of freedom were halved for season, and lower when they were doubled, ranging between 1.6% to 0.9% (the main GLM result was 1.1%) excess total mortality per 50 $\mu g/m^3$ PM_{10} increase. These results underscore the fact that the magnitude of sensitivity of the results due to model specification (in this case, degrees of freedom alone) can be as great as the potential bias caused by the GAM convergence problem.

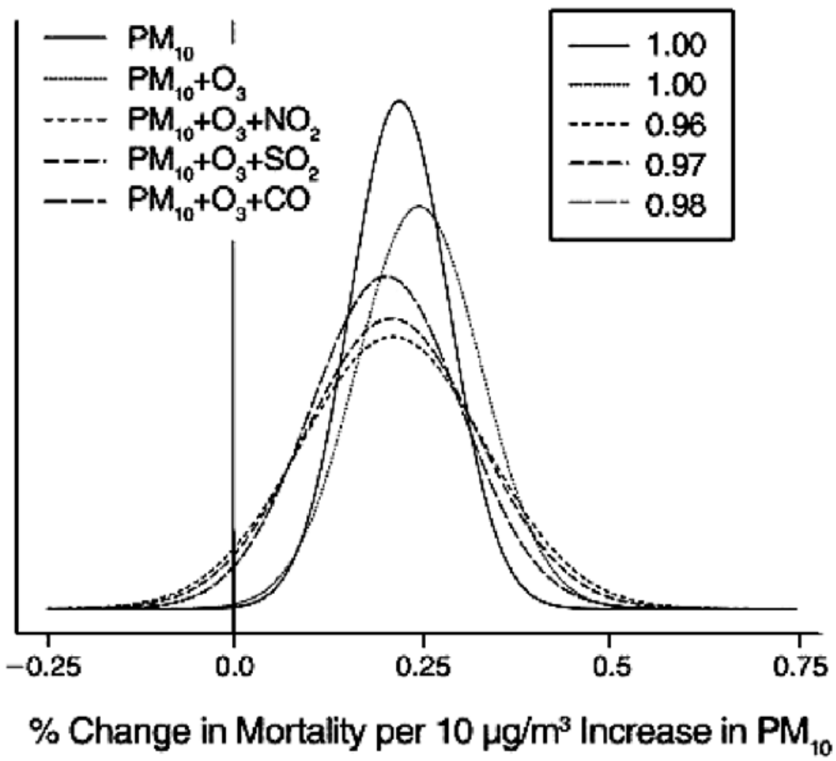

Figure 8-4. Marginal posterior distributions for effect of PM_{10} on total mortality at lag 1 with and without control for other pollutants, for the 90 cities. The numbers in the upper right legend are the posterior probabilities that the overall effects are greater than 0.

Source: Dominici et al. (2003).

HEI (2003a) states that the revised NMMAPS 90 individual-city mortality results show that, in general, the estimates of PM effect are shifted downward and the confidence intervals are widened. In the revised analyses, a second stage meta-analysis was used to combine results on effects of PM and other pollutants on health outcomes across cities. Tightening the convergence criteria in GAM obtained a substantially lower estimate of effect of PM_{10} combined over all cities, and use of GLM with natural splines decreased the estimate further. The revised analyses yielded a small, but statistically significant, effect of PM_{10} at lag 1 on total mortality, now estimated to be 0.21% per 10 µg/m^3, with a posterior standard error of 0.06%. HEI (2003a) agrees with the investigators' conclusions that the qualitative conclusions of NMMAPS II have not changed although the evidence for an effect of PM_{10} at lag 0 and lag 2 is less convincing under the new models. The NMMAPS II report found that the PM_{10} effect remained when copollutants were introduced into the model (Samet et al., 2000a); and this conclusion has not changed.

The extent of reduction in PM_{10} excess risk estimate due to the change in the convergence criteria (2.3% per 50 µg/m^3 PM_{10} using default versus 1.4% using stringent) using GAM models in the 90 cities study appears to be greater than those reported in most of other reanalysis studies. This may be in part due to the smaller risk estimate (2.3%) in the original study compared to other studies (> 3%), as the smaller coefficient is likely more strongly affected as a relative reduction. This may also be in part due to the more "aggressive" adjustment for possible weather effects (discussed later) used in this study, which may have increased the concurvity between PM and the covariates (which included four smoothing terms for weather adjustment). Dominici et al. (2002) reported that the higher the concurvity, the larger the potential bias that a GAM model with default convergence criteria could produce.

In summary, the 90-cities NMMAPS study provides extremely useful information regarding the following: (1) the magnitude of combined PM_{10} risk estimate; (2) the lack of sensitivity of PM_{10} risk estimates to gaseous co-pollutants; (3) indications of some regional heterogeneity in PM_{10} risk estimates across the U.S.; (4) the shape of concentration-response relationship (discussed in a later section); and (5) the range of sensitivity of PM_{10} risk estimates to the extent of smoothing of covariates in their original weather model specification. One major uncertainty that has not been examined in this study is the sensitivity of the PM_{10} risk estimates to different weather model specifications (e.g., use of two temperature terms, rather than four).

U.S. 10-Cities Studies

In another set of multi-city analyses, Schwartz (2000a,b), Schwartz and Zanobetti (2000), Zanobetti and Schwartz (2000), Braga et al. (2000), and Braga et al. (2001) analyzed 1987-1995 air pollution and mortality data from ten U.S. cities (New Haven, CT; Birmingham, AL; Pittsburgh, PA; Detroit, MI; Canton, OH; Chicago, IL; Minneapolis-St. Paul, MN; Colorado Springs, CO; Spokane, WA; and Seattle, WA.) or subsets (4 or 5 cities) thereof. The selection of these cities was based on the availability of daily (or near daily) PM_{10} data. All of these original studies utilized GAM Poisson models with default convergence criteria. Of these studies, Schwartz (2003) reanalyzed the data from Schwartz (2000a), Schwartz (2000b), and Braga et al. (2001) using GAM with stringent convergence criteria as well as alternative models such as

GLM with natural cubic splines or penalized splines, both of which are expected to give correct standard errors. The main original results of the study were presented in the Schwartz (2000a) paper; and the other studies noted above focused on each of several specific issues, including potential confounding, effect modification, distributed lag, and threshold. In this section, the results for the three reanalysis studies noted above are discussed.

In the reanalysis (Schwartz, 2003b) of the main results (Schwartz, 2000a), daily total (non-accidental) mortality in each of the 10 cities was fitted using a GAM Poisson model (with stringent convergence criteria) or a GLM Poisson model with natural splines, adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time. The data were also analyzed by season (November through April as heating season). The inverse-variance weighted averages of the ten cities' estimates were used to combine results. PM_{10} (average of lag 0 and 1 days) was significantly associated with total deaths, and the effect size estimates were comparable in summer and winter. Adjusting for other pollutants did not substantially change the PM_{10} effect size estimates. The combined percent-excess-death estimate for total mortality was 3.4% (95% CI = 2.6 – 4.1) per 50 $\mu g/m^3$ increase in the average of lag 0 and 1 days PM_{10} (essentially unchanged from the original study) using GAM with stringent convergence criteria. The PM_{10} risk estimate using GLM with natural splines was 2.8% (95% CI = 2.0 – 3.6).

In the reanalysis (Schwartz, 2003b) of the study of multi-day effects of air pollution (Schwartz, 2000b), constrained (quadratic model over 0 through 5 day lags) and unconstrained (0 through 5 day lags) distributed lag models were fitted in each city. The overall estimate was computed using the inverse-variance weighted average of individual city estimates. Among the results obtained using GAM with stringent convergence criteria, the PM_{10} effect size estimate was 6.3% (95% CI = 4.9 – 7.8) per 50 $\mu g/m^3$ increase for the quadratic distributed lag model, and 5.8% (95% CI = 4.4 – 7.3) for the unconstrained distributed lag model. Corresponding values using the penalized splines were somewhat smaller (~ 5.3%). These values are about twice the effect-size estimate for single-day PM_{10} in the original report or the two-day mean PM_{10} reported in the reanalysis above (this reanalysis did not report results for single-day or 2-day mean PM_{10}). These results suggest a possibility that PM effects may be underestimated when only single-day PM indices are used.

Schwartz (2003b) also reanalyzed the data from Braga et al.'s (2001) study to examine the lag structure of PM_{10} association with specific cause of mortality in the 10 cities. Unconstrained distributed lags for 0 through 5 days as well as two-day mean were fitted in each city for COPD, pneumonia, all cardiovascular, and myocardial infarction deaths using GAM with stringent convergence criteria and penalized spline models. Combined estimates by lag were obtained across the 10 cities. The distributed lag estimates were generally larger than the two-day mean estimates for COPD and pneumonia mortality, but they were comparable for all cardiovascular and myocardial infarction mortality. For example, in the results using GAM with stringent convergence criteria, the PM_{10} effect size estimate was 11.0% (95% CI = 7.2 – 14.8) per 50 µg/m^3 increase for two-day mean model, and 16.8% (95% CI = 8.3 – 25.9) for the unconstrained distributed lag model. Note that these values are substantially larger than those reported for total non-accidental deaths.

The PM_{10} risk estimates from these 10 cities studies appear to be larger than those from the 90 cities study. Aside from the difference in the number of cities analyzed, the difference in weather model specification and the extent of smoothing for temporal trends may have contributed to the difference in the size of PM_{10} risk estimates. This issue is further discussed in Section 8.2.2.3.5.

Reanalyses of Harvard Six Cities Study

Both the original Harvard Six Cities Study time-series analysis (Schwartz et al., 1996a) and the replication analysis by Klemm et al. (2000), which essentially replicated Schwartz et al.’s original findings, used GAM Poisson models with default convergence criteria. Schwartz (2003a) and Klemm and Mason (2003) conducted reanalyses of the Harvard Six Cities data to address the GAM statistical issues.

Schwartz (2003a) reported the risk estimates for $PM_{2.5}$ only, but provided results using several other spline smoothing methods (natural splines, B-splines, penalized splines, and thin plate splines) in addition to GAM with stringent convergence criteria. The risk estimate combined across the six cities per 25 µg/m^3 in $PM_{2.5}$ (average of lag 0 and 1 day) using GAM with stringent convergence criteria was 3.5% (95% CI = 2.5 – 4.5), as compared to the original value of 3.7% (95% CI = 2.7 – 4.7). The corresponding value from a GLM model with natural splines was 3.3% (95% CI = 2.2 – 4.3). The values using B-splines, penalized splines, and thin plate splines were somewhat lower (3.0%, 2.9%, and 2.6%, respectively). However, when the Harvard Six Cities were examined individually in the reanalysis of Schwartz using GLM and penalized splines, Boston and St. Louis gave significant associations with $PM_{2.5}$ and Steubenville gave a significant association with coarse PM.

Klemm and Mason's reanalysis (2003) reported risk estimates for $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} (PM_{15} or PM_{10}), and SO_4^{-2}. They also conducted sensitivity analyses using GLM with natural splines that approximated the degrees of freedom used in the LOESS smoothers in the GAM models, as well as 12 knots per year and 4 knots per year for smoothing of temporal trends. The $PM_{2.5}$ and $PM_{10-2.5}$ total non-accidental mortality risk estimates combined across the six cities per 25 µg/m^3 (average of lag 0 and 1 day) using GAM with stringent convergence criteria were 3.0% (95% CI = 2.1 – 4.0) and 0.8% (95% CI = −0.5, 2.0), respectively. The corresponding PM_{10} mortality excess risk estimate per 50 µg/m^3 (average of lag 0 and 1 day) was 3.6% (95% CI = 2.1, 5.0). In their sensitivity analysis, increasing the degrees of freedom for temporal trends for natural splines in GLM models from 4 knots/year to 12 knots/year markedly reduced PM risk estimates. For example, the $PM_{2.5}$ risk estimate per 25 µg/m^3 was reduced from 2% in the 4 knots/year model to 1% in the 12 knots/year model. The results showing the smaller PM risk estimates for larger degrees of freedom for smoothing of temporal trends are consistent with similar findings reported for the reanalysis of 90 cities study.

Although PM effect estimates from the Klemm and Mason (2003) reanalysis are somewhat smaller than those from Schwartz (2003; e.g., 3.5% by Schwartz versus 3.0% by Klemm and Mason for $PM_{2.5}$ using strict convergence criteria), the results are essentially comparable. Both studies also showed that the comparable GLM models produced smaller risk estimates than GAM models.

8.2.2.3.2 Canadian Multicity Studies

Burnett et al. (2000) analyzed various PM indices (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, CoH, and 47 elemental component concentrations for fine and coarse fractions) and gaseous air pollutants (NO_2, O_3, SO_2, and CO) for association with total mortality in the 8 largest Canadian cities: Montreal, Ottawa-Hull, Toronto, Windsor, Winnipeg, Calgary, Edmonton, and Vancouver. This study differs from Burnett et al. (1998a) in that it included fewer cities but more recent years of data (1986-1996 versus 1980-1991) and detailed analyses of particle mass components by size and elemental composition. Each city's mortality, pollution, and weather variables were separately filtered for seasonal trends and day-of-week patterns. The residual series from all cities were then combined and analyzed in a GAM Poisson model. In Burnett and Goldberg's reanalysis (2003) of the eight cities data, they only examined the PM indices $PM_{2.5}$, $PM_{10-2.5}$, and PM_{10} using GAM models with more stringent convergence criteria. The reanalysis used co-adjustment regression (i.e., simultaneous regression), rather than the regression with pre-filtered data that was the main approach of the original analysis. The reanalysis also considered several sensitivity analyses including models with and without day-of-week adjustment and several alternative approaches (fitting criteria and extent of smoothing) to adjust for temporal trends using natural splines.

Adjusting for temporal trends, smoothing of same-day temperature, pressure, and day-of-week effects, the pooled PM effect estimates across the eight Canadian cities were: 3.7% (95% CI = 1.4-6.0) per 25 μg/m^3 increase in $PM_{2.5}$; 2.1% (0.1-4.2) per 25 μg/m^3 increase $PM_{10-2.5}$; and 3.6% (95% CI = 1.3-5.8) per 50 μg/m^3 increase PM_{10}. These effect size estimates are fairly close to the estimates reported in the original study, despite the differences in the regression approach (pre-filtering and GAM with default convergence criteria in the original study versus co-adjustment and using GAM with stringent convergence criteria). The temporal adjustment of the above model used LOESS smoothing with span of approximately 0.022 (= 90 days/4012 study days). Sensitivity analysis included several choices of degrees of freedom for natural splines of temporal trend, with two fitting criteria (i.e., Bartlett's test for white noise and AIC) and either using the same degrees of freedom for all the eight cities or varying degrees of freedom for each city. The PM risk estimates based on natural splines were generally smaller than those based on LOESS smoothers. The PM risk estimates also varied inversely with the number of knots for temporal trend. That is, the more details of the temporal trend were described by natural splines, the smaller the PM risk estimates became. The reported $PM_{2.5}$ risk estimates per 25 μg/m^3 increase were 3.0% (t=3.12), 2.8% (t=2.28), 2.2% (t=2.14), 2.1% (t=2.07), and 1.9% (t=1.72) for knot/year, knot/6 months, knot/3 months, knot/2 months, and knot/1 month, respectively. The corresponding values for 25 μg/m^3 increase in $PM_{10-2.5}$ were 3.9% (t=3.42), 2.9% (t=2.52), 2.1% (t=1.69), 1.8% (t=1.46), and 1.2% (t=0.91), suggesting greater sensitivity of $PM_{10-2.5}$ risk estimates to the extent of temporal smoothing. The authors suggested that this was likely due to the stronger correlation between (and temporal trends in) mortality and mass concentrations for $PM_{10-2.5}$ (average correlation among cities of –0.45) than for $PM_{2.5}$ (−0.36). Because the relative significance and size of $PM_{2.5}$ and $PM_{10-2.5}$ risk estimates varied depending on the model and extent of smoothing for temporal trend, it is difficult to determine the relative importance of the two size-fractionated PM indices in this study.

8.2.2.3.3 European Multi-City APHEA Study Analyses

The Air Pollution and Health: A European Approach (APHEA) project is a multi-center study of short-term effects of air pollution on mortality and hospital admissions within and across a number of European cities having a wide range of geographic, climatic, sociodemographic, and air quality patterns. The obvious strength of this approach is its ability to evaluate potential confounders or effect modifiers in a consistent manner. It should be noted that PM indices measured in those cities varied. In APHEA1, the PM indices measured were mostly black smoke (BS), except for Paris, Lyon (PM_{13}); Bratislava, Cologne, and Milan (TSP); and Barcelnoa (BS and TSP). In APHEA2, 10 out of the 29 cities used actual PM_{10} measurements; and, in 11 additional cities, PM_{10} levels were estimated based on regression models relating collocated PM_{10} measurements to BS or TSP. In the remaining 8 cities, only BS measurements were available (14 cities had BS measurements). As discussed below, there have been several papers published that present either a meta-analysis or pooled summary estimates of these multi-city mortality results: (1) Katsouyanni et al. (1997) — SO_2 and PM results from 12 cities; (2) Touloumi et al. (1997) — ambient oxidants (O_3 and NO_2) results from six cities; (3) Zmirou et al. (1998) — cause-specific mortality results from 10 cities (see Section 8.2.2.5); (4) Samoli et al. (2001) — a reanalysis of APHEA1 using a different model specification (GAM) to control for long-term trends and seasonality; and (5) Katsouyanni et al. (2001) — APHEA2, with emphasis on the examination of confounding and effect modification. The original APHEA protocol used sinusoidal terms for seasonal adjustment and polynomial terms for weather variables in Poisson regression models. Therefore, publications 1 through 3 above are not subject to the GAM default convergence issue. Publications 4 and 5 did use GAM Poisson model with default convergence criteria, but the investigators have reanalyzed the data using GAM with more stringent convergence criteria, as well as GLM with natural splines (Katsouyani et al., 2003; Samoli et al., 2003). The discussions presented below on publications 4 and 5 are focused on the results from the reanalyses.

APHEA1 Sulfur Dioxide and Particulate Matter Results for 12 Cities

The Katsouyanni et al. (1997) analyses evaluated data from the following cities: Athens, Barcelona, Bratislava, Cracow, Cologne, Lodz, London, Lyons, Milan, Paris, Poznan, and Wroclaw. In the western European cities, an increase of 50 µg/m^3 in SO_2 or BS was associated with a 3% (95% CI = 2.0, 4.0) increase in daily mortality; and the corresponding figure was 2% (95% CI = 1.0, 3.0) for estimated PM_{10} (they used conversion: PM_{10} = TSP*0.55). In the 31 central/eastern European cities, the increase in mortality associated with a 50 µ g/m^3 change was 0.8% (CI = 0.1, 2.4) for SO_2 and 0.6% (CI = 0.1, 1.1) per 50 µg/m^3 change in BS. Estimates of cumulative effects of prolonged (two to four days) exposure to air pollutants were comparable to those for one day effects. The effects of both pollutants (BS, SO_2) were stronger during the summer and were mutually independent. Regarding the contrast between the western and central/eastern Europe results, the authors speculated that this could be due to differences in exposure representativeness; differences in pollution toxicity or mix; differences in proportion of sensitive sub-population; and differences in model fit for seasonal control. Bobak and Roberts (1997) commented that the heterogeneity between central/eastern and western Europe could be due to the difference in mean temperature. However, Katsouyanni and Touloumi (1998) noted that, having examined the source of heterogeneity, other factors could apparently explain the difference in estimates as well as or better than temperature.

APHEA1 Ambient Oxidants (Ozone and Nitrogen Dioxide) Results for Six Cities

Touloumi et al. (1997) reported on additional APHEA data analyses, which evaluated (a) short-term effects of ambient oxidants on daily deaths from all causes (excluding accidents), and (b) impacts on effect estimates for NO_2 and O_3 of including a PM measure (BS) in multi-pollutant models. Six cities in central and western Europe provided data on daily deaths and NO_2 and/or O_3 levels. Poisson autoregressive models allowing for overdispersion were fitted. Significant positive associations were found between daily deaths and both NO_2 and O_3. Increases of 50 µg/m^3 in NO_2 (1-hour maximum) or O_3 (1-hour maximum) were associated with a 1.3% (95% CI = 0.9-1.8) and 2.9% (95% CI = 1.0-4.9) increase in the daily mortality, respectively. There was a tendency for larger effects of NO_2 in cities with higher levels of BS: when BS was included in the model, the coefficient for NO_2 was reduced by half (but remained significant) whereas the pooled estimate for the O_3 effect was only slightly reduced. The authors speculated that the short-term effects of NO_2 on mortality might be confounded by other vehicle-derived pollutants (e.g., airborne ambient PM indexed by BS measurements). Thus, while this study reports only relative risk levels for NO_2 and O_3 (but not for BS), it illustrates the importance of confounding of NO_2 and PM effects and the relative limited confounding of O_3 and PM effects.

APHEA1: A Sensitivity Analysis for Controlling Long-Term Trends and Seasonality

The original study (Samoli et al., 2001) attempted to examine the sensitivity of APHEA1 results to how the temporal trends were modeled (i.e., sine/cosine in the APHEA1 versus LOESS smoother using GAM with default convergence criteria). Samoli et al. (2003) reanalyzed the data using GAM with more stringent convergence criteria, as well as GLM with natural splines. Thus, the reanalysis allowed a comparison of results across a fixed functional model (sine/cosine), a non-parametric smoother (GAM with LOESS), and a parametric smoother (GLM with natural splines). The combined estimate across cities for percent excess in total non-accidental mortality per 50 $\mu g/m^3$ increase in BS using GAM with stringent convergence criteria (2.3%; 95% CI = 1.9-2.7) was bigger than that using sine/cosine (1.3%; 95% CI = 0.9-1.7). The GAM with stringent convergence criteria reduced the combined estimate by less than 10% compared to that from GAM with default convergence criteria. The corresponding estimate using GLM with natural splines (1.2%; 95% CI = 0.7-1.7) was comparable to that from the sine/cosine model but smaller than that using GAM. The contrast between western and eastern Europe in the original APHEA1 study (2.9% for west versus 0.6% for east) was less clear in the results using GAM with stringent convergence criteria (2.7% versus 2.1%) or GLM with natural splines (1.6% versus 1.0%). These results indicate that the apparent regional heterogeneity found in the original APHEA1 study could be sensitive to model specification. Because the number of cities used in the APHEA1 study is relatively small (eight western and five central-eastern cities), the apparent regional heterogeneity found in the earlier publications could also be due to chance. These reanalysis results also suggest that the results are somewhat sensitive to the model specification of temporal trends.

APHEA2: Confounding and Effect Modification Using Extended Data

The APHEA2 original study (Katsouyanni et al. 2001) included more cities (29 cities) and a more recent study period (variable years in 1990-1997, as compared to 1975-1992 in APHEA1). Also, the APHEA2 original study used a GAM (with default convergence criteria) Poisson model with LOESS smoothers to control for season and trends. Katsouyanni et al. (2003) reanalyzed the data using GAM with more stringent convergence criteria, as well as two parametric approaches: natural splines and penalized splines. Because the reanalysis GAM results changed the PM_{10} risk estimates only slightly from the original estimates and the investigators mention that the patterns of effect modification were preserved in their reanalyses regardless of model specification, the qualitative description of the effect modification below relies on the original study. The PM_{10} estimates for various models are from the reanalysis results.

The analyses put emphasis on effect modification by city-specific factors. Thus, the city-specific coefficients from the first stage of Poisson regressions were modeled in the second stage regression using city-specific characteristics as explanatory variables. Inverse-variance weighted pooled estimates (fixed-effects model) were obtained as part of this model. When substantial heterogeneity was observed, the pooled estimates were obtained using random-effects models. These city-specific variables included (1) air pollution level and mix, such as average air pollution levels and PM/NO_2 ratio (as an indicator of traffic-generated PM); (2) climatic variables, such as mean temperature and relative humidity; (3) health status of the population, such as the age-adjusted mortality rates, the percentage of persons over 65 years of age, and smoking prevalence; and (4) geographic area (three regions: central-eastern, southern, and north-western). The study also addressed the issue of confounding by simultaneous inclusion of gaseous co-pollutants in city-specific regressions and obtained the pooled PM estimates for each co-pollutant included. Unlike APHEA1, in which the region (larger PM estimates in western Europe than in central-eastern Europe) was highlighted as the important factor, APHEA2 found several effect modifiers. NO_2 (i.e., index of high pollution from traffic) was an important one. The cities with higher NO_2 levels showed larger PM effects as did the cities with a warmer climate. The investigators noted that this might be due to the better estimation of population exposures with outdoor community monitors (because of more open windows). Also, the cities with low standardized mortality rate showed larger PM effects. The investigators speculated that this may be because a smaller proportion of susceptible people (to air pollution) are available in a population with a large age-standardized mortality rate. Interestingly, in the pooled PM risk estimates from models with gaseous pollutants, it was also NO_2 that affected (reduced) PM risk estimates most. For example, in the fixed-effects models, approximately 50% reductions in both PM_{10} and BS coefficients were observed when NO_2 was included in the model. SO_2 only minimally reduced PM coefficients; whereas O_3 actually increased PM coefficients. Thus, in this analysis, NO_2 was implicated both as a confounder and an effect modifier. The overall random-effects model combined estimate for total mortality for 50 µg/m^3 increase in PM_{10} were 3.0% (95% CI = 2.0, 4.1), 2.1% (95% CI = 1.2, 3.0), and 2.8% (95% CI = 1.8, 3.8), for GAM (stringent convergence criteria), natural splines, and penalized splines models, respectively. The original estimate using GAM with default convergence criteria (3.1%) was thus reduced by 4%. While the effect estimates varied somewhat depending on the choice of GAM with LOESS, natural splines, or penalized splines, the investigators reported that the patterns of effect modification (by NO_2, etc.) were preserved.

8.2.2.3.4 Comparison of Effects Estimates from Multi-City Studies

Based on different pooled analyses of data combined across multiple cities, the percent excess (total, non-accidental) deaths estimated per 50 µg/m^3 increase in PM_{10} in the above multi-city studies were (1) 1.4% using GAM (1.1% using GLM) at lag 1-day in the 90 largest U.S. cities (the Northeast region results being about twice as high); (2) 3.4% using GAM (2.8% using GLM) for average of 0 and 1 day lags in 10 U.S. cities; (3) 3.6% using GAM (2.7% using GLM) for 1 day lag PM_{10} in the 8 largest Canadian cities; and (4) 3.0% using GAM (2.1% using GLM) in APHEA2 for average of 0 and 1 day lags for 29 European cities during 1990-1997.

Note that the estimate for the NMMAPS 90 cities study is somewhat smaller than those for the rest of the multi-city studies and the range reported in the previous PM AQCD (2.5 to 5%). There may be several possible explanations for this, but model specification for weather is likely one major factor. The 90 cities study used much more “aggressive” adjustment for possible weather effects than most studies. The 90 cities analysis included four separate weather terms: (1) smoothing splines (natural splines when GLM was used) of same-day temperature with 6 degrees of freedom; (2) smoothing splines of the average of lag 1 through 3 day temperature with 6 degrees of freedom; (3) smoothing splines of same-day dewpoint with 3 degrees of freedom; and, (4) smoothing splines of the average of lag 1 through 3 day dewpoint with 3 degrees of freedom. In contrast, most of the other studies used only one or two terms for weather variables. For example, the Harvard Six Cites Study used a LOESS smoother (or natural splines or other smoothers in reanalysis) of same-day temperature with a span of 0.5 and a LOESS smoother of same-day dewpoint with a span of 0.5. Note that the 90 cities study not only used more terms for weather effects, but it also used more degrees of freedom for temperature than Schwartz et al.'s analysis (according to Klemm and Mason's reanalysis, the span of 0.5 in LOESS corresponds to approximately 3.5 degrees of freedom). It should also be noted here that the purpose of the inclusion of dewpoint in these models is often explained as "to adjust for possible effects of humidity"; but, in fact, dewpoint and temperature are highly correlated ($r > 0.9$) in most cities. Thus, although the inclusion of these terms may statistically (i.e., by AIC, etc.) provide a better fit, the epidemiologic implications of the use of these terms is not yet clear. While extreme temperature, hot or cold, is known to cause excess mortality, it is not clear at this time whether these models are adequately modeling the weather effects in the more moderate range (which is much of the data). Thus, the inclusion in the NMMAPS modeling of several weather terms with more degrees of freedom most likely provides "conservative" PM risk estimates. That is, the NMMAPS excess risk estimates of 1.1% or 1.4% per 50 $\mu g/m^3$ PM_{10} increase may well underestimate the PM_{10}-total mortality effect-size suggested by two other well conducted multicity studies to fall in the range of 2.7% to 3.6% per 50 $\mu g/m^3$ PM_{10} increment for U.S. and Canadian cities.

Another factor that may contribute to the difference in PM risk estimates is the extent of smoothing to adjust for temporal trends. Several of the reanalysis studies (Dominici et al., 2002; Burnett and Goldberg, 2003; Ito, 2003; Klemm and Mason, 2003) consistently reported, though to varying extents, that using more degrees of freedom for temporal trends tended to reduce PM coefficients. That is, when more details in the short-term fluctuations of mortality were ascribed to temporal trends, PM risk estimates were reduced. For example, in Dominici et al.'s (2002) sensitivity analysis, the PM_{10} risk estimate was larger (1.6% per 50 $\mu g/m^3$ increase in PM_{10}) for the GLM model with 3 degrees of freedom per year that the estimate using 7 degrees of freedom (1.1%). Note that, in general, the presumed objective of including temporal trends in the mortality regression is to adjust for potential confounding (measured or unmeasured) by time-varying factors that change seasonally or in shorter time spans (e.g., influenza epidemics).

However, ascribing “too short” temporal fluctuations to these “confounding temporal trends” may inadvertently take away PM effects. Because the “right” extent of smoothing is not known, these sensitivity analyses are useful. In the reanalyses mentioned above, the PM risk estimates could change by a factor of two when a range of degrees of freedom was applied even for a model specification in which all the other terms were kept unchanged.

Based on the results from the reanalysis studies, it has become apparent that different smoothing approaches can also affect PM risk estimates. For example, the models with natural splines (parametric smoothing) appear, in general but not always, to result in smaller PM risk estimates than GAM models with LOESS or smoothing splines. GAM models may possibly suffer from biased standard error of risk estimates, but they also seem to fit the data better (i.e., based on AIC) than GLM models with natural splines. Thus, it is not clear which smoothers provide the most appropriate PM risk estimates. In any case, the choice of these smoothers does not seem to affect PM risk estimates (~ 10 to 30%) as much as the range of weather model specifications or the range of the degrees of freedom for temporal trends adjustment do (as large as a factor of two).

A less explored issue is the effect of multi-day effects of PM. The PM_{10} risk estimates summarized above are either for a single-day lag (U.S. 90 cities study, Canadian 8 cities study, and APHEA1), or an average of two days (U.S. 10 cities study and APHEA2). However, the reanalysis of U.S. 10 cities study data suggests that the multi-day PM effect, accounting for 0 through 5 day lag, could be twice as large as the effect sizes estimated from single or two-day average models and even bigger (~ 3 to 4 fold) when more specific cause of death categories were examined. This issue warrants further investigation.

In summary, considering all the options in model specifications that can affect the PM risk estimates, the reported combined PM_{10} total non-accidental mortality risk estimates from multi-city studies are in good agreement, in the range of 1.0 to 3.5% per 50 $\mu g/m^3$ increase in single or two-day average PM_{10}. The U.S. 90 cities study provides estimates towards the lower end of this range. Combinations of choices in model specifications (the number of weather terms and degrees of freedom for smoothing of mortality temporal trends) alone may explain the extent of the difference in PM_{10} risk estimates across studies. The range for these newly available combined estimates from multi-cities studies overlap with the range of PM_{10} estimates (2.5 to

5%, obtained from single cities studies) previously reported in the 1996 PM AQCD, but extends to somewhat lower values.

8.2.2.4 U.S. Single-City Studies

In addition to the new multi-city studies mentioned above, many new studies have presented findings on relationships between mortality and short-term exposure to PM using data from individual cities. The results of all such studies are presented in detail in Appendix 8A-1, and the results of U.S. and Canadian studies are highlighted in Table 8-1. The following discussion provides some additional focus on the results of some recent U.S. studies, especially those including PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ data. Results of analyses using $PM_{2.5}$ and $PM_{10-2.5}$ measurements are also discussed further in Section 8.2.2.5.

Moolgavkar (2000a) evaluated associations between short-term measures of major air pollutants and daily deaths in three large U.S. metropolitan areas (Cook Co., IL, encompassing Chicago; Los Angeles Co., CA; and Maricopa Co., AZ, encompassing Phoenix) during a 9-year period (1987-1995). Moolgavkar (2003) reanalyzed the data for Cook Co. and Los Angeles Co., but not Maricopa Co. using GAM with stringent convergence criteria as well as GLM with natural splines. Ozone was analyzed in the original analysis but not in the reanalysis (it was only positive and significant in Cook county in the original analysis). This section describes the results from the reanalysis. Total non-accidental deaths, deaths from cardiovascular disease (CVD) and chronic obstructive lung disease (COPD) were analyzed in relation to 24-h readings for PM, CO, NO_2, and SO_2 averaged over all monitors in a given county. Cerebrovascular mortality was analyzed in the original analysis but not in the reanalysis (its association with air pollution was weak in the original analysis). The results of cause-specific mortality analyses are described in a later section. Daily readings were available for each of the gaseous pollutants in both Cook Co. and Los Angeles Co., as were PM_{10} values for Cook Co. However, PM_{10} and $PM_{2.5}$ values were only available every sixth day in Los Angeles Co. PM values were highest in summer in Cook Co. and in the winter and fall in Los Angeles Co.; whereas the gases (except for O3) were highest in winter in both counties. The PM indices were moderately correlated (r = 0.30 to 0.73) with CO, NO_2, and SO_2 in Cook Co. and Los Angeles Co. Total non-accidental, CVD, and COPD deaths were all highest during winter in both counties.

Adjusting for temperature and relative humidity effects in separate analyses for each mortality endpoint for these two counties, varying patterns of results were found, as noted in Appendix A, Table 8A-1. Moolgavkar (2003) also reported sensitivity of results to different degrees of freedom (df) for smoothing of temporal trends (30 df and 100 df).

As for Cook County results, PM_{10} was significantly associated with total non-accidental mortality at lag 0 (most significant) and 1 day in GAM models with both 30 df and100 df for smoothing of temporal trends, as well as in a GLM model with 100 df for smoothing of temporal trends. The gaseous pollutants were also significantly associated with total non-accidental mortality at various lags (wider lags than PM_{10}), but most significant at lag 1 day. These associations did not appear to be sensitive to the extent of smoothing for temporal trends, at least at their most significant lags. In two pollutant models (results were not shown in tables but described in text), the PM_{10} association remained "robust and statistically significant" at lag 0 day; whereas the coefficients for the gases became non-significant. However, at lag 1 day, the PM_{10} association became non-significant and the gases remained significant. Thus, some extent of "sharing" of the association is apparent, and whichever pollutant is more strongly associated than the other at that lag tended to prevail in the two pollutant models in this data set.

For Los Angeles County, CO was more significantly associated (positive and significant at lag 0 through 3 days) with mortality than PM_{10} (positive and significant at lag 2) or $PM_{2.5}$ (positive and significant at lag 1). In two pollutant models in which CO and PM indices were included simultaneously at PM indices = "best" lags, CO remained significant; whereas PM coefficients became non-significant (and negative for cases with 30 df for temporal smoothing). For Los Angeles data, the PM coefficients appeared to be more sensitive to the choice of the degrees of freedom than to the default versus stringent convergence criteria. GLM models tended to produce smaller risk estimates than GAM models. Moolgavkar also reported that these associations were robust to varying the extent of smoothing for weather covariates.

The results for these two cities do not reflect a common pattern. In Cook Co., all the pollutants were associated with mortality, and their relative importance varied depending on the lag day, whereas CO showed the strongest mortality associations in Los Angeles. Moolgavkar concluded that, considering the substantial differences that can result from different analytic strategies, no particular numeric estimates were too meaningful, although the patterns of associations appeared to be robust.

Ostro et al. (2000; reanalyzed Ostro et al., 2003) conducted a study in Coachella Valley, CA, using PM_{10} data collected from 1989-1998, and $PM_{2.5}$ and $PM_{10-2.5}$ data collected during the last 2.5 years of the study period. Both $PM_{2.5}$ and $PM_{10-2.5}$ were estimated for the remaining years to increase the power of the analyses, but only $PM_{10-2.5}$ could be reliably estimated so predicted $PM_{2.5}$ data were not used. Original analyses used GAMs, with smoothing functions for time and indicators for day of week. Different lags for temperature, humidity and dewpoint were tested for use in the models, then pollutants were added individually then in combination. In reanalyses, more stringent convergence criteria and natural splines were used, but the reanalyses were only done for cardiovascular mortality. For cardiovascular mortality, significant associations were found for $PM_{10-2.5}$ and PM_{10}, but not $PM_{2.5}$ (possibly due to low range of $PM_{2.5}$ concentrations and reduced sample size for $PM_{2.5}$ data), and PM risk estimates were higher for multi-day averages. The PM risk estimates were slightly reduced in the reanalyses using GAM with stringent convergence criteria or using GLM; and sensitivity analysis showed that results were not sensitive to alternative degrees of freedom for temporal trends and temperature.

In Santa Clara County, CA, total, cardiovascular, and respiratory deaths were regressed on PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, COH, nitrate, sulfate, O_3, CO, NO_2, adjusting for time trend, season, and minimum and maximum temperature, using a Poisson GAM model (Fairley, 1999; reanalyzed Fairley, 2003). Reanalyses included stringent convergence criteria, as well as natural splines and an additional indicator for ozone (daily number of hours exceeding 60 ppb). In the reanalyses, the PM coefficients were either unchanged, or only slightly decreased or increased; and the original findings, including the pattern in two-pollutant models, were unchanged. $PM_{2.5}$ and nitrate were most significantly associated with mortality, but significant associations were reported for all pollutants except $PM_{10-2.5}$ in single-pollutant models. In two- and four- pollutant models, $PM_{2.5}$ or nitrate remained significant for total mortality but the other pollutants did not. The $PM_{2.5}$ risk estimates for respiratory deaths were larger than those for total or cardiovascular deaths but the associations were only significant for total mortality.

Lippmann et al. (2000; reanalyzed Ito, 2003) used data from Detroit for a 1992-1994 study period that included measurements of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, sulfate, H+, O_3, SO_2, NO_2, and CO. Associations with total (non-accidental), cardiovascular, respiratory, and other deaths were analyzed using GAM Poisson models, adjusting for season, temperature, and relative humidity. Analyses were also done for an earlier 1985-1990 study period that included measurements of

PM_{10} and TSP along with the gaseous co-pollutants. Reanalyses were done using stringent convergence criteria as well as natural splines, as well as additional sensitivity analyses to examine the influence of alternative weather models and selection of degrees of freedom on model results. In reanalyses, PM coefficients were often reduced (but sometimes unchanged or increased) somewhat when GAM with stringent convergence criteria or GLM/natural splines were used. The reductions in coefficients were not differential across PM components; the original conclusion regarding the relative importance of PM components remained the same. PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$ were more significantly associated with mortality outcomes than sulfate or H+. PM coefficients were generally not sensitive to inclusion of gaseous pollutants. PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$ effect size estimates were comparable in terms of the same distributional increment (5th to 95th percentile). Both PM_{10} (lag 1 and 2 day) and TSP (lag 1 day), but not TSP-PM_{10} or TSP- $SO_4^=$, were significantly associated with respiratory mortality for the 1985-1990 period. The simultaneous inclusions of gaseous pollutants with PM_{10} or TSP reduced the PM effect size by 0 to 34%. Effect size estimates for total, circulatory, and "other" categories were smaller than for respiratory mortality.

Chock et al. (2000) evaluated associations between daily mortality and several air pollution variables (PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, CO, O_3, NO_2, SO_2) in two age groups (< 75 yr., > 75 yr.) in Pittsburgh, PA, during a 3-year period (data on $PM_{2.5}$ and $PM_{10\text{-}2.5}$ were only available for half of the study period). Poisson GLM regression was used, including filtering of data based on cubic B-spline functions to adjust for seasonal trends; models included indicators for day of week, and temperature was modeled as a V-shape function. Single- and multi-pollutant models were run for 0, 1, 2, and 3 day lags. Single- and multi-pollutant non-seasonal models show significant positive associations between PM_{10} and daily mortality, but seasonal models showed much multi-collinearity, masking association of any pollutant with mortality. $PM_{2.5}$ and $PM_{10\text{-}2.5}$ were both positively associated with mortality, but the coefficients were unstable in this small data set when stratified by age group and season, thus no conclusions were drawn on relative role of $PM_{2.5}$ and $PM_{10\text{-}2.5}$. In conclusions, the authors emphasize issues of seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients for $PM_{2.5}$ and $PM_{10\text{-}2.5}$.

Using data for Philadelphia and the seven-county Philadelphia metropolitan area from 1992-1995, twelve mortality variables, as categorized by area, age, and cause, were regressed on

29 pollution variables (PM components, O_3, SO_2, NO_2, CO, and by sub-areas), yielding 348 regression results (Lipfert et al., 2000a). Both dependent and explanatory variables were pre-filtered using the19-day-weighted average filter prior to OLS regression. Covariates were selected from filtered temperature (several lagged and averaged values), indicator variables for hot and cold days and day-of-week using stepwise procedure, and the average of current and previous days' pollution levels were used. Significant associations were reported for a wide variety of gaseous and particulate pollutants, especially for peak O_3. No systematic differences were seen according to particle size or chemistry. Mortality for one part of the metropolitan area could be associated with air quality from another, not necessarily neighboring part.

Mar et al. (2000; reanalyzed Mar et al., 2003) evaluated associations between air pollutants and total (non-accidental) and cardiovascular deaths in Phoenix for only those who resided in the zip codes located near the air pollution monitor. GAM Poisson models were used, adjusting for season, temperature, and relative humidity, and a variety of air pollution variables were used, including O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were evaluated. Factor analysis was also conducted on chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC); and factor scores were included in the mortality analyses. Reanalysis was done using stringent convergence criteria as well as natural splines only for cardiovascular mortality. In the reanalysis, small reductions were seen in risk estimates for PM mass concentration indices using GAM/stringent convergence criteria or GLM/natural splines. For source factors, there were moderate reductions in risk estimates for the motor vehicle factor, but slight increases for the regional sulfate factor and slight reductions in the coefficients for EC and OC. Cardiovascular mortality was significantly associated with CO, NO_2, SO_2, $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$, OC and EC. Combustion-related factors and secondary aerosol factors were also associated with cardiovascular mortality. Soil-related factors, as well as individual variables that are associated with soil were negatively associated with total mortality.

In all of the studies discussed above, some statistically significant associations between mortality and PM indicators, especially $PM_{2.5}$ and PM_{10} were found. In multi-pollutant models, PM coefficients were often robust to inclusion of gaseous pollutants, but sometimes reduced for specific co-pollutants (see co-pollutant model discussion in Section 8.4).

8.2.2.5 The Role of Particulate Matter Components

Delineation of the roles of specific ambient PM components in contributing to associations between short-term PM exposures and mortality requires evaluation of several factors, e.g., size, chemical composition, surface characteristics, and the presence of gaseous co-pollutants. While possible combinations of these factors can in theory be limitless, the actual data tend to cover definable ranges of aerosol characteristics and co-pollutant environments due to typical source characteristics (e.g., fine particles tend to be combustion products in most cities). Newly available studies conducted in the last few years have begun to provide more extensive information on the roles of PM components; and their results are discussed below in relation to three topics: (1) PM particle size (e.g., $PM_{2.5}$ versus $PM_{10-2.5}$); (2) chemical components; and (3) source oriented evaluations.

The ability to compare the relative roles of different PM size fractions and various PM constituents is restricted by the limitations of the available studies. Comparisons nevertheless can be attempted, using such information as the relative level of significance and/or the strength of correlation between component estimate and health outcome. The relative significance across cities/studies is influenced by the sample size and the level of the pollutants. The width of the confidence band also needs to be taken into account, according more weight for studies with narrower confidence bands. Caution in interpretation of such information, however, is warranted because of potential measurement error and possible high correlations between indices being compared. Additionally, limitations of single-city studies must be recognized.

8.2.2.5.1 Particulate Matter Particle Size Evaluations

With regard to the relative importance of the fine and coarse fractions of inhalable PM_{10} particles capable of reaching thoracic regions of the respiratory tract, at the time of the 1996 PM AQCD only one acute mortality study (Schwartz et al., 1996a) had examined this issue. That study (which used GAM with default convergence criteria in analyzing Harvard Six-City study data) suggested that fine particles ($PM_{2.5}$), distinctly more so than coarse fraction ($PM_{10-2.5}$) particles, were associated with daily mortality. Recent reanalyses using GAM with more stringent convergence criteria have yielded only slightly smaller $PM_{2.5}$ effect-size estimates (Schwartz et al., 2003). It should also be noted that (a) the Klemm et al. (2000) reanalysis reconstructed the data and replicated the original analyses (using GAM with default convergence criteria) and (b) the Klemm and Mason (2003) reanalysis, using GAM with stringent convergence criteria and GLM with parametric smoothers, also essentially reproduced the original investigators' results.

Since the 1996 PM AQCD, several new studies have used size-fractionated PM data to investigate the relative importance of fine ($PM_{2.5}$) versus coarse ($PM_{10-2.5}$) fraction particles. Table 8-2 provides synopses of those studies with regard to the relative importance of the two size fractions, as well as some characteristics of the data. The average levels of $PM_{2.5}$ ranged from about 13 to 30 µg/m^3 in the U.S. cities, but much higher average levels were measured in Santiago, Chile (64.0 µg/m3). As can be seen in Table 8-2, in the northeastern U.S. cities (Philadelphia, PA and Detroit, MI), there was more $PM_{2.5}$ mass than $PM_{10-2.5}$ mass on the average; whereas in the western U.S. (Phoenix, AZ; Coachella Valley, CA; Santa Clara County, CA) the average $PM_{10-2.5}$ levels were higher than $PM_{2.5}$ levels. It should be noted that the three Phoenix studies in Table 8-2 use much the same data set; all used fine and coarse particle data from EPA's 1995-1997 platform study. Seasonal differences in PM component levels should also be noted. For example, in Santa Clara County and in Santiago, Chile, winter $PM_{2.5}$ levels averaged twice those during summer. The temporal correlation between $PM_{2.5}$ and $PM_{10-2.5}$ ranged between 0.30 and 0.65. Such differences in ambient PM mix features from season to season or from location to location complicates assessment of the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$.

To facilitate a quantitative overview of the effect size estimates and their corresponding uncertainties from these studies, the percent excess risks are plotted in Figure 8-5. These excluded the Clyde et al. study (for which the model specification did not obtain RRs for $PM_{2.5}$ and $PM_{10-2.5}$ separately) and the Smith et al. study (which did not present linear term RRs for $PM_{2.5}$ and $PM_{10-2.5}$). Note that, in most of the original studies, the RRs were computed for comparable distributional features (e.g., interquartile range, mean, 5th -to-95th percentile, etc.). However, the increments derived and their absolute values varied across studies; therefore, the RRs used in deriving the excess risk estimates delineated in Figure 8-5 were re-computed for consistent increments of 25 µg/m^3 for both $PM_{2.5}$ and $PM_{10-2.5}$. Note also that re-computing the RRs per 25 µg/m^3 in some cases changed the relative effect size between $PM_{2.5}$ and $PM_{10-2.5}$, but it did not affect the relative significance. All of the studies found positive associations between both the fine and coarse PM indices and increased mortality risk. However, most of the studies

TABLE 8-2. SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ AND $PM_{10\text{-}2.5}$

Author, City	Means (µg/m^3); ratio of $PM_{2.5}$ to PM_{10}; and correlation between $PM_{2.5}$ and $PM_{10\text{-}2.5}$	Results regarding relative importance of $PM_{2.5}$ versus $PM_{10\text{-}2.5}$ and comments.
Fairley (1999 & 2003)* Santa Clara County, CA	$PM_{2.5}$ mean = 13; $PM_{2.5}/PM_{10}$ =0.38; r = 0.51.	Of the various pollutants (including PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, sulfates, nitrates, CoH, CO, NO_2, and O_3), the strongest associations were found for ammonium nitrate and $PM_{2.5}$. $PM_{2.5}$ was significantly associated with mortality, but $PM_{10\text{-}2.5}$ was not, separately and together in the model. Winter $PM_{2.5}$ level is more than twice that in summer. The daily number of O_3 ppb-hours above 60 ppb was also significantly associated with mortality.
Ostro et al. (2000 & 2003)* Coachella Valley, CA	$PM_{2.5}$ (Palm Springs and Indio, respectively) mean = 12.7, 16.8; $PM_{2.5}/PM_{10}$ = 0.43, 0.35; r = 0.46, 0.28.	Coarse particles dominate PM_{10} in this locale. $PM_{2.5}$ was available only for the last 2.5 years; and a predictive model could not be developed, so that a direct comparison of $PM_{2.5}$ and $PM_{10\text{-}2.5}$ results is difficult. Cardiovascular mortality was significantly associated with PM_{10} (and predicted $PM_{10\text{-}2.5}$), whereas $PM_{2.5}$ was mostly negatively (and not significant) at the lags examined.
Clyde et al. (2000) Phoenix, AZ	$PM_{2.5}$ mean = 13.8; $PM_{2.5}/PM_{10}$ = 0.30; r = 0.65.	Using the Bayesian Model Averaging that incorporates model selection uncertainty with 29 covariates (lags 0- to 3-day), the effect of coarse particle (most consistent at lag 1 day) was stronger than that for fine particles. The association was for mortality defined for central Phoenix area where fine particles ($PM_{2.5}$) are expected to be uniform.
Mar et al. (2000 & 2003)* Phoenix, AZ 1995-1997	$PM_{2.5}$ (TEOM) mean = 13; $PM_{2.5}/PM_{10}$ = 0.28; r = 0.42.	Cardiovascular mortality was significantly associated with both $PM_{2.5}$ (lags 1, 3, and 4) and $PM_{10\text{-}2.5}$ (lag 0) with similar effect size estimates. Of all the pollutants (SO_2, NO_2, and elemental carbon were also associated), CO was most significantly associated with cardiovascular mortality.
Smith et al. (2000) Phoenix, AZ	Not reported, but likely same as Clyde's or Mar's data from the same location.	In linear PM effect model, the authors found a statistically significant mortality association with $PM_{10\text{-}2.5}$, but not with $PM_{2.5}$. In the models allowing for a threshold, they found evidence of a threshold for $PM_{2.5}$ (in the range of 20-25), but not for $PM_{10\text{-}2.5}$. A seasonal interaction in the $PM_{10\text{-}2.5}$ effect was also reported: the effect is highest in spring and summer when the anthropogenic concentration of $PM_{10\text{-}2.5}$ is lowest.
Lippmann et al. (2000); Ito, (2003)* Detroit, MI 1992-1994	$PM_{2.5}$ mean=18; $PM_{2.5}/PM_{10}$ =0.58; r = 0.42.	Both $PM_{2.5}$ and $PM_{10\text{-}2.5}$ were positively (but not significantly) associated with mortality outcomes to a similar extent. Simultaneous inclusion of $PM_{2.5}$ and $PM_{10\text{-}2.5}$ also resulted in comparable effect sizes. Similar patterns were seen in hospital admission outcomes.
Lipfert et al. (2000a) Philadelphia, PA 1992-1995.	$PM_{2.5}$ mean=17.3; $PM_{2.5}/PM_{10}$ =0.72.	The authors conclude that no systematic differences were seen according to particle size or chemistry. However, when $PM_{2.5}$ and $PM_{10\text{-}2.5}$ were compared, $PM_{2.5}$ (at lag 1 or average of lag 0 and 1) was more significantly (with larger attributable risk estimates) associated with cardiovascular mortality than $PM_{10\text{-}2.5}$.

TABLE 8-2 (cont'd). SYNOPSIS OF SHORT-TERM MORTALITY STUDIES THAT EXAMINED RELATIVE IMPORTANCE OF $PM_{2.5}$ AND $PM_{10\text{-}2.5}$

Author, City	Means (μg/m³); ratio of $PM_{2.5}$ to PM_{10}; and correlation between $PM_{2.5}$ and $PM_{10\text{-}2.5}$	Results regarding relative importance of $PM_{2.5}$ versus $PM_{10\text{-}2.5}$ and comments
Klemm and Mason (2000) Atlanta, GA	$PM_{2.5}$ mean = 19.9; $PM_{2.5}/PM_{10}$ = 0.65	No significant associations were found for any of the pollutants examined, possibly due to a relatively short study period (1-year). The coefficient and t-ratio were larger for $PM_{2.5}$ than for $PM_{10\text{-}2.5}$.
Klemm et al. (2000); Klemm and Mason (2003)* 6 U.S. cities	Mean $PM_{2.5}$ ranges from 11.3 to 29.6; Mean $PM_{10\text{-}2.5}$ ranges from 6.6 to 16.1; Mean $PM_{2.5}/PM_{10}$ ranges from 50.1% to 66% in the six cities.	This reanalysis of the Harvard Six-Cities time-series analysis by Schwartz et al. (1996a) found significant associations between total mortality and $PM_{2.5}$ in 3 cities and in pooled effect, but no significant association with $PM_{10\text{-}2.5}$ in the reanalysis of the replication study for any city. These results essentially confirmed the findings of the original study by Schwartz et al. (1996a).
Chock et al. (2000) Pittsburgh, PA	Data distribution not reported. $PM_{2.5}/PM_{10}$ = 0.67	Seasonal dependence of correlation among pollutants, multi-collinearity among pollutants, and instability of coefficients were all emphasized in discussion and conclusion. These considerations and the small size of the data set (stratified by age group and season) limit confidence in finding of no consistently significant associations for any size fractions.
Burnett et al. (2000); Burnett and Goldberg (2003)* 8 Canadian cities	$PM_{2.5}$ mean=13.3; $PM_{2.5}/PM_{10}$ =0.51; r = 0.37.	Both $PM_{2.5}$ and $PM_{10\text{-}2.5}$ were significantly associated with total non-accidental mortality. Results using varying extent of smoothing of mortality temporal trends show that there is no consistent pattern of either PM mass index being more important. The authors note that $PM_{10\text{-}2.5}$ was more sensitive to the type of smother and amount of smoothing.
Cifuentes et al. (2000) Santiago, Chile 1988-1996	$PM_{2.5}$ mean=64.0; $PM_{2.5}/PM_{10}$ =0.58; r = 0.52.	In GLM results for the whole years, only $PM_{2.5}$ and NO_2 were consistently significantly associated with total non-accidental mortality.

Note: * next to author name indicates that the study was originally analyzed using GAM models only with default convergence criteria using at least two non-parametric smoothing terms.

did not have large enough sample sizes to separate out what often appear to be relatively small differences in effect size estimates; but two of the studies do show distinctly larger mortality associations with $PM_{2.5}$ than for non-significant $PM_{10\text{-}2.5}$ effects. For example, the Klemm et al. (2000) and Klemm and Mason's (2003) re-computation of the Harvard Six Cities time-series study reconfirmed the original Schwartz et al. (1996a) finding that $PM_{2.5}$ was significantly associated with excess mortality, but $PM_{10\text{-}2.5}$ across all cities was not (although the Schwartz [2003a] reanalyses reconfirmed the original findings of statistically significant $PM_{10\text{-}2.5}$-mortality

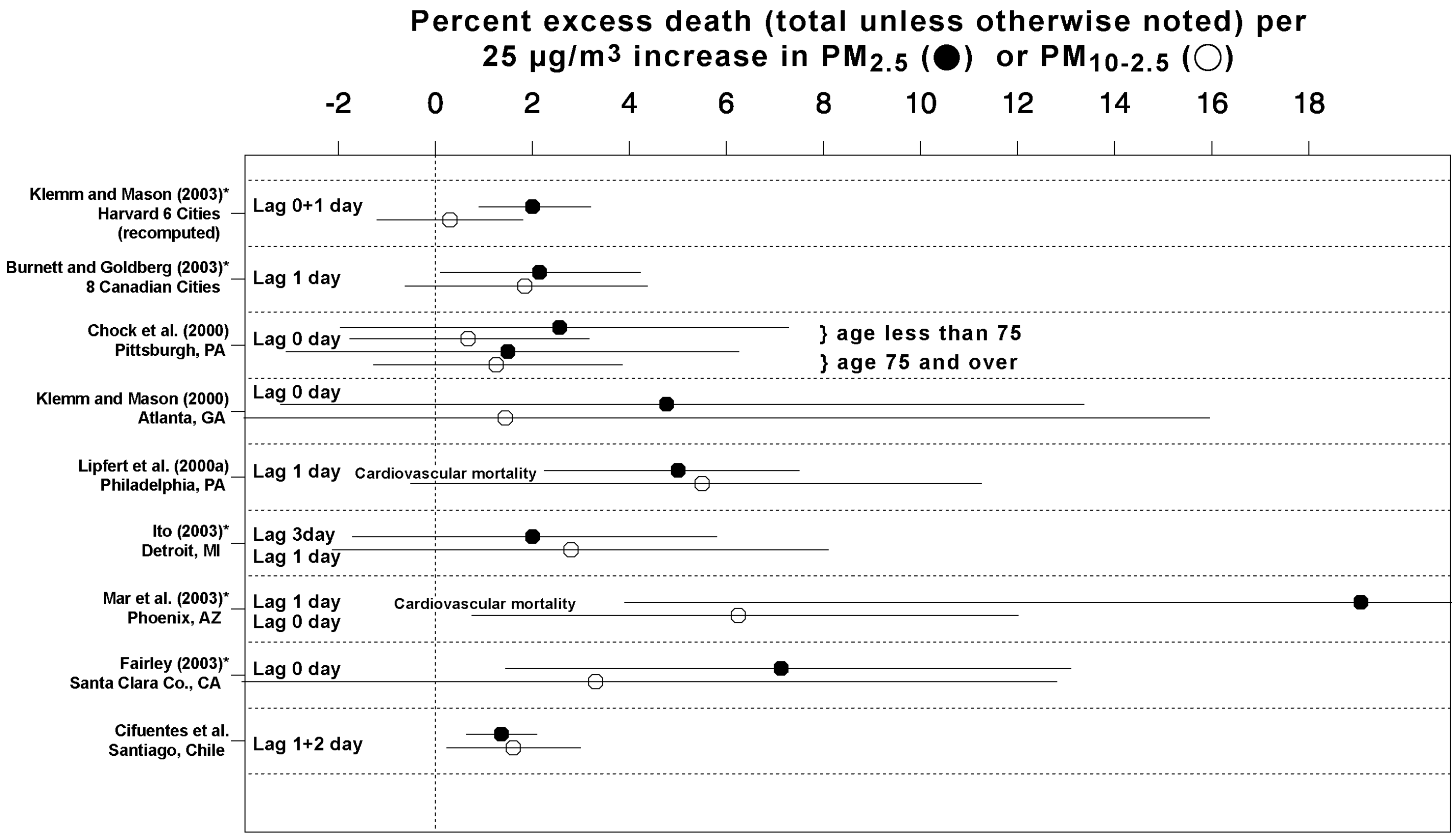

Figure 8-5. Percent excess risks estimated per 25 µg/m^3 increase in $PM_{2.5}$ or $PM_{10-2.5}$ from new studies evaluating both $PM_{2.5}$ and $PM_{10-2.5}$, based on single pollutant (PM only) models. The asterisk next to reference indicates reanalysis of data using GLM with natural splines. Other studies used GLM or OLS.

relationship in Steubenville, OH). Similar findings of $PM_{2.5}$ being significantly associated with mortality were obtained in Santa Clara County (Fairley, 1999; Fairley 2003). Two studies suggested that $PM_{10-2.5}$ was more important than $PM_{2.5}$: Coachella Valley, CA (Ostro et al., 2000 & 2003) and Phoenix, AZ (Clyde et al., 2000). There were five studies in which the importance of $PM_{2.5}$ and $PM_{10-2.5}$ were considered to be similar or, at least, not distinguishable: Philadelphia, PA (Lipfert et al., 2000a); Detroit, MI (Lippmann et al., 2000; reanalysis by Ito 2003); Phoenix, AZ (Mar et al., 2000 and reanalysis in 2003); Eight Canadian cities (Burnett at al., 2000; reanalysis by Burnett and Goldberg, 2003); and Santiago, Chile (Cifuentes et al., 2000).

In the reanalysis (Burnett and Goldberg, 2003) of the Canadian 8-city study (Burnett et al., 2000), the relative importance of $PM_{2.5}$ and $PM_{10-2.5}$ was not clear, but both PM indices were significant in single pollutant models. In GAM models (stringent convergence criteria) with LOESS smoothers, $PM_{2.5}$ was more significant and showed larger risk estimates than $PM_{10-2.5}$. However, in sensitivity analysis in which varying degrees of freedom for mortality temporal trends were applied in GLM models, the effect size and significance for these PM indices were often comparable. The authors commented that $PM_{10-2.5}$ coefficient was more sensitive to the extent of temporal smoothing than $PM_{2.5}$.

The Lippmann et al. (2000) results and a reanalysis (Ito, 2003) for Detroit are also noteworthy in that additional PM indices were evaluated besides those depicted in Figure 8-5, and the overall results obtained may be helpful in comparing fine- versus coarse-mode PM effects. In analyses of 1985 to 1990 data, PM-mortality relative risks and their statistical significance were generally in descending order: PM_{10}, TSP-SO_4^{-2}, and TSP-PM_{10}. For the 1992-1994 period, relative risks for equivalent distributional increment (e.g., IQR) were comparable among PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ for both mortality and hospital admissions categories; and SO_4^{-2} was more strongly associated with most outcomes than H^+. Consideration of the overall pattern of results led the authors to state that the mass of the smaller size index could explain a substantial portion of the variation in the larger size indices. In these data, on average, $PM_{2.5}$ accounted for 60% of PM_{10} (up to 80% on some days) and PM_{10} for 66% of TSP mass. The temporal correlation between TSP and $PM_{2.5}$ was r = 0.63, and that for $PM_{2.5}$ and PM_{10} was r = 0.90, suggesting that much of the apparent larger particle effects may well be mainly driven by temporally covarying smaller $PM_{2.5}$ particles. The stronger associations for sulfates than H^+, suggestive of non-acid fine particle effects, must be caveated by noting the very low H^+ levels present (often at or near non-detection limit).

Three research groups, using different methods, have examined the same Phoenix, AZ data set. While these groups used somewhat different approaches, there is some consistency among their results in that $PM_{10-2.5}$ appeared to emerge as the likely more important predictor of mortality versus $PM_{2.5}$. In the Clyde et al. (2000) analysis, PM-mortality associations were found only for the geographic area where $PM_{2.5}$ was considered uniformly distributed, but the association was with $PM_{10-2.5}$, not $PM_{2.5}$. Based on the Bayes Information Criterion, the highly ranked models consistently included 1-day lagged $PM_{10-2.5}$. Smith et al. (2000) analyses found that, based on a linear PM effect, $PM_{10-2.5}$ was significantly associated with total mortality, but $PM_{2.5}$ was not. However, Smith et al.'s finding that $PM_{2.5}$ may have a threshold effect further complicates a simple comparison of the two size-fractionated mass concentration indices. In the Mar et al. (2000 & 2003) analyses, cardiovascular mortality (CVM) was significantly associated with both $PM_{2.5}$ and $PM_{10-2.5}$. CVM was also significantly associated with a motor vehicle source category with loading of $PM_{2.5}$, EC, OC, CO, NO_2, and some trace metals, as shown by the factor analyses discussed later. The $PM_{2.5}$ in Phoenix is mostly generated from motor vehicles, whereas $PM_{10-2.5}$ consists mainly of two types of particles: (a) crustal particles from natural (wind blown dust) and anthropogenic (construction and road dust) processes, and (b) organic particles from natural biogenic processes (endotoxin and molds) and anthropogenic (sewage aeration) processes. The crustal particles, however, are also likely contaminated with metals secondarily deposited over many years as the result of emissions from smelters operating until recently in the Phoenix area.

In summary, the issue regarding the relative importance of $PM_{2.5}$ and $PM_{10-.25}$ has not yet been fully resolved. Caution in interpreting size-fraction PM studies is warranted due to the problem of measurement error and the correlation between the two size fractions. Limitations of single-city studies have been noted. While the limited sample size prevented clear statistical distinction of the relative roles played by $PM_{2.5}$ and $PM_{10-.25}$, recent studies show mixed results, with some studies suggesting coarse particle effects. The relative importance may also vary depending on the chemical constituents in each size fraction, which may vary from city to city. Nevertheless, a number of studies published since the 1996 PM AQCD do appear to substantiate associations between $PM_{2.5}$ and increased total and/or CVD mortality. Consistent with the 1996

PM AQCD findings, effect-size estimates from the new studies generally fall within the range of about 2 to 6% excess total mortality per 25 μg/m^3 $PM_{2.5}$. The coarse particle ($PM_{10-2.5}$) effect-size estimates also tend to fall in the same range.

Crustal Particle Effects

Since the 1996 PM AQCD, several studies have yielded interesting new information concerning possible roles of crustal wind-blown particles or crustal particles within the fine particle fraction (i.e., $PM_{2.5}$) in contributing to observed PM-mortality effects.

Schwartz et al. (1999), for example, investigated the association of coarse particle concentrations with non-accidental deaths in Spokane, WA, where dust storms elevate coarse PM concentrations. During the 1990-1997 period, 17 dust-storm days were identified. The PM_{10} levels during those storms averaged 263 μg/m^3, compared to 39 μg/m^3 for the entire period. The coarse particle domination of PM_{10} data on those dust-storm days was confirmed by a separate measurement of PM_{10} and $PM_{1.0}$ during a dust storm in August, 1996: the PM_{10} level was 187 μg/m^3, while $PM_{1.0}$ was only 9.5 μg/m^3. The deaths on the day of a dust storm were contrasted with deaths on control days (n = 95 days in the main analysis and 171 days in the sensitivity analysis), which are defined as the same day of the year in other years when dust storms did not occur. The relative risk for dust-storm exposure was estimated using Poisson regressions, adjusting for temperature, dewpoint, and day of the week. Various sensitivity analyses considering different seasonal adjustment, year effects, and lags were conducted. The expected relative risk for these storm days with an increment of 221 μg/m^3 would be about 1.04, based on PM_{10} relative risk from past studies, but the estimated RR for high PM_{10} days was found to be only 1.00 (95% CI = 0.95-1.05) per 50 μg/m^3 PM_{10} change in this study. Schwartz et al. concluded that there was no evidence to suggest that coarse (presumably crustal) particles were associated with daily mortality.

Ostro et al. (2000 & 2003) analyzed the Coachella Valley, CA data for 1989-1998. This desert valley, where coarse particles of geologic origin comprise circa 50-60% of annual-average PM_{10} (> 90% during wind episodes throughout the year), includes the cities of Palm Springs and Indio, CA. Cardiovascular deaths were analyzed using GAM (with stringent convergence criteria) and GLM Poisson models adjusting for temperature, humidity, day-of-week, season, and time. The actual $PM_{2.5}$ and $PM_{10-2.5}$ data were available for the last 2.5 years. Predictive models for $PM_{2.5}$ and $PM_{10-2.5}$ concentrations were developed for earlier years, but the model for $PM_{2.5}$ was not considered successful and, therefore, was not used. Thus, a strict comparison of risk estimates for $PM_{2.5}$ and $PM_{10-2.5}$ in this data set is difficult. Cardiovascular mortality was positively associated with both PM_{10} and $PM_{10-2.5}$ at multiple lags between 0 and 2 day lags; whereas $PM_{2.5}$ coefficient was positive only at lag 4 day. These results hint at crustal particle effects possibly being important in this desert situation, but the ability to discern more clearly the role of fine particles would likely be improved by analyses of more years of actual data for $PM_{2.5}$.

Laden et al. (2000) and Schwartz (2003b) analyzed Harvard Six-Cities Study data and Mar et al. (2000) analyzed the Phoenix data to investigate the influence of crustal particles in $PM_{2.5}$ samples on daily mortality. These studies are discussed in more detail in Section 8.2.2.4.3 on the source-oriented evaluation of PM; and only the basic results regarding crustal particles are mentioned here. The elemental abundance data (from X-ray fluorescence spectroscopy analysis of daily filters) were analyzed to estimate the concentration of crustal particles in $PM_{2.5}$ using factor analysis. Then the association of mortality with fine crustal mass was estimated using Poisson regression (regressing mortality on factor scores for "crustal factor"), adjusting for time trends and weather. No positive association was found between fine crustal mass factor and mortality.

The above results, overall, mostly suggest that crustal particles (coarse or fine) per se are not likely associated with daily mortality. However, as noted in the previous section, three analyses of Phoenix, AZ data do suggest that $PM_{10-2.5}$ was associated with mortality. The results from one of the three studies (Smith et al., 2000) indicate that coarse particle-mortality associations are stronger in spring and summer, when the anthropogenic portion of $PM_{10-2.5}$ is lowest as determined by factor analysis. However, during spring and summer, biogenic processes (e.g., wind-blown pollen fragments, fungal materials, endotoxins, and glucans) may contribute more to the $PM_{10-2.5}$ fraction in the Phoenix area, clouding any attribution of observed $PM_{10-2.5}$ effects there to crustal particles alone, per se. (See the discussion of bioaerosols in Chapter 7 and, also in Section 8.4.3 of this chapter).

Ultrafine Particle Effects

Wichmann et al. (2000) evaluated the attribution of PM effects to specific size fractions, including both the number concentration (NC) and mass concentration (MC) of particles in a given size range. To respond to the GAM convergence issues, Stolzel et al. (2003) reanalyzed the data, using GAM with stringent convergence criteria and GLM with natural splines. The study was carried out in the small German city of Erfurt (pop. 200,000) in the former German Democratic Republic. Erfurt was heavily polluted by particles and SO_2 in the 1980s, and excess mortality was attributed to high levels of TSP by Spix et al. (1993). Concentrations of PM and SO_2 have markedly dropped since then. The present study provides a much more detailed look at the health effects of ultrafine particles (diameter < 0.1 µm) than earlier studies and enables examination of effects in relation to number counts for fine and ultrafine particles, as well as in relation to their mass.

The Mobile Aerosol Spectrometer (MAS), developed by Gessellschaft für Strahlenforschung (GSF), produces number and mass concentrations in three size classes of ultrafines (0.01 to 0.1 µm) and three size classes of larger fine particles (0.1 µm to 2.5 µm). The mass concentration $MC_{0.01\text{-}2.5}$ is well correlated with gravimetric $PM_{2.5}$, and the number concentration $NC_{0.01\text{-}2.5}$ is well correlated with total particle counts from a condensation particle counter (CPC). Mortality data were coded by cause of death, with some discrimination between underlying causes and prevalent conditions of the deceased. In the reanalysis, daily mortality data were fitted using a Poisson GAM (with stringent convergence criteria) and GLM, with adjustments for weather variables, time trends, day of week, and particle indices. Weekly data for all of Germany on influenza and similar diseases was also included in the model. In the original analysis, two types of models were fitted; one used the best single-day lag for air pollution and a second used the best polynomial distributed lag (PDL) model for air pollution. Both linear (i.e., raw) and log-transformed pollution indices were examined. PDL models in the original analysis generally had larger and more significant PM effects than single-day lag models, but the reanalysis by Stolzel et al. (2003) focused on single-day lag results only. Therefore, the numerical results in the following discussion will only include the single day lag results from the reanalysis. It should be noted that, unlike most of the recent reanalyses that have been conducted to address the GAM conversion issue, the reanalysis results from this study were virtually unchanged from the original results.

Both mass and number concentrations at the size ranges examined were mostly positively (and significantly or nearly significantly) associated with total non-accidental mortality. The best single-day lags reported were mostly 0 or 1 day lag for mass concentrations and the 4 day lag for number concentrations. For example, the estimated excess risk for $MC_{0.01\text{-}2.5}$ at lag 1 day was about 3.9% (CI = 0, 7.7) per 25 μg/m^3. The corresponding number for smaller fine particles, $MC_{0.01\text{-}1.0}$, was 3.5% (CI = −0.4, 7.7). For number concentration, the estimated excess risk for $NC_{0.01\text{-}2.5}$ at lag 4 day was about 4.1% (CI = −0.9, 9.3) per IQR (13,269 particles/cm^3). The corresponding number for smaller fine particles, $NC_{0.01\text{-}1.0}$, was 4.6% (CI = −0.3, 9.7) per IQR (12,690 particles/cm^3). An examination of the all the results for $MC_{0.01\text{-}2.5}$ and $NC_{0.01\text{-}0.1}$ shown for lags 0 through 5 days indicates that the associations were mostly positive for these mass and number concentrations, except for the "dip" around 2 or 3 day lags.

The estimated excess risks are reduced, sometimes drastically, when co-pollutants (especially SO_2 and NO_2) are included in a two-pollutant model. This is not surprising, as the number and mass concentrations of various ultrafine and fine particles in all size ranges are rather well correlated with gaseous co-pollutants, except for the intermodal size range $MC_{1.0\text{-}2.5}$. The number correlations range from 0.44 to 0.62 with SO_2, from 0.58 to 0.66 with NO_2, and from 0.53 to 0.70 with CO. The mass correlations range from 0.53 to 0.62 with SO_2, from 0.48 to 0.60 with NO_2, and from 0.56 to 0.62 with CO. The authors found that ultrafine particles, CO and NO_2 form a group of pollutants strongly identified with motor vehicle traffic. Immediate and delayed effects seemed to be independent in two-pollutant models, with single-day lags of 0 to 1 days and 4 to 5 days giving 'best fits' to data. The delayed effect of ultrafine particles was stronger than that for NO_2 or CO. The large decreases in excess risk for number concentration, particularly when NO_2 is a co-pollutant with $NC_{0.01\text{-}0.1}$, clearly involves a more complex structure than simple correlation. The large decrease in excess risk when SO_2 is a co-pollutant with $MC_{0.01\text{-}2.5}$ is not readily explained and is discussed in some detail in Wichmann et al. (2000).

SO_2 is a strong predictor of excess mortality in this study; and its estimated effect is little changed when different particle indicators are included in a two-pollutant model. The authors noted ". . .the [LOESS] smoothed dose response curve showed most of the association at the left end, below 15 μg/m^3, a level at which effects were considered biologically implausible. . ." Replacement of sulfur-rich surface coal has reduced mean SO_2 levels in Erfurt from 456 μg/m^3 in 1988 to 16.8 μg/m^3 during 1995 to 1998 and to 6 μg/m^3 in 1998. The estimated concentration-response functions for SO_2 are very different for these time periods, comparing Spix et al. (1993) versus Wichmann et al. (2000) results. Wichmann et al. concluded "These inconsistent results for SO_2 strongly suggested that SO_2 was not the causal agent but an indicator for something else." The authors offered no specific suggestions as to what the "something else" might be, but they did finally conclude that their studies from Germany strongly supported PM air pollution as being more relevant than SO_2 to observed mortality outcomes.

8.2.2.5.2 Chemical Components

Several new studies from the U.S., Canada, and The Netherlands examined mortality associations with specific chemical components of ambient PM. Table 8-3 shows the chemical components examined in these studies; the mean concentrations for Coefficient of Haze (CoH), sulfate, and H^+; and indications of those components found to be associated with increased mortality.

Coefficient of Haze, Elemental Carbon, and Organic Carbon

CoH is highly correlated with elemental carbon (EC) and is often considered as a good PM index for motor vehicle sources, although other combustion processes such as space heating likely also contribute to CoH levels. Several studies (Table 8-3) examined CoH; and, in most cases, positive and significant associations with mortality outcomes were reported. In terms of relative significance of CoH in comparison to other PM components, CoH was not the clearly most significant PM component in most of these studies. The average level of CoH in these studies ranged from 0.24 (Montreal, Quebec) to 0.5 (Santa Clara County, CA) 1000 linear feet. The correlations between CoH and NO_2 or CO in these studies (8 largest Canadian cities; Santa Clara County, CA) were moderately high (r .0.7 to 0.8) and suggested a likely motor vehicle contribution. Both EC and OC were significant predictors of cardiovascular mortality in the Phoenix study; their effect sizes per IQR were comparable to those for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$. Also, both EC and OC represented major mass fractions of $PM_{2.5}$ (11% and 38%, respectively) and were correlated highly with $PM_{2.5}$ (r = 0.84 and 0.89, respectively). They were also highly correlated with CO and NO_2 (r = 0.8 to 0.9), indicating their associations with an "automobile" factor. Thus, the CoH and EC/OC results from the Mar et al. (2000 and 2003) study suggest that PM components from motor vehicle sources are likely associated with mortality. In a recent

TABLE 8-3. NEWLY AVAILABLE STUDIES OF MORTALITY RELATIONSHIPS TO PM CHEMICAL COMPONENTS

Author, City	Mean CoH (1000ft)	Mean $SO_4^=$ (ug/m³)	Mean H^+ (nmol/m³)	Other PM components analyzed	Specific PM components found to be associated with mortality (comments).
Burnett et al. (2000); Burnett and Goldberg (2003)* 8 largest Canadian cities, 1986-1996.	0.26	2.6		PM_{10}, $PM_{2.5}$, $PM_{10\text{-}.5}$, and 47 trace elements	PM_{10}, $PM_{2.5}$, CoH, sulfate, Zn, Ni, and Fe were significantly associated with total mortality in the original analysis. The reanalysis only analyzed mass concentration indices.
Fairley (1999 & 2003)*; Santa Clara County, CA.	0.5	1.8		PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, and nitrate	CoH, sulfate, nitrate, PM_{10}, and $PM_{2.5}$ were associated with mortality. $PM_{2.5}$ and nitrate most significant.
Goldberg et al. (2000); Goldberg and Burnett (2003); Goldberg et al. (2003)* Montreal, Quebec, Canada. 1984-1993.	0.24	3.3		Predicted $PM_{2.5}$, and extinction coefficient (visual- range derived).	CoH and extinction coefficient were associated with the deaths that were classified as having congestive heart failure before death based on medical records. Associations were stronger in warm season.
Lipfert et al., (2000a) Philadelphia, PA. 1992-1995.	0.28	5.1	8.0	Nepherometry, NH_4^+, TSP, PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$	Essentially all PM components were associated with mortality.
Lippmann et al. (2000); Ito (2003)* Detroit, MI. 1992-1994.		5.2	8.8	PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$	PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$ were more significantly associated with mortality outcomes than sulfate or H^+.
Klemm and Mason (2000) Atlanta, GA 1998-1999		5.2	8.8	Nitrate, EC, OC, oxygenated HC, PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$	"Interim" results based on one year of data. No statistically significant associations for any pollutants. Those with t-ratio of at least 1.0 were H^+, PM_{10}, and $PM_{2.5}$.
Mar et al. (2000 & 2003)* Phoenix, AZ. 1995-1997.				EC, OC, TC, PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$	EC, OC, TC, PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$ were associated with cardiovascular mortality.
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.		12.7		PM_{15}, $PM_{2.5}$, cyclohexane-solubles (CX), dichloromethane-solubles (DCM), and acetone-solubles (ACE).	PM_{15}, PM2.5, sulfate, CX, and ACE were significantly associated with total and/or cardiovascular mortality in Newark and/or Camden.
Hoek et al. (2000 & 2003)* The Netherlands. 1986-1994.		3.8 (median)		PM_{10}, BS, and nitrate	Sulfate, nitrate, and BS were more consistently associated with total mortality than was PM_{10}.

*Note: The study was originally analyzed by GAM models only using default convergence criteria and at least two non-parametric smoothing terms and was recently reanalyzed by GAM using stringent convergence criteria and/or other non-GAM analyses.

study in Montreal, Quebec, by Goldberg et al. (2000 and 2003), CoH appeared to be correlated with the congestive heart failure mortality (as classified based on medical records) more strongly than other PM indices such as the visual-range derived extinction coefficient (considered to be a good indicator of sulfate). However, the main focus of the study was the role of cardiorespiratory risk factors for air pollution, and the investigators warned against comparing the relative strength of associations among PM indices, pointing out complications such as likely error involved in the visual range measurements. Additionally, the estimated $PM_{2.5}$ values were predicted from other PM indices, including CoH and extinction coefficient, making it difficult to compare straightforwardly the relative importance of PM indices.

Sulfate and Hydrogen Ion

Sulfate and H^+, markers of acidic components of PM, have been hypothesized to be especially harmful components of PM (Lippmann and Thurston, 1996). The newly available studies that examined sulfate are shown in Table 8-3; two of them also analyzed H^+ data. The sulfate concentrations ranged from 1.8 μg/m^3 (Santa Clara County, CA) to 12.7 μg/m^3 (three NJ cities). Aside from the west versus east coast contrast, the higher levels observed in the three NJ cities are likely due to their study period coverage of the early 1980's, when sulfate levels were higher. Sulfate explained 25 to 30% of $PM_{2.5}$ mass in eastern U.S. and Canadian cities, but it was only 14% of $PM_{2.5}$ mass in Santa Clara County, CA. The H^+ levels measured in Detroit and Philadelphia were low. The mean H^+ concentration for Detroit, MI (the H^+ was actually measured in Windsor, a Canadian city a few miles from downtown Detroit), 8.8 nmol/m^3, was low as compared to the reported detection limit of 15.1 nmol/m^3 (Brook et al., 1997) for the measurement system used in the study. Note that the corresponding detection limit for sulfate was 3.6 nmol/m^3 (or 0.34 μg/m^3); and the mean sulfate level for Detroit was 54 nmol/m^3 (or 5.2 μg/m^3), so that the signal-to-noise ratio is expected to be higher for sulfate than for H^+. Thus, the ambient levels and possible relative measurement errors for these data should be considered in interpreting the relative strength of mortality associations in these data.

Sulfate was a statistically significant predictor of mortality, at least in single pollutant models, in: Santa Clara County, CA; Philadelphia, PA; Newark, NJ; and Camden, NJ, but not in Elizabeth, NJ; Detroit, MI; or Montreal, CN. However, it should be noted that the relative significance across the cities is influenced by the sample size (both the daily mean death counts and number of days available), as well as the range of sulfate levels and should be interpreted with caution. Figure 8-6 shows the excess risks (± 95% CI) estimated per 5 µg/m^3 increase in 24-h sulfate reported in these studies compared to the reanalysis results of the earlier Six Cities Study result by Klemm and Mason (2003). The largest estimate was seen for Santa Clara County, CA; but the wide confidence band (possibly due to the small variance of the sulfate, because its levels were low) should be taken into account. In addition, the sulfate effect in the Santa Clara County analysis was eliminated once $PM_{2.5}$ was included in the model, perhaps being indicative of sulfate mainly serving as a surrogate for fine particles in general there. In any case, more weight should be accorded to estimates from other studies with narrower confidence bands. In the other studies, the effect size estimates mostly ranged from about 1 to 4% per 5 µg/m^3 increase in 24-h sulfate.

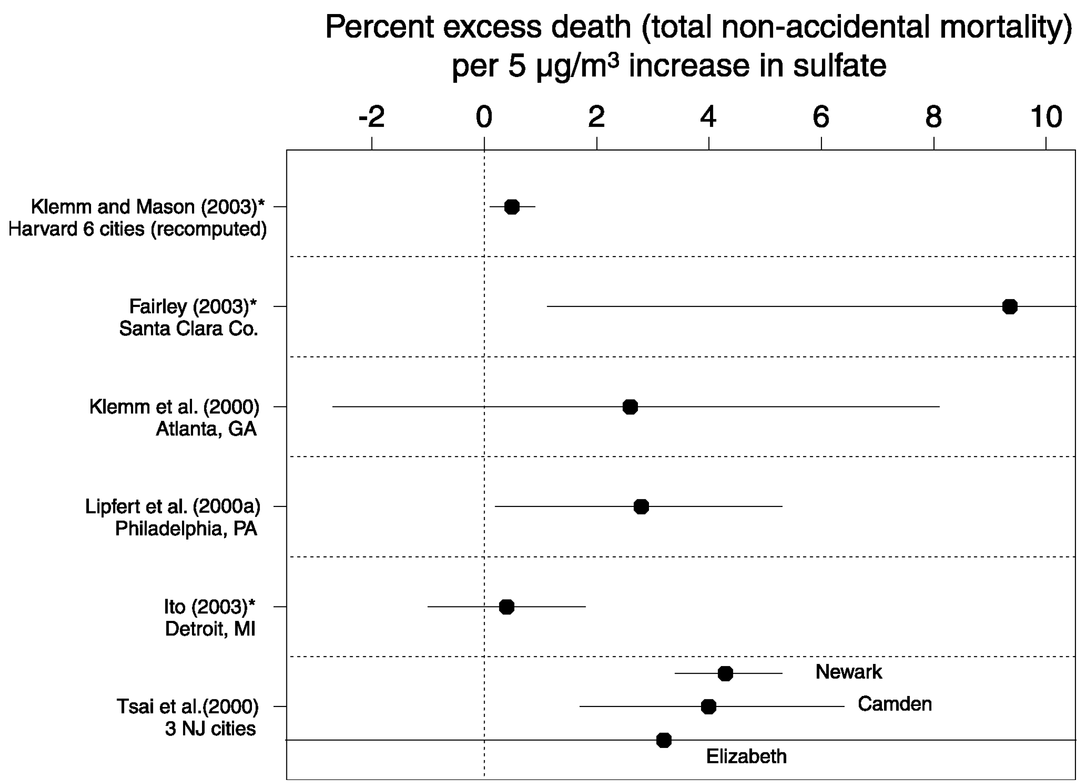

Figure 8-6. Excess risks estimated per 5 µg/m^3 increase in sulfate, based on the studies in which both $PM_{2.5}$ and $PM_{10-2.5}$ data were available.

The relative significance of sulfate and H^+ compared to other PM components is not clear in the existing small number of publications. Because each study included different combinations of co-pollutants that had different extents of correlation with sulfate and because multiple mortality outcomes were analyzed, it is difficult to assess the overall importance of sulfate across the available studies. The fact that the Lippmann et al. (2000) study and the reanalysis by Ito (2003) found that Detroit, MI data on H^+ and sulfate were less significantly associated with mortality than the size-fractionated PM mass indices may be due to acidic aerosols levels being mostly below the detection limit in that data. In this case, it appears that the Detroit PM components show mortality effects even without much acidic input.

In summary, assessment of new study results for individual chemical components of PM suggest that an array of PM components (mainly fine particle constituents) are associated with mortality outcomes, including CoH, EC, OC, sulfate, and nitrate. The variations seen with regard to the relative significance of these PM components across studies may be in part due to differences in their concentrations from locale to locale. This issue is further discussed below as part of the assessment of new studies involving source-oriented evaluation of PM components.

8.2.2.5.3 Source-Oriented Evaluations

Several new studies have conducted source-oriented evaluation of PM components. In these studies, daily concentrations of PM components (i.e., trace elements) and gaseous co-pollutants were analyzed using factor analysis to estimate daily concentrations due to underlying source types (e.g., motor vehicle emissions, soil, etc.), which are weighted linear combinations of associated individual variables. The mortality outcomes were then regressed on those factors (factor scores) to estimate the effect of source types rather than just individual variables. These studies differ in terms of specific objectives/focus, the size fractions from which trace elements were extracted, and the way factor analysis was used (e.g., rotation). The main findings from these studies regarding the source-types identified (or suggested) and their associations with mortality outcomes are summarized in Table 8-4.

The Laden et al. (2000) analysis of Harvard Six Cities data for 1979-1988 (reanalyzed by Schwartz, 2003) aimed to identify distinct source-related fractions of $PM_{2.5}$ and to examine each fraction's association with mortality. Fifteen elements in the fine fraction samples were routinely found above their detection limits and included in the data analysis. For each of the six

TABLE 8-4. SUMMARY OF SOURCE-ORIENTED EVALUATIONS OF PM COMPONENTS IN RECENT STUDIES

Author, City	Source types identified (or suggested) and associated variables	Source types associated with mortality (Comments)
Laden et al., (2000); Schwartz (2003)* Harvard Six Cities. 1979-1988.	*Soil and crustal material*: Si *Motor vehicle emissions:* Pb *Coal combustion*: Se *Fuel oil combustion*: V *Salt*: Cl Note: the trace elements are from $PM_{2.5}$ samples	Strongest increase in daily mortality was associated with the mobile source factor. Coal combustion factor was also positively associated with mortality. Crustal factor from fine particles not associated (negative but not significant) with mortality. Coal and mobile sources account for the majority of fine particles in each city.
Mar et al. (2000 & 2003)* Phoenix, AZ. 1995-1997.	***$PM_{2.5}$ (from DFPSS) trace elements:*** *Motor vehicle emissions and re-suspended road dust:* Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2 *Soil*: Al, Si, and Fe *Vegetative burning*: OC, and K_S (soil-corrected potassium) *Local SO_2 sources*: SO_2 *Regional sulfate*: S	*$PM_{2.5}$ factors results:* Motor vehicle factor (1 day lag), vegetative burning factor (3 day lag), and regional sulfate factor (0 day lag) were significantly positively associated with cardiovascular mortality.
	$PM_{10\text{-}2.5}$ (from dichot) trace elements: *Soil*: Al, Si, K, Ca, Mn, Fe, Sr, and Rb *A source of coarse fraction metals*: Zn, Pb, and Cu *A marine influence*: Cl	Factors from dichot $PM_{10\text{-}2.5}$ trace elements not analyzed for their associations with mortality because of the small sample size (every 3^{rd}-day samples from June 1996).
Tsai et al. (2000). Newark, Elizabeth, and Camden, NJ. 1981-1983.	*Motor vehicle emissions:* Pb, CO *Geological (Soil)*: Mn, Fe *Oil burning*: V, Ni *Industrial*: Zn, Cu, Cd (separately) *Sulfate/secondary aerosol*: sulfate Note: the trace elements are from PM_{15} samples	Oil burning, industry, secondary aerosol, and motor vehicle factors were associated with mortality.

*Note: The study was originally analyzed using GAM models only with default convergence criteria using at least two non-parametric smoothing terms, but was later reanalyzed using more stringent convergence criteria and/or other approaches.

cities, up to 5 common factors were identified from among the 15 elements, using specific rotation factor analysis. Using the Procrustes rotation (a type of oblique rotation), the projection of the single tracer for each factor was maximized. This specification of the tracer element was based on (a) knowledge from previous source apportionment research; (b) the condition that the regression of total fine mass on that element must result in a positive coefficient; and (c) the identifications of additional local source factors that positively contributed to total fine mass regression. Three source factors were identified in all six cities: (1) a soil and crustal material factor with Si as a tracer; (2) a motor vehicle exhaust factor with Pb as a tracer; and (3) a coal combustion factor with Se as a tracer. City-specific analyses also identified a fuel combustion factor (V), a salt factor (Cl), and selected metal factors (Ni, Zn, or Mn). In the original analysis by Laden et al., a GAM Poisson regression model (with default convergence criteria), adjusting for trend/season, day-of-week, and smooth function of temperature/dewpoint, was used to estimate impacts of each source type (using absolute factor scores) simultaneously for each city. In the reanalysis reported by Schwartz (2003a), GAM models with LOESS smoothers were replaced with penalized splines. Summary estimates across cities were obtained by combining the city-specific estimates, using inverse-variance weights. The identified factors and their tracers are listed in Table 8-4. The reanalysis using penalized splines changed somewhat the risk estimates for source-apportioned mass concentrations in each city compared to those in the original GAM results (increasing estimates in some cities and reducing them in others), but the combined estimates across the six cities did not change substantially. The combined estimates indicated that the largest increase in daily mortality was associated with the mobile source associated fine mass concentrations, with an excess death risk increase of 9.3% (95% CI: 4.0, 14.9) per 25 $\mu g/m^3$ source-apportioned $PM_{2.5}$ (average of 0 and 1 day lags). The corresponding value for the $PM_{2.5}$ mass apportioned for the coal combustion factor was 2.0% (95% CI: −0.3, 4.4). The crustal factor was not associated with mortality (-5.1%; 95% CI = −13.9, 4.6).

Mar et al. (2000) analyzed PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$ measured by two methods, and various sub-components of $PM_{2.5}$ for their associations with total (non-accidental) and cardiovascular deaths in Phoenix, AZ during 1995-1997, using both individual PM components and factor analysis-derived factor scores. In the original analysis, GAM Poisson models (with default convergence criteria) were used and adjusted for season, temperature, and relative humidity. In the reanalysis (Mar et al., 2003), GAM models with stringent convergence criteria and GLM models with natural splines were used. Only cardiovascular mortality was analyzed in the reanalysis; and the results for that category are summarized here. The evaluated air pollution variables included O_3, SO_2, NO_2, CO, TEOM PM_{10}, TEOM $PM_{2.5}$, TEOM $PM_{10-2.5}$, DFPSS $PM_{2.5}$, S, Zn, Pb, soil, soil-corrected K (KS), nonsoil PM, OC, EC, and TC. Lags 0 to 4 days were evaluated. A factor analysis conducted on the chemical components of DFPSS $PM_{2.5}$ (Al, Si, S, Ca, Fe, Zn, Mn, Pb, Br, KS, OC, and EC) identified factors for motor vehicle emissions/resuspended road dust; soil; vegetative burning; local SO_2 sources; and regional sulfate (see Table 8-4). The results of mortality regression with these factors suggested that the motor vehicle factor (lag 1 day), vegetative burning factor (3 day lag), and regional sulfate factor (0 day lag) each had significant positive associations with cardiovascular mortality. The $PM_{2.5}$ mass was not apportioned to these factors in this study; so information on the excess-deaths estimate per source-apportioned $PM_{2.5}$ concentrations was not available. The authors also analyzed elements from dichot $PM_{10\text{-}2.5}$ samples and identified soil, a source of coarse fraction metals (industry), and marine influence factors. However, these factors were not analyzed for their associations with mortality outcomes due to the short measurement period (starting in June 1996 with every 3rd-day sampling).

It should be noted here that the Smith et al. (2000) analysis of Phoenix data also included factor analysis on the elements from the coarse fraction and identified essentially the same factors ("a source of coarse fraction metals" factor in Mar et al.'s study was called "the anthropogenic elements" in Smith et al.'s study). While Smith et al. did not relate these factors to mortality (due to a small sample size), they did show that the anthropogenic elements were low in summer and spring, when the $PM_{10\text{-}2.5}$ effect was largest. These results suggest that the $PM_{10\text{-}2.5}$ effects may not necessarily be due to anthropogenic components of the coarse particles, biogenically-contaminated coarse particles perhaps being key during the warmer months (as noted in Chapter 7 discussions of bioaerosols).

Tsai et al. (2000) conducted an exploratory analysis of mortality in relation to specific PM source types for three New Jersey cities (Camden, Newark, and Elizabeth) using factor analysis - Poisson regression techniques. During the three-year study period (1981-1983), extensive chemical speciation data were available, including nine trace elements, sulfate, and particulate organic matter. Total (excluding accidents and homicides), cardiovascular, and respiratory mortality were analyzed. A factor analysis of trace elements and sulfate was first conducted and identified several major source types: motor vehicle (Pb, CO); geological (Mn, Fe); oil burning (V, Ni); industrial (Zn, Cu); and sulfate/secondary aerosols (sulfate). In addition to Poisson regression of mortality on these factors, an alternative approach was also used, in which the inhalable particle mass (IPM, $D_{50} < 15$ μm) was first regressed on the factor scores of each of the source types to apportion the PM mass and then the estimated daily PM mass for each source type was included in Poisson regression, so that RR could be calculated per mass concentration basis for each PM source type. Oil burning (V, Ni), various industrial sources (Zn, Cd), motor vehicle (Pb, CO), and secondary aerosols, as well as the individual PM indices IPM, FPM (D_{50} < 3.5 μm), and sulfates, were all associated with total and/or cardiorespiratory mortality in Newark and Camden, but not in Elizabeth. In Camden, the RRs for the source-oriented PM were higher (1.10) than those for individual PM indices (1.02).

In summary, these source-oriented factor analyses studies suggest that a number of source types are associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning. The crustal factor from fine particles was not associated with mortality in the Harvard Six Cities data. In Phoenix, where coarse particles were reported to be associated with mortality, the associations between the factors related to coarse particles (soil, marine influence, and anthropogenic elements) and mortality could not be evaluated due to the small sample size. Thus, although some unresolved issues remain (mainly due to the lack of sufficient data), the limited results from the source-oriented evaluation approach (using factor analysis) thus far seem to implicate fine particles of anthropogenic origin as being most important (versus crustal particles of geologic origin) in contributing to increased mortality risks.

8.2.2.6 New Assessments of Cause-Specific Mortality

Consistent with similar findings described in the 1996 PM AQCD, most of the newly available studies summarized in Tables 8-1 and 8A-1 that examined non-accidental total, circulatory, and respiratory mortality categories (e.g., Samet et al., 2000a,b and the reanalysis by Dominici et al., 2002 and 2003) found significant PM associations with both cardiovascular and/or respiratory-cause mortality. Several studies (e.g., Fairley, 1999), his reanalysis, 2003; Wordley et al., 1997; Prescott et al., 1998) reported estimated PM effects that were generally higher for respiratory deaths than for circulatory or total deaths. Once again, the NMMAPS results for U.S. cities are among those of particular note here due to the large study size and the combined, pooled estimates derived for various U.S. regions.

The NMMAPS 90-cities analyses not only examined all-cause mortality (excluding accidents), but also evaluated cardiorespiratory and other remaining causes of deaths. Results were presented for all-cause, cardiorespiratory, and “other” mortality for lag 0, 1, and 2 days. The investigators commented that, compared to the result for cardiorespiratory deaths showing 1.6% (CI = 0.8, 2.4) increase per 50 μg/m^3 PM_{10} in a GLM model (versus 1.1% for total non-accidental mortality using GLM), there was less evidence for non-cardiorespiratory deaths. However, the estimates for “other” mortality, though less than half those for cardiorespiratory mortality, were nevertheless positive, with a fairly high posterior probability (e.g., 0.92 at lag 1 day) that the overall effects were greater than zero. It should be noted that the “other” (other than cardiorespiratory) underlying cause of mortality may include deaths that had contributing cardiovascular or respiratory causes. For example, Lippmann et al. (2000) noted that the “other” (non-circulatory and non-respiratory) mortality showed seasonal cycles and apparent influenza peaks, suggesting that this series may have also been influenced by respiratory contributing causes. Thus, interpretation of the observed associations between PM and broad “specific” categories of underlying causes of death may not be straightforward.

Another U.S. study, that of Moolgavkar (2000a), evaluated possible PM effects on cause-specific mortality across a broad range of lag times (0-5 days) in Cook Co., IL; Los Angeles Co., CA; and Maricopa Co., AZ. Total non-accidental mortality, as well as deaths related to cardiovascular disease (CVD), cerebrovascular disease (CRV), and chronic obstructive lung disease (COPD) were analyzed in the original study. The data for Cook Co. and Maricopa Co. were reanalyzed using GAM model with stringent convergence criteria and GLM model with natural splines (Moolgavkar, 2003). Cerebrovascular disease mortality was not reanalyzed because there was little evidence of association for PM with this category at any lag in any of the three counties analyzed. Moolgavkar reported that varying patterns of results were obtained for PM indices in evaluations of daily deaths related to CVD and COPD in the two counties. In the Cook Co. (Chicago) area, the association of PM_{10} with CVD mortality was statistically significant at a lag of 3 days based on a single-pollutant analysis and remained significantly associated with CVD deaths with a 3-day lag in two pollutant models including one or another of CO, NO_2, SO_2, or O_3. In Los Angeles single-pollutant analyses, CVD mortality was significantly associated with PM_{10} (2 day lag) and $PM_{2.5}$ (0 and 1 day lag). Their percent excess risk estimates were up to twice those for total non-accidental mortality. In a two-pollutant model with CO (most strongly positively associated with mortality in Los Angeles Co. among the pollutants), PM_{10} risk estimates were reduced. However, $PM_{2.5}$ excess risk estimates in the two-pollutant model with CO nearly doubled (2.5% per 25µg/m^3 increase in $PM_{2.5}$ to 4.8% using GLM); whereas that for CO became significantly negative. Obviously, CO and $PM_{2.5}$ were correlated (r ≈ 0.58), and the estimated associations were likely confounded between these two pollutants in this locale. With regard to COPD deaths, PM_{10} was significantly associated with COPD mortality (lag 2 days) in Cook Co., but in Los Angeles Co., both PM_{10} and (especially) $PM_{2.5}$ showed erratic associations with COPD mortality at varying lags, alternating positive and negative (significantly, at lag 3 day) coefficients. The combination of the every 6^{th}-day PM data in Los Angeles (versus daily PM_{10} in Cook Co.) and relatively small daily counts for COPD (median = 6/day versus 57/day for CVD) makes the effective sample size of COPD mortality analysis small and the results unstable.

Zmirou et al. (1998) presented cause-specific mortality analyses results for 10 of the 12 APHEA European cities (APHEA1). Using Poisson autoregressive models parametrically adjusting for trend, season, influenza epidemics, and weather, each pollutant's relative risk was estimated for each city and "meta-analyses" of city-specific estimates were conducted. The pooled excess risk estimates for cardiovascular mortality were 1.0% (0.3, 1.7) per 25 μg/m^3increase in BS and 2.0% (0.5, 3.0) per 50 μg/m^3increase in SO_2 in western European cities. The pooled risk estimates for respiratory mortality in the same cities were 2.0% (0.8, 3.2) and 2.5% (1.5, 3.4) for BS and SO_2, respectively.

Seeking unique cause-specificity of effects associated with various pollutants has been difficult because the "cause specific" categories examined are typically rather broad (usually cardiovascular and respiratory) and overlap and because cardiovascular and respiratory conditions tend to occur together. Examinations of more specific cardiovascular and respiratory subcategories may be necessary to test hypotheses about any specific mechanisms, but smaller sample sizes for more specific sub-categories may make a meaningful analysis difficult. The Hoek et al. (2000 and 2001) study and its reanalysis by Hoek (2003) took advantage of a larger sample size to examine cause-specific mortality. The large sample size, including the whole population of the Netherlands (mean daily total deaths ~330, or more than twice that of Los Angeles County), allowed examination of specific cardiovascular causes of deaths. The reanalysis using GAM with stringent convergence criteria as well as GLM with natural splines either did not change or even increased the effect estimates. Deaths due to heart failure, arrhythmia, and cerebrovascular causes were more strongly (~2 to 4 times larger excess risks) associated with air pollution than the overall cardiovascular deaths. The investigators concluded that specific cardiovascular causes (such as heart failure) were more strongly associated with air pollution than total cardiovascular mortality, but noted that the largest contribution to the association between air pollution and cardiovascular mortality was from ischemic heart disease (about half of all CVD deaths). The analyses of specific respiratory causes, COPD, and pneumonia yielded even larger risk estimates (e.g., ~ 6 to 10 times, respectively, larger than that for overall cardiovascular deaths). Estimated PM_{10} excess risks per 50 μg/m^3 PM_{10} (average of 0 through 6 day lags) were 1.2% (0.2, 2.3), 0.9% (−0.8, 2.7), 2.7% (−4.2, 10.1), 2.4% (−2.3, 7.4), 6.1% (1, 11.4), and 10.3% (3.7, 17.2), respectively, for total non-accidental, cardiovascular, arrhythmia, heart failure, COPD, and pneumonia, using GAM models with stringent convergence criteria. Thus, the results from this study with a large effective sample size also confirm past observations that PM risk estimates for specific causes of cardiovascular or respiratory mortality can be larger than those estimated for total non-accidental mortality.

As mentioned earlier in the multi-cities results section, Schwartz (2003) reanalyzed data from Braga et al. (2001) to examine the lag structure of PM_{10} associations with specific causes of mortality in ten U.S. cities. The pattern of larger PM_{10} excess risk estimates for respiratory categories than for cardiovascular categories found in this study was similar to that in the Hoek et al. analyses noted above. For example, the combined risk estimates across 10 cities per 50 μg/m^3 increase in PM_{10} (2-day mean) were 4.1% (2.5, 5.6), 7.7% (4.1, 11.5), and 11.0% (7, 15.1) for cardiovascular, COPD, and pneumonia, respectively, using GAM with stringent convergence criteria. These values were even larger for unconstrained distributed lag models.

The Goldberg et al. (2000) study, and its reanalyses (Goldberg et al., 2003; Goldberg and Burnett, 2003) in Montreal, CN, investigated the role of co-morbidity prior to deaths in PM-mortality associations for various subcategories, including cancer, acute lower respiratory disease, chronic coronary artery disease, and congestive heart failure (CHF). They could classify deaths into these subcategories using medical records from the universal Quebec Health Insurance Plan (QHIP). This way of classifying deaths would presumably take into account more detailed information on the disease condition prior to death than the “underlying cause” in the death records. Thus, the PM-mortality associations could be compared by using subcategories classified from death records versus those classified from QHIP medical records. The Goldberg and Burnett (2003) reanalysis found that total non-accidental mortality (which was significantly associated with PM indices in the original report using GAM with default convergence criteria) was not associated with PM indices in GLM models. They reported that the associations between PM and non-accidental mortality were rather sensitive to weather model specification and did not find significant PM associations with most of the subcategories as defined from either QHIP or underlying cause. However, they did find significant associations between CoH, NO_2, and SO_2 and the CHF deaths as defined from QHIP, but not the CHF deaths as defined from underlying cause. The association was even stronger in warm seasons. It should be noted, however, that while the period for this study was relatively long (~10 years) and the counts for the total non-accidental deaths were not small (median = 36 deaths per day), the counts for various subcategories were quite small (e.g., CHF underlying cause mortality mean = 0.75 per day).

Another study (Gouveia and Fletcher, 2000), using data from Sao Paulo, Brazil, 1991-1993, examined child mortality (age under 5 years). The Poisson auto-regressive model included parametric terms (e.g., quadratic, two-piece linear temperature etc.) to adjust for weather and temporal trends. Although Gouveia and Fletcher found significant associations between air pollution and elderly mortality, they did not find statistically significant associations between air pollution and child respiratory mortality (the PM_{10} coefficient was negative and not significant). However, it should be noted that the average daily respiratory mortality counts for this study were relatively small (~2.4/day). With the modest length of observations (3 years), the statistical power of the data was likely less than desirable, and there may not have been sufficient power to elucidate the range of short-term PM effects on child respiratory mortality. Again, evaluation of the role of varying contributing conditions to PM-mortality associations are often challenged by the sample size problem.

Overall, then, the above assessment of newly available studies provides interesting additional new information with regard to cause-specific mortality related to ambient PM. That is, a growing number of studies continue to report increased cardiovascular- and respiratory-related mortality risks as being significantly associated with ambient PM measures at one or another varying lag times. When specific subcategories of cardiovascular disease were examined in a large population (The Netherlands study by Hoek et al.), some of the subcategories such as heart failure were more strongly associated with PM and other pollutants than total cardiovascular mortality. Largest effect estimates are most usually reported for 0-1 day lags (with some studies also now noting a second peak at 3-4 day lags). A few of the newer studies also report associations of PM metrics with “other” (i.e., non-cardiorespiratory) causes, as well. However, at least some of these “other” associations may also be due to seasonal cycles that include relationships to peaks in influenza epidemics that may imply respiratory complications as a contributing cause to the “other” deaths. Alternately, the “other” category may include sufficient numbers of deaths due to diabetes or other diseases which may also involve cardiovascular complications as contributing causes. Varying degrees of robustness of PM effects are seen in the newer studies, as typified by PM estimates in multiple pollutant models containing gaseous co-pollutants. That is, some studies show little effect of gaseous pollutant inclusion on estimated PM effect sizes, some show larger reductions in PM effects to non-significant levels upon such inclusion, and a number also report significant associations of cardiovascular and respiratory effects with one or more gaseous co-pollutants. Thus, the newer studies both further substantiate PM effects on cardiovascular- and respiratory-related mortality, while also pointing toward possible significant contributions of gaseous pollutants to such cause-specific mortality. The magnitudes of the PM effect size estimates are consistent with the range of estimates derived from the few earlier available studies assessed in the 1996 PM AQCD.

8.2.2.7 Salient Points Derived from Assessment of Studies of Short-Term Particulate Matter Exposure Effects on Mortality

The most salient key points to be extracted from the above discussion of newly available information on short-term PM exposures relationships to mortality can be summarized as follow:

PM_{10} effects estimates. Since the 1996 PM AQCD, there have been more than 80 new time-series PM-mortality analyses published. Estimated mortality relative risks in these studies are generally positive, statistically significant, and consistent with the previously reported PM-mortality associations. However, due to the concerns regarding the GAM convergence issue, quantitative evaluations were made here based only on the studies that either did not use GAM Poisson model with default convergence criteria or on those studies that have reanalyzed the data using more stringent convergence criteria and/or used fully parametric approaches. Of particular importance are several studies which evaluated multiple cities using consistent data analytical approaches. The NMMAPS analyses for the largest 90 U.S. cities (Samet et al., 2000a,b; Dominici et al., 2002 and 2003), derived a combined nationwide excess risk estimate of about 1.4% (1.1% using GLM) increase in total (non-accidental) mortality per 50 μg/m^3increase in PM_{10}. Other well-conducted multi-city analyses, as well as various single city analyses, obtained larger PM_{10}-effect size estimates for total non-accidental mortality, generally falling in the range of 2 to 3.5% per 50 μg/m^3increase in PM_{10}. This is consistent with, but somewhat lower than,

the range of PM_{10} risk estimates given in the 1996 PM AQCD. However, somewhat more geographic heterogeneity is evident among the newer multi-city study results than was the case among the fewer studies assessed in the 1996 PM AQCD. In the NMMAPS analysis of the 90 largest U.S. cities data, for example, the risk estimates varied by U.S. geographic region, with the estimate for the Northeast being the largest (approximately twice the nation-wide estimates). The observed heterogeneity in the estimated PM risks across cities/regions could not be explained by city-specific explanatory variables, such as mean levels of pollution and weather, mortality rate, sociodemographic variables (e.g., median household income), urbanization, or variables related to measurement error. Notable apparent heterogeneity was also seen among effects estimates for PM (and SO_2) indices in the multi-city APHEA studies conducted in European cities. In APHEA2, they found that several city-specific characteristics, such as NO_2 levels and warm climate, were important effect modifiers. The issue of heterogeneity of effect estimates is discussed further in Section 8.4.

Model specification Issue: The investigations of the GAM convergence issue also led to examination of the sensitivity of the PM risk estimates to different model specifications. Several reanalyses examined the sensitivity of results to varying the degrees of freedom for smoothing of weather and temporal trends. PM risk estimates were often reduced when more degrees of freedom were given to model temporal trends. While what constitutes an "adequate" extent of smoothing (from an epidemiologic viewpoint) is currently not known, the overall assessment of PM risk estimates should take into consideration the range of sensitivity of results to this aspect of model specification.

*Confounding and effect modification by other pollutant*s. Numerous new short-term PM exposure studies not only continue to report significant associations between various PM indices and mortality, but also between gaseous pollutants (O_3, SO_2, NO_2, and CO) and mortality. In most of these studies, simultaneous inclusions of gaseous pollutants in the regression models did not meaningfully affect the PM-effect size estimates. This was the case for the NMMAPS 90 cities study with regard to the overall combined U.S. regional and nationwide risk estimates derived for that study. The issue of confounding is discussed further in Section 8.4.

*Fine and coarse particle effect*s. Newly available studies provide generally positive (and often statistically significant) $PM_{2.5}$ associations with mortality, with effect size estimates falling in the range reported in the 1996 PM AQCD. New results from Germany appear to implicate both ultrafine (nuclei-mode) and accumulation-mode fractions of urban ambient fine PM as being important contributors to increased mortality risks. As to the relative importance of fine and coarse particles, in the 1996 PM AQCD there was only one acute mortality study (Schwartz et al., 1996a) that examined this issue. The results of that study of six U.S. cities suggested that fine particles ($PM_{2.5}$), were associated with daily mortality, but not coarse particles ($PM_{10\text{-}2.5}$), except for in Steubenville, OH.. Now, eight studies have analyzed both $PM_{2.5}$ and $PM_{10\text{-}2.5}$ for their associations with mortality. While the results from some of these new studies (e.g., the Santa Clara County, CA analysis [Fairley, 1999]) did suggest that $PM_{2.5}$ was more important than $PM_{10\text{-}2.5}$ in predicting mortality fluctuations, other studies (e.g., Phoenix, AZ analyses [Clyde et al., 2000; Mar et al., 2000; Smith et al., 2000]) suggest that $PM_{10\text{-}2.5}$ may also be important in at least some locations. Seasonal dependence of size-related PM component effects observed in some of the studies complicates interpretations.

Chemical components of PM. Several new studies have examined the role of specific chemical components of PM. The studies conducted in U.S., Canadian, and European cities showed mortality associations with specific fine particle components of PM, including sulfate, nitrate, and CoH; but their relative importance varied from city to city, likely depending on their levels (e.g., no clear associations in those cities where H^+ and sulfate levels were very low, i.e., circa non-detection limits). The results of several studies that investigated the role of crustal particles, although somewhat mixed, overall do not appear to support associations between crustal particles and mortality (see also the discussion of source-oriented evaluations presented below).

*Source-oriented evaluation*s. Several studies conducted source-oriented evaluations of PM components using factor analysis. The results from these studies generally indicated that several combustion-related source-types are likely associated with mortality, including motor vehicle emissions, coal combustion, oil burning, and vegetative burning. The crustal factor from fine particles was not associated with total non-accidental mortality in the Harvard Six Cities data, and the soil (i.e., crustal) factor from fine particles in the Phoenix data was not associated with cardiovascular mortality. Thus, the source-oriented evaluations seem to implicate fine particles of anthropogenic origin as being most important in contributing to increased mortality, but generally do not support increased mortality risks being related to short-term exposures to crustal materials in U.S. ambient environments.

Cause-specific mortality. Findings for new results concerning cause-specific mortality comport well with those for total (non-accidental) mortality, the former showing generally larger effect size estimates for cardiovascular, respiratory, and/or combined cardiorespiratory excess risks than for total mortality risks. An analysis of specific cardiovascular causes in a large population (The Netherlands) suggested that specific causes of deaths (such as heart failure) were more strongly associated with PM (and other pollutants) than total cardiovascular mortality.

Lags. In general, maximum effect sizes for total mortality appear to be obtained with 0-1 day lags, with some studies indicating a second peak for 3-4 days lags. There is also some evidence that, if effects distributed over multiple lag days are considered, the effect size may be larger than for any single maximum-effect-size lag day. Lags are discussed further in Section 8.4.

Threshold. Few new short-term mortality studies explicitly address the issue of thresholds. One study that analyzed Phoenix, AZ data (Smith et al., 2000) did report some limited evidence suggestive of a possible threshold for $PM_{2.5}$. However, several different analyses of larger PM_{10} data sets across multiple cities (Dominici, et al., 2002; Daniels et al., 2000; and reanalysis by Dominici et al., 2003) generally provide little or no support to indicate a threshold for PM_{10} mortality effects. Threshold issues are discussed further in Section 8.4.

8.2.3 Mortality Effects of Long-Term Exposure to Ambient Particulate Matter

8.2.3.1 Studies Published Prior to the 1996 Particulate Matter Criteria Document

8.2.3.1.1 Aggregate Population Cross-Sectional Chronic Exposure Studies

Mortality effects associated with chronic, long-term exposure to ambient PM have been evaluated in cross-sectional studies and, more recently, in prospective cohort studies. A number of older cross-sectional studies from the 1970s provided indications of increased mortality associated with chronic (annual average) exposures to ambient PM, especially with respect to fine mass or sulfate (SO_4^{-2}) concentrations. However, questions unresolved at that time regarding the adequacy of statistical adjustments for other potentially important covariates (e.g., cigarette smoking, economic status, etc.) across cities tended to limit the degree of confidence that was placed by the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) on such purely "ecological" studies or on quantitative estimates of PM effects derived from them. Evidence comparing the toxicities of specific PM components was relatively limited, although the sulfate and acid components were discussed in detail in the 1986 PM AQCD (U.S. Environmental Protection Agency, 1986).

8.2.3.1.2 Semi-Individual (Prospective Cohort) Chronic Exposure Studies

Prospective cohort, semi-individual studies of mortality associated with chronic exposures to air pollution of outdoor origins have yielded especially valuable insights into the adverse health effects of long-term PM exposures. Such semi-individual cohort studies using subject-specific information about relevant covariates (such as cigarette smoking, occupation, etc.) typically are capable of providing more certain findings of long-term PM exposure effects than are purely "ecological studies" (Künzli and Tager, 1997). The new, better designed cohort studies, as discussed below, have largely confirmed the magnitude of PM effect estimates derived from past cross-sectional studies.

The extensive Harvard Six-Cities Study (Dockery et al., 1993) and the American Cancer Society (ACS) Study (Pope et al., 1995) agreed in their findings of statistically significant positive associations between fine particles and excess mortality, although the ACS study did not evaluate the possible contributions of other air pollutants. Neither study considered multi-pollutant models, although the Six-City study did examine various PM and gaseous pollutant indices (including total particles, $PM_{2.5}$, SO_4^{-2}, H^+, SO_2, and ozone), and found that sulfate and $PM_{2.5}$ fine particles were most strongly associated with mortality. The excess RR estimates originally reported for total mortality in the Six-Cities study (and 95 percent confidence intervals, CI) per increments in PM indicator levels were: Excess RR = 18% (CI = 6.8%, 32%) for 20 $\mu g/m^3$ PM_{10}; excess RR = 13.0% (CI = 4.2%, 23%) for 10 $\mu g/m^3$ $PM_{2.5}$; and excess RR = 13.4% (CI = 5.1%, 29%) for 5 $\mu g/m^3$ SO_4^{-2}. The estimates for total mortality derived from the ACS study were excess RR = 6.6% (CI = 3.5%, 9.8%) for 10 $\mu g/m^3$ $PM_{2.5}$ and excess RR 3.5% (CI = 1.9%, 5.1%) for 5 $\mu g/m^3$ SO_4^{-2}. The ACS pollutant RR estimates were smaller than those from the Six-Cities study, although their 95% confidence intervals overlap. In some cases in these studies, the life-long cumulative exposure of the study cohorts included distinctly higher past PM exposures, especially in cities with historically higher PM levels (e.g., Steubenville, OH); but more current PM measurements were used to estimate the chronic PM exposures.

In the ACS study, the pollutant exposure estimates were based on concentrations at the start of the study (during 1979-1983). In addition, the average age of the ACS cohort was 56, which could overestimate the pollutant RR estimates and perhaps underestimate the life-shortening associated with PM associated mortality. Still, although caution must be exercised regarding use of the reported quantitative risk estimates, the Six-Cities and ACS semi-individual studies provided consistent evidence of significant mortality associations with long-term exposure to ambient PM.

In contrast to the Six-Cities and ACS studies, early results reported by Abbey et al. (1991) and Abbey et al. (1995a) from another prospective cohort study, the Adventist Health Study on Smog (AHSMOG), found no significant mortality effects of previous PM exposure in a relatively young cohort of California nonsmokers. However, these analyses used TSP as the PM exposure metric, rather than more health-relevant PM metrics such as PM_{10} or $PM_{2.5}$, included fewer subjects than the ACS study, and considered a shorter follow-up time than the Six-Cities study (ten years versus 15 years for the Six-Cities study). Further, the AHSMOG study included only nonsmokers (indicated by the Six-Cities Study as having lower pollutant RR's than smokers), suggesting that a longer follow-up time than considered in the past (10 years) might be required to have sufficient power to detect significant pollution effects than would be needed in studies that include smokers (such as the Six-Cities and ACS studies). Thus, greater emphasis was placed in the 1996 PM AQCD on the results of the Six-Cities and ACS studies.

Overall, the previously available chronic PM exposure studies collectively indicated that increases in mortality are associated with long-term exposure to ambient airborne particles; and effect size estimates for total mortality associated with chronic PM exposure indices appeared to be much larger than those reported from daily mortality PM studies. This suggested that a major fraction of the reported mortality relative risk estimates associated with chronic PM exposure likely reflects cumulative PM effects above and beyond those exerted by the sum of acute exposure events (i.e., assuming that the latter are fully additive over time). The 1996 PM AQCD (Chapter 12) reached several conclusions concerning four key questions about the prospective cohort studies, as noted below:

(1) Have potentially important confounding variables been omitted?

"While it is not likely that the prospective cohort studies have overlooked plausible confounding factors that can account for the large effects attributed to air pollution, there may be some further adjustments in the estimated magnitude of these effects as individual and community risk factors are included in the analyses." These include individual variables such as education, occupational exposure to dust and fumes, and physical activity, as well as ecological (community) variables such as regional location, migration, and income distribution. Further refinement of the effects of smoking status may also prove useful."

(2) Can the most important pollutant species be identified?

"The issue of confounding with co-pollutants has not been resolved for the prospective cohort studies . . . Analytical strategies that could have allowed greater separation of air pollutant effects have not yet been applied to the prospective cohort studies." The ability to separate the effects of different pollutants, each measured as a long-term average on a community basis, was clearly most limited in the Six Cities study. The ACS study offered a much larger number of cities, but did not examine differences attributable to the spatial and temporal differences in the mix of particles and gaseous pollutants across the cities. The AHSMOG study constructed time- and location-dependent pollution metrics for most of its participants that might have allowed such analyses, but no results were reported.

(3) Can the time scales for long-term exposure effects be evaluated?

"Careful review of the published studies indicated a lack of attention to this issue. Long-term mortality studies have the potential to infer temporal relationships based on characterization of changes in pollution levels over time. This potential was greater in the Six Cities and AHSMOG studies because of the greater length of the historical air pollution data for the cohort [and the availability of air pollution data throughout the study]. The chronic exposure studies, taken together, suggest that there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles, and that at least some fraction of these deaths are likely to occur between acute exposure episodes. If this interpretation is correct, then at least some individuals may experience some years of reduction of life as a consequence of PM exposure."

(4) Is it possible to identify pollutant thresholds that might be helpful in health assessments?

"Model specification searches for thresholds have not been reported for prospective cohort studies. . . . Measurement error in pollution variables also complicates the search for potential threshold effects. . . . The problems that complicate threshold detection in the population-based studies have a somewhat different character for the long-term studies."

8.2.3.2 New Prospective Cohort Analyses of Mortality Related to Chronic Particulate Matter Exposures

Considerable further progress has been made towards addressing the above issues. As an example, extensive reanalyses (Krewski et al., 2000) of the Six-Cities and ACS Studies (sponsored by HEI), indicate that the published findings of the original investigators (Dockery et al., 1993; Pope et al., 1995) are based on substantially valid data sets and statistical analyses. The HEI reanalysis project demonstrated that small corrections in input data have very little effect on the findings and that alternative model specifications further substantiate the robustness of the originally reported findings. In addition, some of the above key questions have been further investigated by Krewski et al. (2000) via sensitivity analyses (in effect, new analyses) for the Six City and ACS studies data sets, including consideration of a much wider range of confounding variables. Newly published analyses of ACS data for more extended time periods (Pope et al., 2002) further substantiate original findings and also provide much clearer, stronger evidence for ambient PM exposure relationships with increased lung cancer risk. Newer published analyses of AHSMOG data (Abbey et al., 1999; Beeson et al., 1998) also extend the ASHMOG findings and show some analytic outcomes different from earlier analyses reported out from the study. Results from the Veterans' Administration- Washington University (hereafter called "VA") prospective cohort study are also now available (Lipfert et al., 2000b). Other additional, new studies suggestive of possible effects of sub-chronic PM exposures on fetal and infant development/mortality (Woodruff et al., 1997; Lipfert, 2000; Chen et al., 2002) are also discussed below.

8.2.3.2.1 Health Effects Institute Reanalyses of the Six-Cities and ACS Studies

The overall objective of the HEI "Particle Epidemiology Reanalysis Project" was to conduct a rigorous and independent assessment of the findings of the Six Cities (Dockery et al., 1993) and ACS (Pope et al., 1995) Studies of air pollution and mortality. The following description of approach, key results, and conclusions is largely extracted from the Executive Summary of the HEI final report (Krewski et al., 2000). The HEI-sponsored reanalysis effort was approached in two steps:

- Part I: Replication and Validation. The Reanalysis Team sought to test (a) whether the original studies could be replicated via a quality assurance audit of a sample of the original data and (b) whether the original numeric results could be validated.
- Part II: Sensitivity Analyses. The Reanalysis Team tested the robustness of the original analyses to alternate risk models and analytic approaches.

The Part I audit of the study population data for both the Six Cities and ACS Studies and of the air quality data in the Six Cities Study revealed that data were of generally high quality with few exceptions. In both studies, a few errors were found in the data coding for and exclusion of certain subjects; but when those subjects were included in the analyses, they did not materially change the results from those originally reported. Because the air quality data used in the ACS Study could not be audited, a separate air quality database was constructed for the sensitivity analyses in Part II.

The Reanalysis Team was able to replicate the original results for both studies using the same data and statistical methods as used by the original investigators, as shown in Table 8-5. The Reanalysis Team confirmed the original point estimates. For the Six Cities Study, they reported the excess relative risk of mortality from all causes associated with an increase in fine particles of 10 $\mu g/m^3$ to be 14%, close to the 13% reported by the original investigators. For the ACS Study, they reported the relative risk of all-cause mortality associated with a 10 $\mu g/m^3$ increase in fine particles to be 7.0% in the reanalysis, close to the original 6.6% value.

The Part II sensitivity analysis applied an array of different models and variables to determine whether the original results would remain robust to different analytic assumptions and model specifications. The Reanalysis Team first applied the standard Cox model used by the original investigators and included variables in the model for which data were available from both original studies, but had not been used in the published analyses (e.g., physical activity, lung function, marital status). The Reanalysis Team also designed models to include interactions between variables. None of these alternative models produced results that materially altered the original findings.

TABLE 8-5. COMPARISON OF SIX CITIES AND AMERICAN CANCER SOCIETY (ACS) STUDY FINDINGS FROM ORIGINAL INVESTIGATORS AND HEALTH EFFECTS INSTITUTE REANALYSIS

Type of Health Effect & Location	Indicator	Mortality Risk per Increment in PM[a]	
Original Investigators' Findings		Total Mortality Excess Relative Risk (95% CI)	Cardiopulmonary Mortality Excess Relative Risk (95% CI)
Six City[b]	$PM_{2.5}$	13% (4.2%, 23%)	18% (6.0%, 32%)
Six City[b]	$PM_{15/10}$	18% (6.8%, 32%)	e
ACS Study[c]	$PM_{2.5}$	6.6% (3.5%, 9.8%)	12% (6.7%, 17%)
HEI reanalysis Phase I: Replication			
Six City Reanalysis[d]	$PM_{2.5}$	14% (5.4%, 23%)	19% (6.5%, 33%)
	PM_{15}	19% (6.1%, 34%)	20% (2.9%, 41%)
ACS Study Reanalysis[d]	$PM_{2.5}$	7.0% (3.9%, 10%)	12% (7.4%, 17%)
	PM_{15} (dichot)	4.1% (0.9%, 7.4%)	7.3% (3.0%, 12%)
	PM_{15} (SSI)	1.6% (−0.8%, 4.1%)	5.7% (2.5%, 9.0%)

[a]Estimates calculated on the basis of differences between the most-polluted and least-polluted cities, scaled to increments of 20 μg/m³ increase for PM_{10} and 10 μg/m³ increments for PM_{15} and $PM_{2.5}$.
[b]Dockery et al. (1993).
[c]Pope et al. (1995).
[d]Krewski et al. (2000).
[e]Results presented only by smoking category subgroup.

Next, for both the Six Cities and ACS Studies, the Reanalysis Team investigated the possible effects of fine particles and sulfate on a range of potentially susceptible subgroups of the population. These analyses did not find differences in PM-mortality associations among subgroups based on various personal characteristics (e.g., including gender, smoking status,exposure to occupational dusts and fumes, and marital status). However, estimated effects of fine particles did vary with educational level: the association between an increase in fine particles and mortality tended to be higher for individuals without a high school education than for those with more education. The Reanalysis Team postulated that this finding could be attributable to some unidentified socioeconomic effect modifier. The authors concluded "The Reanalysis Team found little evidence that questionnaire variables had led to confounding in either study, thereby strengthening the conclusion that the observed association between fine particle air pollution and mortality was not the result of a critical covariate that had been neglected by the Original Investigators." (Krewski et al., 2000, pp. 219-220).

In the ACS study, the Reanalysis Team tested whether the relationship between ambient concentrations and mortality was linear. They found some indications of both linear and nonlinear relationships, depending upon the analytic technique used, suggesting that the shapes of the concentration-response relationships warrant additional research in the future.

One of the criticisms of both original studies has been that neither analyzed the effects of change in pollutant levels over time. In the Six Cities Study, for which such data were available, the Reanalysis Team tested whether effect estimates changed when certain key risk factors (smoking, body mass index, and air pollution) were allowed to vary over time. In general, the reanalysis results did not change when smoking and body mass index were allowed to vary over time. The Reanalysis Team did find for the Six Cities Study, however, that when the general decline in fine particle levels over the monitoring period was included as a time-dependent variable, the association between fine particles and all-cause mortality was reduced (Excess RR = 10.4%, 95% CI = 1.5%, 20%). This would be expected, because the most polluted cities would likely have the greatest decline as pollution controls were applied. Despite this adjustment, the $PM_{2.5}$ effect estimate continued to be positive and statistically significant.

To test the validity of the original ACS air quality data, the Reanalysis Team constructed and applied its own air quality dataset from available historical data. In particular, sulfate levels with and without adjustment were found to differ by about 10% for the Six Cities Study. Both the original ACS Study air quality data and the newly constructed dataset contained sulfate levels inflated by 50% due to artifactual sulfate. For the Six Cities Study, the relative risks of mortality were essentially unchanged with adjusted or unadjusted sulfate. For the ACS Study, adjusting for artifactual sulfate resulted in slightly higher relative risks of mortality from all causes and cardiopulmonary disease compared with unadjusted data, while the relative risk of mortality from lung cancer was lower after the data had been adjusted. Thus, the Reanalysis Team found essentially the same results as the original Harvard Six-Cities and ACS studies, even after using independently developed pollution data sets and adjusting for sulfate artifact.

Because of the limited statistical power to conduct most model specification sensitivity analyses for the Six Cities Study, the Reanalysis Team conducted the majority of its sensitivity analyses using only the ACS Study dataset that considered 151 cities. When a range of city-level (ecologic) variables (e.g., population change, measures of income, maximum temperature, number of hospital beds, water hardness) were included in the analyses, the results generally did not change. The only exception was that associations with fine particles and sulfate were reduced when city-level measures of population change or SO_2 were included in the model.

A major product of the Reanalysis Project is the determination that both pollutant variables and mortality appear to be spatially correlated in the ACS Study dataset. If not identified and modeled correctly, spatial correlation could cause substantial errors in both the regression coefficients and their standard errors. The Reanalysis Team identified several methods for addressing this, each of which resulted in some reduction in the estimated regression coefficients. The full implications and interpretations of spatial correlations in these analyses have not been resolved and were noted to be an important subject for future research.

When the Reanalysis Team sought to take into account both the underlying variation from city to city (random effects) and variation from the spatial correlation between cities, positive associations were still found between mortality and sulfates or fine particles. Results of various models, using alternative methods to address spatial autocorrelation and including different ecologic covariates, found fine particle-mortality associations that ranged from 1.11 to 1.29 (the RR reported by original investigators was 1.17) per 24.5 $\mu g/m^3$ increase in $PM_{2.5}$. With the exception of SO_2, consideration of other pollutants in these models did not alter the associations found with sulfates. The authors reported associations that were stronger for SO_2 than for sulfate, which may indicate that artifactual sulfate was "picking up" some of the SO_2 association, perhaps because the sulfate artifact is in part proportional to the prevailing SO_2 concentration (Coutant, 1977). It should be recognized that the Reanalysis Team did not use data adjusted for artifactual sulfate for most alternative analyses. When they did use adjusted sulfate data, relative risks of mortality from all causes and cardiopulmonary disease increased. This result suggests that more analyses with adjusted sulfate might result in somewhat higher relative risks associated with sulfate. The Reanalysis Team concluded: "it suggests that uncontrolled spatial autocorrelation accounts for 24% to 64% of the observed relation. Nonetheless, all our models continued to show an association between elevated risks of mortality and exposure to airborne sulfate" (Krewski et al., 2000, p. 230).

In summary, the reanalyses generally confirmed the original investigators' findings of associations between mortality and long-term exposure to PM, while recognizing that increased mortality may be attributable to more than one ambient air pollution component. Regarding the validity of the published Harvard Six-Cities and ACS Studies, the HEI Reanalysis Report concluded that "Overall, the reanalyses assured the quality of the original data, replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality."

In a further analyses of the Harvard Six City study cohort using a Poisson regression model, Villeneuve et al. (2002) evaluated the relationship between fixed-in-time and time-dependent measures of $PM_{2.5}$ and the risk of mortality among adult, Caucasian participants. The RR of mortality using the Poisson method based upon city-specific exposures that remained constant during the follow up was 1.31 (CI = 1.12 – 1.52), which is similar to results derived from the Cox model used in the original analysis. However, the authors report that "The RR of mortality due to $PM_{2.5}$ exposure decreased when time-dependent measures of air pollution were modeled (Table 8-6). Specifically, when the mean $PM_{2.5}$ level within each city during each period of follow-up was modeled, the RR was 1.16 (95% CI = 1.02 – 1.32). The authors noted that "there were considerable variations in mortality rates across the calendar periods that were modeled," and that "the magnitude of these variations in mortality rates may have dampened any real $PM_{2.5}$ effect on mortality." Villeneuve et al. (2002) concluded that the "attenuated risk of mortality that was observed with a time-dependent index of $PM_{2.5}$ is due to the combined influence of city-specific variations in mortality rates and decreasing levels of air pollution that occurred during follow-up."

Similar results were observed by Villeneuve et al. (2002) irrespective of the exposure window considered. They used various time-dependent indices denoting exposures received in the last two years of follow-up and (b) for exposures lagged 3 – 4 and ≥ 5 years. Effect modification was evaluated by fitting interaction terms that consisted of $PM_{2.5}$ exposure and individual risk factors (body mass index, education, smoking, age, gender, and occupational exposure to dusts). The significance of this term was formally tested by constructing a likelihood ratio test statistic. An interaction effect between $PM_{2.5}$ exposure and age was observed ($p < 0.05$), and they therefore presented stratified analysis by age group (< 60, ≥ 60 years). For each index of $PM_{2.5}$, the RR of all-cause mortality was more pronounced among subjects < 60 years old. There was no effect modification between $PM_{2.5}$ and the other

TABLE 8-6. RELATIVE RISK[a] OF ALL-CAUSE MORTALITY FOR SELECTED INDICES OF EXPOSURE TO FINE PARTICULATE MATTER (per 18.6 μg/m³) BASED ON MULTIVARIATE POISSON REGRESSION ANALYSIS, BY AGE GROUP, FOR HARVARD SIX CITY STUDY DATA[B]

		Age Group (years)		
Model	**$PM_{2.5}$ Exposure City Specific Index**	**Total**	**< 60**	**≥ 60**
1	Exposure to $PM_{2.5}$ remained fixed over the entire follow up period.	1.31 (1.12 – 1.52)	1.89 (1.32 – 2.69)	1.21 (1.02 – 1.43)
2	Exposure to $PM_{2.5}$ was defined according to 13 calendar periods (no smoothing).[a]	1.19 (1.04 – 1.36)	1.52 (1.15 – 2.00)	1.11 (0.95 – 1.29)
3	Exposure to $PM_{2.5}$ was defined according to 13 calendar periods (smoothed).[b]	1.16 (1.02 – 1.32)	1.43 (1.10 – 1.85)	1.09 (0.93 – 1.26)
4	Time dependent estimate of $PM_{2.5}$ received during the previous two years.	1.16 (1.02 – 1.31)	1.42 (1.09 – 1.82)	1.08 (0.94 – 1.25)
5	Time dependent estimate of $PM_{2.5}$ received 3 - 5 years before current year.	1.14 (1.02 – 1.27)	1.35 (1.08 – 1.87)	1.08 (0.95 – 1.22)
6	Time dependent estimate of $PM_{2.5}$ received > 5 years before current year.	1.14 (1.05 – 1.23)	1.34 (1.11 – 1.59)	1.09 (0.99 – 1.20)

[a] Relative risks were adjusted by age, gender, body mass, index, education, number of years smoked (at baseline), occupational exposures and number of cigarettes smoked weekly.
[b] For each city, exposure to $PM_{2.5}$ was estimated for 13 calendar periods using loglinear regression based on annual mean $PM_{2.5}$ levels. The calendar periods used were: 1970-1978, 1979, 1981, . . . 1989, and 1990+. PM2.5 associations with all-cause mortality assessed for male Caucasian participants in Six Cities Study.

Source: Villeneuve et al. (2002).

individual risk factors. The RR for PM-associated mortality did not depend on when exposure occurred in relation to death, possibly because dof little variation between the time-dependent city-specific $PM_{2.5}$ exposure indices (r > 0.9) and the fact that the rank ordering of the cities changed little during follow-up.

8.2.3.2.2 The ACS Study Extension

Pope et al. (2002) extended the analyses (Pope et al., 1995) and reanalyses (Krewski et al., 2000) of the ACS CPS-II cohort to include an additional eight years of follow-up data. The new study has a number of advantages over the previous analyses, in that it (a) doubles the follow-up time from eight to sixteen years and triples the number of deaths; (b) expands the ambient air pollution data substantially, including two recent years of fine particle data and adding data on gaseous co-pollutants; (c) improves statistical adjustments for occupational exposure; (d) incorporates data on dietary covariates believed to be important factors in mortality, including total fat consumption, and consumption of vegetables, citrus fruit, and high-fiber grains; and (e) uses recent developments in non-parametric spatial smoothing and random effects statistical models as input to the Cox proportional hazards model. Each participant was identified with a specific metropolitan area, and mean pollutant concentrations were calculated for all metropolitan areas with ambient air monitors in the one to two years prior to enrollment. Ambient pollution during the follow-up period was extracted from the AIRS data base. Averages of daily averages of the gaseous pollutants were used except for ozone, where the average daily 1-hour maximum was calculated for the whole year and for the typical peak ozone quarter (July, August, September). Mean sulfate concentrations for 1990 were calculated from archived quartz filters, virtually eliminating the historical sulfate artifact leading to overestimation of sulfate concentrations.

The Krewski et al. (2000), Burnett et al. (2001a), and Pope et al. (2002) studies were concerned that survival times of participants in nearby locations might not be independent of each other, due to missing, unmeasured, or mis-measured risk factors or their surrogates that may be spatially correlated with air pollution, thus violating an important assumption of the Cox proportional hazards model. Thus, model fitting proceeded in two stages, the first of which was an adjusted relative risk model with a standard Cox proportional hazards model including individual-specific covariates and indicator variables for each metropolitan area, but not air pollutants. In the second stage, the adjusted log(relative risks) were fitted to fine particle concentrations or other air pollutants by a random effects linear regression model.

Models were estimated separately for each of four mortality (total, cardiopulmonary, lung cancer, and causes other than cardiopulmonary or lung cancer deaths) endpoints for the entire follow-up period and for fine particles in three time periods (1979-1983, 1999-2000, and the average of the mean concentrations in these two periods). The results are shown in Table 8-7. Figures 8-7, 8-8, and 8-9 show the results displayed in Figures 2, 3, and 5 of Pope et al. (2002). Figure 8-7 shows that a smooth non-parametric model can be reasonably approximated by a linear model for all-cause mortality, cardiopulmonary mortality, and other mortality; but the log(relative risk) model for lung cancer appears to be non-linear, with a steep linear slope up to

TABLE 8-7. SUMMARY OF RESULTS FROM THE EXTENDED ACS STUDY*

Cause of death	$PM_{2.5}$, average over 1979-1983	$PM_{2.5}$, average over 1999-2000	$PM_{2.5}$, average over all seven years
All causes	4.1% (0.8, 7.5%)	5.9% (2.0, 9.9%)	6.2% (1.6, 11.0%)
Cardiopulmonary	5.9% (1.5, 10.5%)	7.9% (2.3, 14.0%)	9.3% (3.3, 15.8%)
Lung cancer	8.2% (1.1, 15.8%)	12.7% (4.1, 21.9%)	13.5% (4.4, 23.4%)
Other	0.8% (−3.0, 4.8%)	0.9% (−3.4, 5.5%)	0.5% (−4.8, 6.1%)

*Adjusted mortality excess risk ratios (95% confidence limits) per 10 μg/m³ $PM_{2.5}$ by cause of death associated with each of the multi-year averages of fine particle concentrations. The multi-year average concentrations are used as predictors of cause-specific mortality for all of the 16 years (1982-1998) of the ACS follow-up study. The excess risk ratios are obtained from the baseline random effects Cox proportional hazards models adjusted for age, gender, race, smoking, education, marital status, BMI, alcohol consumption, occupational dust exposure, and diet. Based on Table 2 in Pope et al. (2002) and more precise data from authors (G. Thurston, personal communication, March 13, 2002).

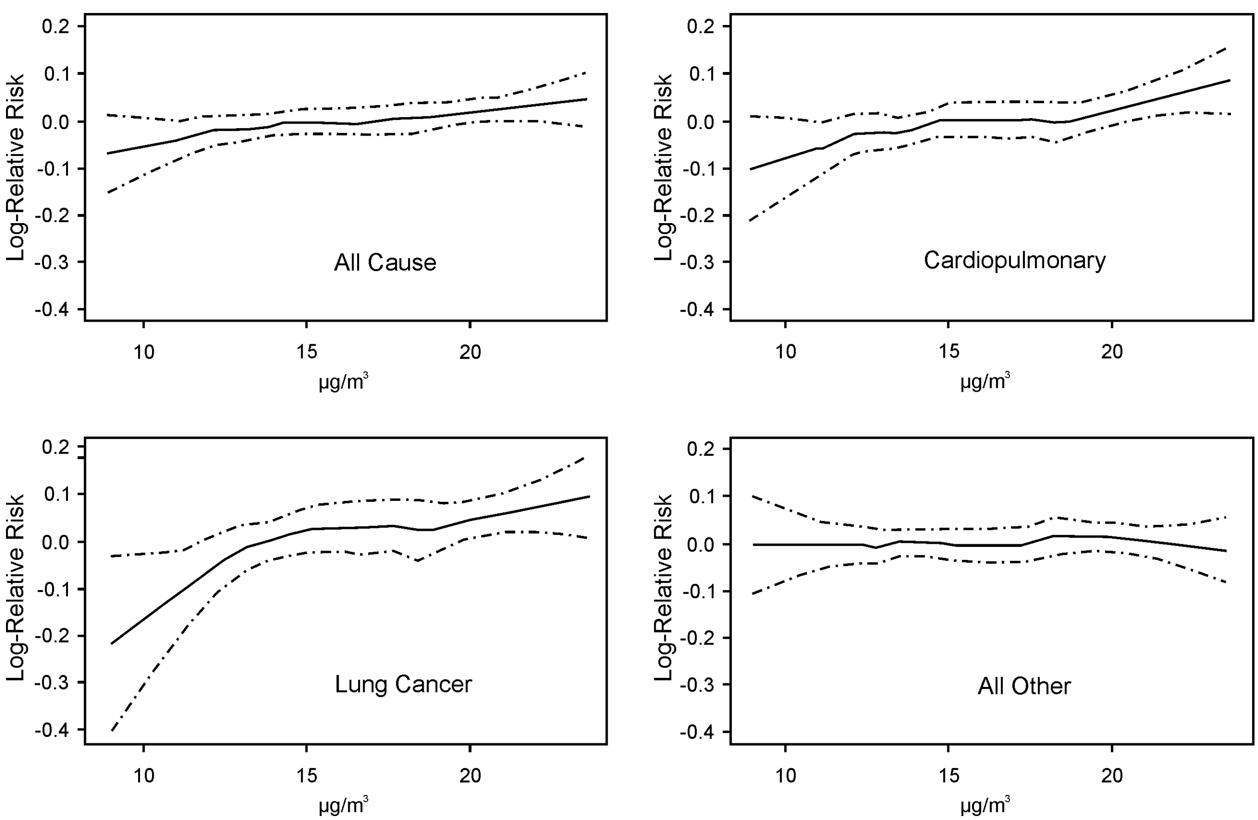

Figure 8-7. Natural logarithm of relative risk for total and cause-specific mortality per 10 μg/m³ $PM_{2.5}$ (approximately the excess relative risk as a fraction), with smoothed concentration-response functions. Based on Pope et al. (2002) mean curve (solid line) with pointwise 95% confidence intervals (dashed lines).

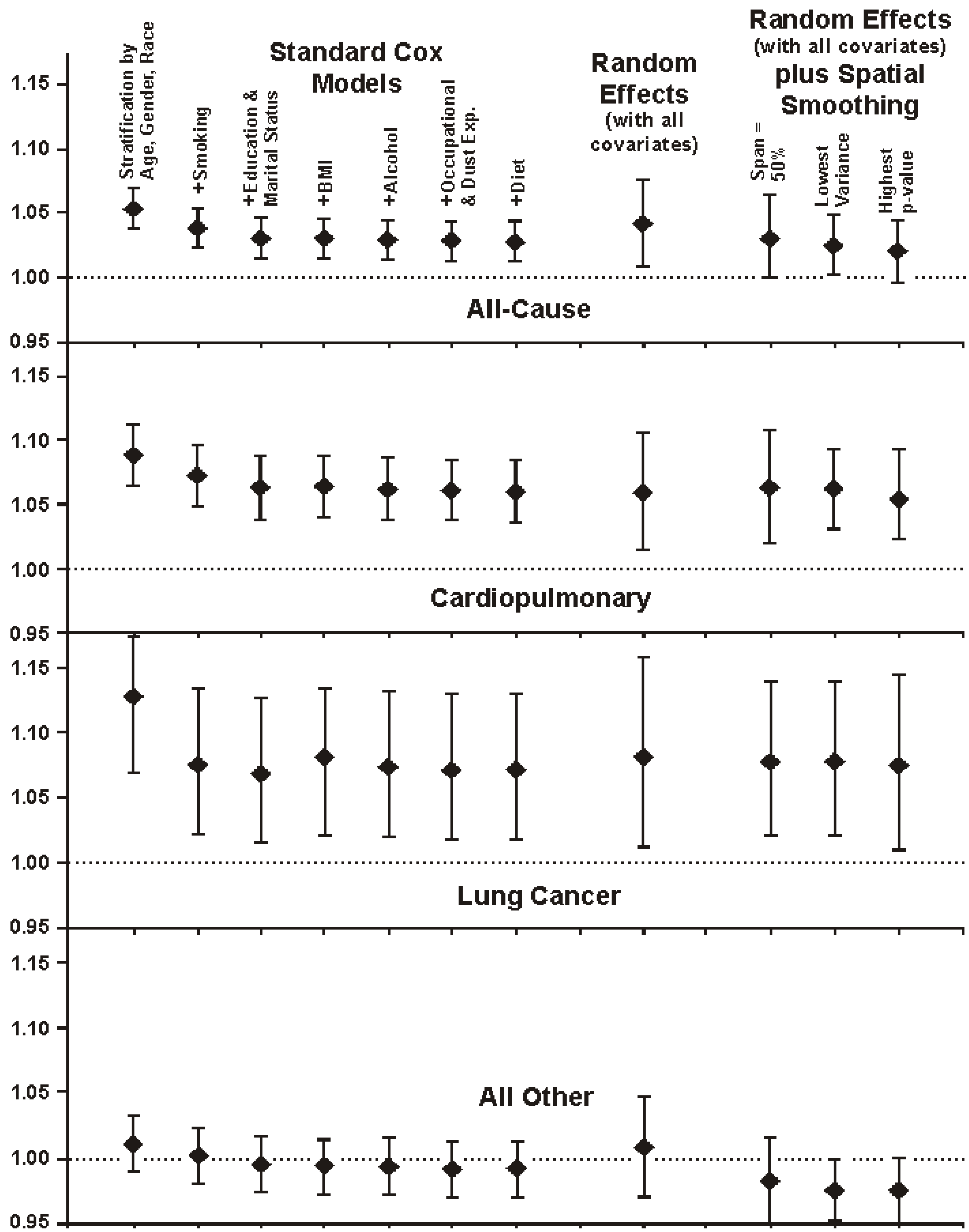

Figure 8-8. Relative risk of total and cause-specific mortality at 10 μg/m^3 (mean of 1979-1983) of alternative statistical models. The standard Cox models are built up in a sequential stepwise manner from the baseline model stratified by age, gender, and race by adding additional covariates. The random effects model allows for additional city-to-city variation, and the spatial smoothing models show the effects of increasingly aggressive adjustment for spatial correlation.

Source: Based on Pope et al. (2002).

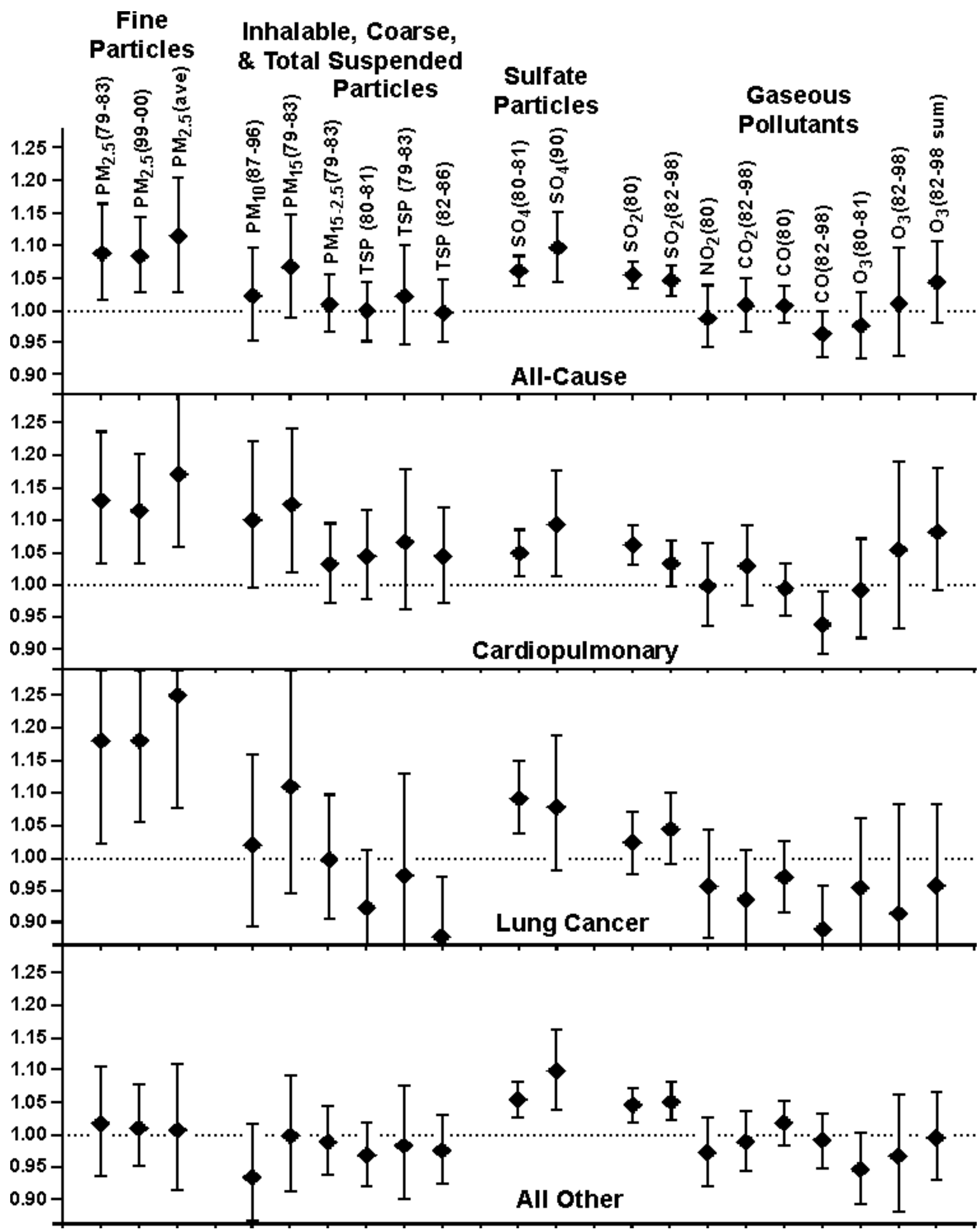

Figure 8-9. Relative risk of total and cause-specific mortality for particle metrics and gaseous pollutants over different averaging periods (years 1979-2000 in parentheses).

Source: Based on Pope et al. (2002).

an annual mean concentration of about 13 μg/m^3 and a flatter linear slope at fine particle concentrations > 13 μg/m^3.

Figure 4 in Pope et al. (2002) shows results for the stratified first-stage models: ages < 60 and > 69 yr are marginally significant for total mortality; ages > 70 are significant for cardiopulmonary mortality; and ages 60-69 for lung cancer mortality. Men are at significantly higher risk for total and lung cancer mortality than are women, but slightly less so for cardiopulmonary mortality (although still significant). Log(RR) decreases significantly from individuals with less than to those with more than a high school education, replicating findings in Krewski et al. (2000), but with twice the time on study. Including smoking status showed increased fine particle RR for cardiopulmonary and lung cancer mortality in never-smokers and least effect in current smokers; however, for total mortality, significant or near-significant effects occurred in both current and never-smokers, but not former smokers.

The second-stage random effects models on the right side of Figure 8-8 have much wider confidence intervals than the first-stage models, but are still statistically significant for total, cardiopulmonary, and lung cancer mortality. Spatial smoothing decreased the magnitude and significance of the fine particle effect for total mortality. For cardiopulmonary mortality, spatial smoothing increased the magnitude of the RR and its significance by reducing the width of the confidence intervals in the “50%-span” and “lowest variance” smoothing methods. For lung cancer mortality, spatial smoothing little changed the magnitude of the RR, but increased its significance by reducing the width of confidence intervals in the “50%-span” and “lowest variance” smoothing methods.

Figure 8-9 shows statistically significant relationships between fine particles and total, cardiopulmonary, and lung cancer mortality no matter which averaging span was used for $PM_{2.5}$ and slightly larger effect estimates for the average concentration of the 1979-1983 and 1999-2000 intervals. PM_{15} for 1979-1983 is significantly associated with cardiopulmonary mortalityand marginally with total mortality; whereas 1987-1996 PM_{15} is not quite significantly associated with cardiopulmonary mortality. Coarse particles ($PM_{15-2.5}$) and TSP are not significantly associated with any endpoint, but are positively associated with cardiopulmonary mortality. Sulfate particles are very significantly associated with all endpoints, including mortality from all other causes, but only marginally for lung cancer mortality using 1990 filters.

Figure 8-9 also shows highly positive significant relationships between SO_2 and total, cardiopulmonary, and other-causes mortality, but a weaker SO_2 association with lung cancer mortality. Only ozone using only the third quarter for 1982-1998 showed a marginally significant relationship with cardiopulmonary mortality, but not the year-round average. The other criteria pollutants, CO and NO_2, are neither significantly nor positively related to any mortality endpoint, unlike some findings for acute PM exposure-mortality studies.

This paper is noteworthy because it confirms that the general pattern of findings in the first eight years of the study (Pope et al., 1995; Krewski et al., 2000) can be reasonably extrapolated to the patterns that remain present with twice the length of time on study and three times the number of deaths. As shown later in Table 8-11, the excess relative risk estimate (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$ for total mortality in the original ACS study (Pope et al., 1995) was 6.6% (3.6, 9.9%); in the ACS reanalysis (Krewski et al., 2000) it was 7.0% (3.9, 10%); and, in the extended ACS data set (Pope et al., 2002), it was 4.1% (0.8, 7.5%) using the 1979-1983 data and 6.2% (1.6, 11%) using the average of the 1979-1983 and 1999-2000 data. The excess relative risk estimate (95% CI) per 10 $\mu g/m^3$ $PM_{2.5}$ for cardiopulmonary mortality in the original ACS study (Pope et al., 1995) was 12% (6.7, 17%); in the ACS reanalysis (Krewski et al., 2000), it was 12% (7.4, 17%); and, in the extended ACS data set (Pope et al., 2002), it was 5.9% (1.5, 10%) using the 1979-1983 data and 9.3% (3.3, 16%) using the average of the 1979-1983 and 1999-2000 data. Thus, the additional data and statistical analyses reported in Pope et al. (2002) yield somewhat smaller estimates than the original study (Pope et al., 1995), but are similar to estimates from the (Krewski et al. (2000) reanalysis of the original ACS data set.

The Pope et al. (2002) JAMA study also considered the PM risks by subgroup characteristics. It was found that the risks were generally (although not significantly) higher for males than females, which might be due to historically greater time spent outdoors by men than women. It was also found that the $PM_{2.5}$ relative risks tended to be higher for non-smokers than smokers. This is consistent with the fact that smokers would have a much higher baseline risk, especially for lung cancer. This would tend to lower the air pollution mortality risk when viewed relative to the much higher smoker baseline risk. $PM_{2.5}$ mortality relative risks also tended to be higher for those with less education, which may be due to related socio-economic factors, or more likely to the generally greater inter-state mobility of higher educated persons. Since the MSA was assumed unchanged from that at the start of the study, this would tend to weaken the

1 association for higher education subjects, as the MSA-based exposure information would tend to
2 have less accuracy in that highly mobile group. This may indicate that the less educated group
3 RR estimates may be more indicative of the true $PM_{2.5}$ effects (i.e., as their exposure information
4 is likely to be more accurate), and therefore that the overall study PM2.5 RR estimates that
5 include the highly educated may be biased low.

6 Based on the above patterns of results, the authors drew the following conclusions:

7 (1) The apparent association between long-term exposure to fine particle pollution and mortality persists with longer follow-up as the participants in the cohort grow older and more of them die.

8 (2) The estimated fine particle effect on cardiopulmonary mortality and cancer mortality remained relatively stable even after adjustment for smoking status, although the estimated effect was larger and more significant for never-smokers versus former or current smokers. The estimates were relatively robust against inclusion of many additional covariates: education, marital status, body mass index (BMI), alcohol consumption, occupational exposure, and dietary factors. However, as the authors note, the data on individual risk factors were collected only at the time of enrollment and have not been updated, so that changes in these factors since 1982 could introduce risk-factor exposure mis-classification and a consequent loss of precision in the estimates that might limit the ability to characterize time dependency of effects. Moreover, it is noteworthy that this study found education to be an effect modifier, with larger and more statistically significant PM effect estimates for persons with less education. This may be due to the fact that less-education is a marker for lower socio-economic status and, therefore, poorer health status and greater pollution susceptibility. These results may also be an indicator that the mobility of the less educated provides better estimates of effects in this study (with no follow up of address changes) than for the more mobile well-educated. In either case, because this cohort comprises a much higher percentage of well-educated persons than the general public, the education effect modification seen suggests that the overall PM effect estimates are likely underestimated by this study cohort versus that which would be found for the general public.

9 (3) Additional assessments for potential spatial or regional differences not controlled in the first-stage model were evaluated. If there are unmeasured or inadequately modeled risk

factors that are different across locations or spatially clustered, then PM risk estimates may be biased. If the clustering is independent or random or independent across areas, then adding a random-effects component to the Cox proportional hazards model can address the problem. However, if location is associated with air pollution, then the spatial correlation may be evaluated using non-parametric smoothing methods.
No significant spatial auto-correlation was found after controlling for fine particles. Even after adjusting for spatial correlation, the estimated $PM_{2.5}$ effects were significant and persisted for cardiopulmonary mortality and lung cancer mortality and were borderline significant for total mortality, but with much wider confidence intervals after spatial smoothing.

10 (4) Fine particles ($PM_{2.5}$) were associated with elevated total, cardiopulmonary, and lung cancer mortality risks, but not other-cause mortality. PM_{10} for 1987-1996 and PM_{15} for 1979-1983 were just significantly associated with cardiopulmonary mortality, but $PM_{10\text{-}2.5}$ and TSP were not associated with total or any cause-specific mortality.
All endpoints but lung cancer mortality were very significantly associated with sulfates, except for lung cancer with 1990 sulfate data. All endpoints except lung cancer mortality were significantly associated with SO_2 using 1980 data as were total and other mortality using the 1982-1998 SO_2 data; but cardiopulmonary and lung cancer mortality had only a borderline significant association with the1982-1998 SO_2 data. None of the other gaseous pollutants showed significant positive associations with any endpoint. Thus, neither coarse thoracic particles nor TSP were significantly associated with mortality; nor were CO and NO_2 on a long-term exposure basis.

11 (5) The concentration-response curves estimated using non-parametric smoothers were all monotonic and nearly linear (except for lung cancer). However, the shape of the curve may become non-linear at much higher concentrations.

12 (6) The excess risk from $PM_{2.5}$ exposure is much smaller than that estimated for cigarette smoking for current smokers in the same cohort (Pope et al., 1995): RR = 2.07 for total mortality, RR = 2.28 for cardiopulmonary mortality, and RR = 9.73 for lung cancer mortality. In the more polluted areas of the United States, the relative risk for substantial obesity (a known risk factor for cardiopulmonary mortality) is larger than that for $PM_{2.5}$, but the relative risk from being moderately overweight is somewhat smaller.

8.2.3.2.3 AHSMOG Analyses

The Adventist Health Study of Smog (AHSMOG), a third major U.S. prospective cohort study of chronic PM exposure-mortality effects, started with enrollment in 1977 of 6,338 non-smoking non-Hispanic white Seventh Day Adventist residents of California, ages 27 to 95 years. All had resided for at least 10 years within 5 miles (8 km) of their then-current residence locations, either within one of the three major California air basins (San Diego, Los Angeles, or San Francisco) or else were part of a random 10% sample of Adventist Health Study participants residing elsewhere in California. The study has been extensively described and its initial results earlier reported elsewhere (Hodgkin et al., 1984; Abbey et al., 1991; Mills et al., 1991).

In more recent AHSMOG analyses (Abbey et al., 1999), the mortality status of subjects after ca. 15-years of follow-up (1977-1992) was determined by various tracing methods and 1,628 deaths (989 female, 639 male) were found in the cohort. This 50% percent increase during the follow-up period (versus previous AHSMOG reports) enhances the power of the latest analyses over past published ones. Of 1,575 deaths from all natural (non-external) causes, 1,029 were cardiopulmonary, 135 were non-malignant respiratory (ICD9 codes 460-529), and 30 were lung cancer (ICD9 code 162) deaths. Abbey et al. (1999) also created another death category, contributing respiratory causes (CRC), which included any mention of nonmalignant respiratory disease as an underlying or “contributing cause” on the death certificate. Numerous analyses were done for the CRC category, due to the large numbers and relative specificity of respiratory causes as a factor in the deaths. Education was used to index socio-economic status, rather than income. Physical activity and occupational exposure to dust were also used as covariates. Cox proportional hazard models adjusted for a variety of covariates or stratified by sex were used. The “time” variable used in most of the models was survival time from date of enrollment, except that age on study was used for lung cancer effects due to the expected lack of short-term effects. Many covariate adjustments were evaluated, yielding results for all non-external mortality as shown in Table 8-8.

As for cause-specific mortality analyses of the AHSMOG data, positive and statistically significant effects on deaths with underlying contributing respiratory causes were also found for 30 day/yr > 100 $\mu g/m^3$ PM_{10} (RR = 1.14, 95% CI = 1.03-1.56) in models that included both sexes and adjustment for age, pack-years of smoking, and BMI. Subsets of the cohort had elevated

TABLE 8-8. RELATIVE RISK OF MORTALITY FROM ALL NONEXTERNAL CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE ASHMOG STUDY

		Females			Males		
Pollution Index	**Pollution Increment**	**RR**	**LCL**	**UCL**	**RR**	**LCL**	**UCL**
PM_{10} > 100, d/yr	30 days/yr	0.958	0.899	1.021	1.082	1.008	1.162
PM_{10} mean	20 μg/m^3	0.95	0.873	1.033	1.091	0.985	1.212
SO_4 mean	5 μg/m^3	0.901	0.785	1.034	1.086	0.918	2.284
O_3 > 100 ppb, h/yr	551 h/yr (IQR)	0.9	0.8	1.02	1.14	0.98	1.32
SO_2 mean	3.72 (IQR)	1	0.91	1.1	1.05	0.94	1.18

LCL = Lower 95% confidence limit UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

risks: (a) former smokers had higher RR's than never-smokers (RR for PM_{10} exceedances for never-smokers was marginally significant by itself); (b) subjects with low intake of anti-oxidant vitamins A, C, E had significantly elevated risk of response to PM_{10}, whereas those with adequate intake did not (suggesting that dietary factors or, possibly, other socio-economic or life style factors for which they are a surrogate may be important covariates); and (c) there also appeared to be a gradient of PM_{10} risk with respect to time spent outdoors, with those who had spent at least 16 h/wk outside being at greater risk from PM_{10} exceedances. The extent to which time spent outdoors is a surrogate for other variables or is a modifying factor reflecting temporal variation in exposure to ambient air pollution is not clear, e.g., if the males spent much more time outdoors than the females, outdoor exposure time could be confounded with gender. When the cardiopulmonary analyses are broken down by gender (Table 8-9), the RR's for female deaths were generally smaller than that for males, but none of the risks for PM indices or gaseous pollutants were statistically significant at $p < 0.05$.

The AHSMOG cancer analyses yielded very mixed results for lung cancer mortality (Table 8-10). For example, RR's for lung cancer deaths were statistically significant for males for PM_{10} and O_3 metrics, but not for females. In contrast, such cancer deaths were significant for mean NO_2 only for females (but not for males), but lung cancer metrics for mean SO_2 were

TABLE 8-9. RELATIVE RISK OF MORTALITY FROM CARDIOPULMONARY CAUSES, BY SEX AND AIR POLLUTANT, FOR AN ALTERNATIVE COVARIATE MODEL IN THE ASHMOG STUDY

Pollution Index	Pollution Increment	Females			Males		
		RR	LCL	UCL	RR	LCL	UCL
PM_{10} > 100, d/yr	30 days/yr	0.929	0.857	1.007	1.062	0.971	1.162
PM_{10} mean	20 µg/m^3	0.933	0.836	1.042	1.082	0.943	1.212
SO_4 mean	5 µg/m^3	0.95	0.793	1.138	1.006	0.926	1.086
O_3 > 100 ppb, h/yr	551 h/yr (IQR)	0.88	0.76	1.02	1.06	0.87	1.29
O_3 mean	10 ppb	0.975	0.865	1.099	1.066	0.92	1.236
SO_2 mean	3.72 (IQR)	1.02	0.9	1.15	1.01	0.86	1.18

LCL = Lower 95% confidence limit UCL = Upper 95% confidence limit

Source: Abbey et al. (1999).

TABLE 8-10. RELATIVE RISK OF MORTALITY FROM LUNG CANCER BY AIR POLLUTANT AND BY GENDER FOR AN ALTERNATIVE COVARIATE MODEL

Pollution Index	Pollution Increment	Smoking Category	Females			Males		
			RR	LCL	UCL	RR	LCL	UCL
PM_{10} > 100, d/yr	30 days/yr	All[1]	1.055	0.657	1.695	1.831	1.281	2.617
PM_{10} mean	20 µg/m^3	All	1.267	0.652	2.463	2.736	1.455	5.147
NO_2 mean	19.78 (IQR)	All	2.81	1.15	6.89	1.82	0.93	3.57
O_3 > 100 ppb, h/yr	551 h/yr (IQR)	All	1.39	0.53	3.67	4.19	1.81	9.69
		never smoker				6.94	1.12	43.08
		past smoker				4.25	1.5	12.07
O_3 mean	10 ppb	All	0.805	0.436	1.486	1.853	0.994	3.453
SO_2 mean	3.72 (IQR)	All	3.01	1.88	4.84	1.99	1.24	3.2
		never smoker	2.99	1.66	5.4			

[1]All = both never smokers and past smokers.
LCL = Lower 95% confidence limit. UCL = Upper 95% confidence limit.

Source: Abbey et al. (1999).

significant for both males and females. This pattern is not readily interpretable, but is reasonably attributable to the very small numbers of cancer-related deaths (18 for females and 12 for males), resulting in wide RR confidence intervals and very imprecise effects estimates.

The analyses reported by Abbey et al. (1999) attempted to separate PM_{10} effects from those of other pollutants by use of two-pollutant models, but no quantitative findings from such models were reported. Abbey et al. did mention that the PM_{10} coefficient for CRC remained stable or increased when other pollutants were added to the model. Lung cancer mortality models for males evaluated co-pollutant effects in detail and indicated that NO_2 was non-significant in all two-pollutant models but the other pollutant coefficients were stable. The PM_{10} and O_3 effects remained stable when SO_2 was added, suggesting possible independent effects, but PM_{10} and O_3 effects were hard to separate because these pollutants were highly correlated in this study. Again, however, the very small number of lung cancer observations and likely great imprecision of reported effects estimates markedly limit the weight that should be accorded to these results.

Other analyses, by Beeson et al. (1998), evaluated essentially the same data as in Abbey et al. (1999), but focused on lung cancer incidence (1977-1992). There were only 20 female and 16 male lung cancer cases among the 6,338 subjects. Exposure metrics were constructed to be specifically relevant to cancer, these being the annual average of monthly exposure indices from January, 1973 through the following months but ending 3 years before date of diagnosis (i.e., representing a 3-year lag between exposure and diagnosis of lung cancer). The covariates in the Cox proportional hazards model were pack-years of smoking and education, and the time variable was attained age. Many additional covariates were evaluated for inclusion, but only ‘current use of alcohol’ met criteria for inclusion in the final model. Pollutants evaluated were PM_{10}, SO_2, NO_2, and O_3. No interaction terms with the pollutants proved to be significant, including outdoor exposure times. The RR estimates for male lung cancer cases were: (a) positive and statistically significant for all PM_{10} indicators; (b) positive and mostly significant for O_3 indicators, except for mean O_3, number of O_3 exceedances > 60 ppb, and in former smokers; (c) positive and significant for mean SO_2, except when restricted to proximate monitors; and (d) positive but not significant for mean NO_2. When analyses are restricted to the use of air quality data within 32 km of the residences of subjects, the RR over the IQR of 24 $\mu g/m^3$ in the full data set is 5.21 (or RR=1.99 per 10 $\mu g/m^3$ PM_{10}). The female RR’s were all much smaller than for males, their being significant for mean SO_2 but not for any indicator of PM_{10} or O_3.

The AHSMOG investigators also attempted to compare effects of fine versus coarse particles (McDonnell et al, 2000). For AHSMOG participants living near an airport (n = 3,769), daily $PM_{2.5}$ levels were estimated from airport visibility using previously-described methods (Abbey et al, 1995b). Given the smaller numbers of subjects in these subset analyses, it is not necessarily surprising that no pollutants were found to be statistically significant, even based on analysis for the male subset near airports (n = 1266). It is important to caveat that (a) the $PM_{2.5}$ exposures were estimated from visibility measurements (increasing exposure measurement error) and yielded a very uneven and clustered distribution of estimated exposures and; (b) the $PM_{10-2.5}$ values were calculated from the differencing of PM_{10} and $PM_{2.5}$, likely adding more measurement error for the coarse particle ($PM_{10-2.5}$) variable.

8.2.3.2.4 The EPRI-Washington University Veterans' Cohort Mortality Study

Lipfert et al. (2000b) reported preliminary results from large-scale mortality analyses for a prospective cohort of up to 70,000 men assembled by the U.S. Veterans Administration (VA) in the mid-1970s. While much smaller than the ACS cohort, this VA study group is similar in that it was not originally formed to study air pollution, but was later linked to air pollution data collected separately, much of it subsequent to the start of the study. The AHSMOG and Six City studies were designed as prospective studies to evaluate long-term effects of air pollution and had concurrent air pollution measurements. The ACS study was also a prospective study, using air pollution data obtained at about the approximate time of enrollment but not subsequently (Pope et al., 1995). The extended ACS data incorporated much more air pollution data, including TSP data back to the 1960s and more recent fine particle data. The VA $PM_{2.5}$ data set was smaller than the TSP data set and similar to the ACS data.

The VA study cohort was male, middle-aged (51 ± 12 years) and included a larger proportion of African-Americans (35%) than the U.S. population as a whole and a large percentage of current or former smokers (81%). The cohort was selected at the time of recruitment as being mildly to moderately hypertensive, with screening diastolic blood pressure (DBP) in the range 90 to 114 mm Hg (mean 96, about 7 mm more than the U.S. population average) and average systolic blood pressure (SBP) of 148 mm Hg. The subjects had all been healthy enough to be in the U.S. armed forces at one time. A comparison of their pre-existing health status at time of study recruitment versus the initial health status of the other cohorts would be of interest. The study that led to the development of this clinical cohort (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970; 1967) was a "landmark" VA cooperative study demonstrating that anti-hypertensive treatment markedly decreased morbidity and mortality (Perry et al., 1982). The clinical cohort itself involved actual clinical rather than research settings. Some differences between the VA cohort and other prospective cohorts are noted below.

Pollutant levels of the county of residence at the time of entry into the study were used for analyses versus levels at the VA hospital area. Contextual socioeconomic variables were also assembled at the ZIP-code and county levels. The ZIP-code level variables were average education, income, and racial mix. County-level variables included altitude, average annual heating-degree days, percentage Hispanic, and socioeconomic indices. Census-tract variables included poverty rate and racial mix. County-wide air pollution variables included TSP, PM_{10}, $PM_{2.5}$, PM_{15}, $PM_{15\text{-}2.5}$, SO_4, O_3, CO, and NO_2 levels at each of the 32 VA clinics where veterans were enrolled. Besides considering average exposures over the entire period, three sequential mortality follow-up periods (1976-81, 1982-88, 1989-96) were also evaluated in separate statistical analyses that attempted to relate mortality in each of those periods to air pollution in different preceding, concurrent, or subsequent periods (i.e., up to 1975, 1975-81, 1982-88, and 1989-86, for TSP in the first three periods, PM_{10} for the last, and NO_2, 95th percentile O_3, and 95th percentile CO for all four periods). Mortality in the above-noted periods was also evaluated in relation to SO_4 in each of the same four periods noted for NO_2, O_3, and CO, and to $PM_{2.5}$, PM_{15}, and $PM_{15\text{-}2.5}$ in 1979-81 and 1982-84.

The participants in the VA Cohort clearly formed an "at-risk" population, and the results by Vasan et al. (2001) make more plausible the hypothesis stated in Lipfert et al. (2000b, p. 62) that ". . . the relatively high fraction of mortality within this cohort may have depleted it of susceptible individuals in the later periods of follow-up." The use of diastolic and systolic blood pressure in the reported regression results may require further evaluation. The role of DBP and SBP as predictors in regression models in the VA Cohort may be considered as closer to the endpoint (mortality) than as a more distal behavioral, environmental, or contextual predictor of mortality such as air pollution, temperature, smoking behavior, BMI, etc. Personal-level variables tend to interact only with each other, as do county-level variables, with little correlation across spatial scales.

The estimated mean risk of cigarette smoking in this cohort (RR = 1.43) is also smaller than that of the Six City cohort (RR = 1.59) and the ACS cohort (RR = 2.07 for current smokers). Some possible differences include the higher proportion of former or current smokers in this cohort (81%) versus 51% in the ACS study and 42 to 53% in the Six City study. A possibly more important factor may be the difference in education levels, as only 12% of the ACS participants had less than a high school education vs 28% of the Six City cohort. Education level was not reported for the VA Cohort. Education differences may be associated with smoking behavior, and the large number of interaction terms used in the VA study model may also partially to account for differences in results obtained across the three ACS, Six-City, VA) studies.

The preliminary screening models used proportional hazards regression models (Miller et al., 1994) to identify age, SBP, DBP, BMI (nonlinear), age and race interaction terms, and present or former smoking as baseline predictors, with one or two pollution variables added. In the final model using 233 terms (of which 162 were interactions of categorized SBP, DBP, and BMI variables with age), the most significant non-pollution variables were SBP, DBP, BMI, and their interactions with age, smoking status, average education, race, poverty, height, and a clinic-specific effect. Lipfert et al. (2000b) noted that the risk of current cigarette smoking (1.43) that they found was lower than reported in other studies. The most consistently positive effects were found for O_3 and NO_2 exposures in the immediately preceding years. This study used peak O_3 rather than mean O_3 as in some other cohort studies. This may account for the higher O_3 and NO_2 effects here. While the PM analyses considering segmented (shorter) time periods gave differing results (including significantly negative mortality coefficients for some PM metrics), when methods consistent with the past studies were used (i.e., many- year average PM concentrations), similar results were reported: the authors found that "(t)he single-mortality-period responses without ecological variables are qualitatively similar to what has been reported before ($SO_4 \geq PM_{2.5} > PM_{15}$)." With ecological variables included, the only significant PM effect was that of TSP up to 1981 on 1976-81 mortality. It might be instructive to evaluate more parsimonious regression models with fewer ecological covariates and interaction terms. It is noteworthy that estimated PM effects appear to be smaller in the later years of the study rather than in the earlier years. This may also be due to cohort depletion. Overall, the authors concluded that "the implied mortality risks of long-term exposure to air pollution were found to be sensitive to the details of the regression model, the time period of exposure, the locations included, and the inclusion of ecological as well as personal variables."

In a follow-up study of the Veterans' Cohort Study, Lipfert et al. (2003) investigated the importance of blood pressure (BP) as a covariate in studies of long-term associations between air quality and mortality. The aims of the article were to summarize quantitative relationships between BP and mortality, to discuss the available information on associations between air quality and BP, and to present results of a proportional hazard regression sensitivity analysis for the Veterans' Cohort. The relationship between BP and air quality was considered by reviewing the literature, by deleting variables from the Veterans' Study proportional hazards regression models, and by stratifying the authors' analyses of that cohort by diastolic blood pressure (DBP) level. The literature review found BP to be an important predictor of survival and found small transient associations between air quality and BP that may be either positive or negative. The regression model sensitivity runs indicated that the Lipfert et al model associations with air pollution were robust to the deletion of the BP variables for the entire cohort. For stratified regressions, the confidence intervals for the air pollution-mortality associations overlapped for the two DBP groups. The authors concluded that there is scant evidence that air pollution affects blood pressure in either healthy or impaired subjects. They go on to note that the inclusion of BP variables is not strictly essential to derive valid estimates of air pollution responses, concluding overall that the associations between air quality and mortality are not mediated through blood pressure.

8.2.3.2.5 Relationship of AHSMOG, Six Cities, ACS and VA Study Findings

The results of the more recent AHSMOG mortality analyses (Abbey et al., 1999; McDonnell et al., 2000) are compared here with findings from the earlier Six Cities study (Dockery et al., 1993), the ACS study (Pope et al., 1995), the HEI reanalyses of the latter two studies, the extension of the ACS study (Pope et al., 2002), and the VA study (Lipfert et al., 2000b). Table 8-11 compares the estimated RR for total, cardiopulmonary, and cancer mortality among the studies. The number of subjects in these studies varies greatly: 8,111 subjects in the

TABLE 8-11. COMPARISON OF EXCESS RELATIVE RISKS OF LONG-TERM MORTALITY IN THE HARVARD SIX CITIES, ACS, AHSMOG, AND VA STUDIES

		Total Mortality		Cardiopulmonary Mortality		Lung Cancer Mortality	
Study	**PM**[1]	**Ex. RR**[2]	**95% CI**	**Ex. RR**	**95% CI**	**Ex. RR**	**95% CI**
Six City[3]	$PM_{2.5}$	13%	(4.2, 23%)	18%	(6.0, 32%)	18%	(−11, 57%)
Six City New[4]	$PM_{2.5}$	14%	(5.4, 23%)	19%	(6.5, 33%)	21%	(−8.4, 60%)
ACS[5]	$PM_{2.5}$	6.6%	(3.5, 9.8%)	12%	(6.7, 17%)	1.2%	(−8,7, 12%)
ACS[6] New	$PM_{2.5}$	7.0%	(3.9, 10%)	12%	(7.4, 17%)	0.8%	(−8.7, 11%)
ACS New	$PM_{15\text{-}2.5}$	0.4%	(−1.4, 2.2%)	0.4%	(−2.2%, 3.1%)	−1.2%	(−7.3%, 5.1%)
ACS New	$PM_{10/15}$ Dichot	4.1%	(0.9, 7.4%)	7.3%	(3.0, 12%)	0.8%	(−8.1, 11%)
ACS New	$PM_{10/15}$ SSI	1.6%	(−0.8, 4.1%)	5.7%	(2.5, 9.0%)	−1.6%	(−9.1, 6.4%)
ACS Extend.[7]	$PM_{2.5}$ 1979-83	4.1%	(0.8, 7.5%)	5.9%	(1.5, 10%	8.2%	(1.1, 16%)
ACS Extend.	$PM_{2.5}$ 1999-000	5.9%	(2.0, 9.9%)	7.9%	(2.3, 14%)	12.7%	(4.1, 22%)
ACS Extend.	$PM_{2.5}$ Avg.	6.2%	(1.6, 11%)	9.3%	(3.3, 16%)	13.5%	(4.4, 23%)
AHSMOG[8]	$PM_{10/15}$	2.1%	(−4.5, 9.2%)	0.6%	(−7.8, 10%)	81%	(14, 186%)
AHSMOG[9]	$PM_{2.5}$	8.5%	(−2.3, 21%)	23%	(−3.0, 55%)	39%	(−21, 150%)
AHSMOG[10]	$PM_{10\text{-}25}$	5.2%	(−8.3, 21%)	20%	(−13, 64%)	26%	(−38, 155%)
VA[10]	$PM_{2.5}$	−10.0%	(−15, −4.6%)				

[1]Increments are 10 µg/m^3 for $PM_{2.5}$ and 20 µg/m^3 for $PM_{10/15}$.
[2]Ex.RR (excess relative risk, percent) = 100 * (RR - 1) where the RR has been converted from the highest-to-lowest range to the standard increment (10 or 20) by the equation.
RR = exp(log(RR for range) × /range).
[3]From (Dockery et al., 1993; Krewski et al., 2000, Part II, Table 21a), original model.
[4]From (Krewski et al., 2000), Part I, Table 21c.
[5]From (Krewski et al., 2000), Part I, Table 25a.
[6]From (Krewski et al., 2000), Part I, Table 25c.
[7]From (Pope et al., 2002).
[8]From (Abbey et al., 1999), pooled estimate for males and females.
[9]From (McDonnell et al., 2000), using two-pollutant (fine and coarse particle) models; males only.
[10]Males only, exposure period 1979-81, mortality 1982-88 from Table 7 (Lipfert et al., 2000b).

Six-Cities Study; 295,223 subjects in the 50 fine particle ($PM_{2.5}$) cities and 552,138 subjects in the 151 sulfate cities of the ACS Study; 6,338 in the AHSMOG Study; and 70,000 in the VA study. This may partially account for differences among their results.

The Six Cities study found significant associations of $PM_{2.5}$ with total and cardiopulmonary (but not lung cancer) mortality, but not with coarse particle indicators. In the Krewski et al. (2000) reanalysis of the ACS study data, significant associations were found for both $PM_{2.5}$ and PM_{15} (excess relative risks of 6.6% for 10 μg/m^3 $PM_{2.5}$ and 4% for 20 μg/m^3 increments in annual $PM_{10/15}$, respectively). The results most recently reported for the AHSMOG study (Abbey et al., 1999; McDonnell et al., 2000) used PM_{10} as its PM mass index and found some significant associations with total mortality and deaths with contributing respiratory causes, even after controlling for potentially confounding factors (including other pollutants). However no pattern of consistent, statistically significant associations between mortality and long-term PM exposure was found. The VA study (Lipfert et al., 2000b), also did not find any association with $PM_{2.5}$. The lack of consistent findings in the AHSMOG study and negative results of the VA study, do not negate the findings of the Six Cities and ACS studies: the ACS studies had a substantially larger study population, and both the Six Cities and ACS studies were based on measured PM data (in contrast with AHSMOG PM estimates based on TSP or visibility measurements) and have been supported through exhaustive reanalyses. The results of these studies, including the reanalyses results for the Six Cities and ACS studies and the results of the ACS study extension, provide substantial evidence for positive associations between long-term ambient PM (especially fine PM) exposure and mortality.

There is no clear consistency in relationships among PM effect sizes, gender, and smoking status across these studies. The AHSMOG study cohort is a primarily nonsmoker group while the VA study cohort had a large proportion of smokers and former smokers in an all-male population. The ACS results show similar and significant associations with total mortality for both “never smokers” and “ever smokers”, although the ACS cohort may include a substantial number of long-term former smokers with much lower risk than current smokers. The Six Cities study cohort shows the strongest evidence of a higher PM effect in current smokers than in non-smokers, with female former smokers having a higher risk than male former smokers. This study suggests that smoking status may be viewed as an effect modifier for ambient PM, just as smoking may be a health effect modifier for ambient O_3 (Cassino et al., 1999).

When the ACS study results are compared with the AHSMOG study results for SO_4^{-2} ($PM_{10\text{-}2.5}$ and PM_{10} were not considered in the ACS study, but were evaluated in ACS reanalyses [Krewski et al., 2000; Pope et al, 2002]), the total mortality effect sizes per 15 μg/m³ SO_4^{-2} for the males in the AHSMOG population fell between the Six-Cities and the ACS effect-size estimates for males (RR = 1.28 for AHSMOG male participants; RR=1.61 for Six-Cities Study male non-smokers; and RR = 1.10 for never smoker males in the ACS study), and the AHSMOG study 95% confidence intervals encompass both of those other studies' sulfate RR's.

8.2.3.2.6 The S-Plus GAM Convergence Problem and Cohort Studies

The long-term pollution-mortality study results discussed above in this section were unaffected by the GAM default convergence issue reported by Dominici et al. (2002) and discussed earlier in this chapter, because they did not use such a model specification. Instead, the cohort studies of long-term PM exposures used Cox Proportional Hazards models. For example, in the recent Pope et al. study (2002), the baseline models were random effects Cox Proportional Hazards models without the inclusion of nonparametric smooths. However, Pope et al. (2002) did include a non-parametric spatial smooth in the model as part of a more extended sensitivity analysis to evaluate more aggressive control of spatial differences in mortality. They found that the estimated pollution-mortality effects were not sensitive to this additional spatial control, so final reported results did not include the smooth; and this study's results, like those from other cohort studies discussed above, were unaffected by the S-Plus convergence issue.

8.2.3.3 Studies by Particulate Matter Size-Fraction and Composition

8.2.3.3.1 Six Cities, ACS, and AHSMOG Study Results

Ambient PM consists of mixtures that may vary in composition over time and from place to place. This should logically affect the relative toxicity of PM indexed by mass at different times or locations. Some semi-individual chronic exposure studies have investigated relative roles of various PM components in contributing to observed air pollution associations with mortality. However, only a limited number of the chronic exposure studies have included direct measurements of chemical-specific constituents of the PM mixes indexed by mass measurements used in their analyses.

As shown in Table 8-12, the Harvard Six-Cities Study (Dockery et al., 1993) results indicated that the $PM_{2.5}$ and SO_4^{-2} RR associations (as indicated by their respective 95% CI's and t-statistics) were more consistent than those for the coarser mass components. Further, the effects of sulfate and non-sulfate $PM_{2.5}$ are quite similar. Acid aerosol (H^+) exposure was also considered by Dockery et al. (1993), but only less than one year of measurements collected near the end of the follow-up period were available in most cities; consequently, the Six-Cities results were much less conclusive for the acidic component of PM than for the other PM metrics measured over many years during the study.

TABLE 8-12. COMPARISON OF ESTIMATED RELATIVE RISKS FOR ALL-CAUSE MORTALITY IN SIX U.S. CITIES ASSOCIATED WITH THE REPORTED INTER-CITY RANGE OF CONCENTRATIONS OF VARIOUS PARTICULATE MATTER METRICS

PM Species	Concentration Range ($\mu g/m^3$)	Relative Risk Estimate	RR 95% CI	Relative Risk t-Statistic
$SO_4^=$	8.5	1.29	(1.06-1.56)	3.67
$PM_{2.5}$ - $SO_4^=$	8.4	1.24	(1.16-1.32)	8.79
$PM_{2.5}$	18.6	1.27	(1.06-1.51)	3.73
$PM_{15-2.5}$	9.7	1.19	(0.91-1.55)	1.81
TSP-PM_{15}	27.5	1.12	(0.88-1.43)	1.31

Source: Dockery et al. (1993); U.S. Environmental Protection Agency (1996a).

Table 8-13 presents comparative $PM_{2.5}$ and SO_4^{-2} results from the ACS study, indicating that both had substantial, statistically significant effects on all-cause and cardiopulmonary mortality. On the other hand, the RR for lung cancer was notably larger (and substantially more significant) for SO_4^{-2} than $PM_{2.5}$ (not significant). The most recent AHSMOG analyses also considered SO_4^{-2} as a PM index for all health outcomes studied except lung cancer, but SO_4^{-2} was not as strongly associated as PM_{10} with mortality and was not statistically significant for any mortality category.

TABLE 8-13. COMPARISON OF REPORTED $SO_4^{=}$ AND $PM_{2.5}$ RELATIVE RISKS FOR VARIOUS MORTALITY CAUSES IN THE AMERICAN CANCER SOCIETY (ACS) STUDY

Mortality Cause	**$SO_4^{=}$ (Range = 19.9 μg/m^3)**			**$PM_{2.5}$ (Range = 24.5 μg/m^3)**		
	Relative Risk	RR 95% CI	RR t-Statistic	Relative Risk	RR 95% CI	RR t-Statistic
All Cause	1.15	(1.09-1.22)	4.85	1.17	(1.09-1.26)	4.24
Cardiopulmonary	1.26	(1.15-1.37)	5.18	1.31	(1.17-1.46)	4.79
Lung Cancer	1.35	(1.11-1.66)	2.92	1.03	(0.80-1.33)	0.38

Source: Pope et al. (1995).

Also, extensive results were reported in Lipfert et al. (2000b) for various components: TSP, PM_{10}, $PM_{2.5}$, $PM_{15\text{-}2.5}$, PM_{15}, SO_4^{-2}. There were no significant positive effects for any exposure period concurrent or preceding the mortality period for any PM component, unlike for O_3.

Harvard Six Cities, ACS, and AHSMOG study results are compared in Table 8-14 (total mortality) and Table 8-15 (cause-specific mortality). Results for the VA study are not shown in Tables 8-14 and 8-15 for two reasons: (a) the VA cohort is all male and largely consists of current or former smokers (81%) and is thusly not comparable to the total or male non-smoker populations of the other studies; and (b) the VA study analyzed a wide variety of exposure periods and mortality periods, making it difficult to summarize or compare with the other results. Also, results for females are not presented, as the overall effects were driven largely by males (female associations generally being statistically nonsignificant).

Estimates for Six Cities parameters were calculated in two ways: (1) mortality RR for the most versus least polluted city in Table 3 of Dockery et al. (1993), adjusted to standard increments; and (2) ecological regression fits in Table 12-18 of U.S. Environmental Protection Agency (1996a). The Six Cities study of eastern and mid-western U.S. cities suggests a strong and highly significant relationship for fine particles and sulfates, a slightly weaker but still highly significant relationship to PM_{10}, and a marginal relationship to $PM_{10\text{-}2.5}$. The ACS study looked at a broader spatial representation of cities, and found a stronger statistically significant relationship to $PM_{2.5}$ than to sulfate (no other pollutants were examined). The AHSMOG study

TABLE 8-14. COMPARISON OF TOTAL MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 µg/m^3)	Six Cities	All	1.50[a]; 1.53[b]	2.94[a]; 3.27[b]
		Male Nonsmoker	1.28[a]	0.81[a]
	AHSMOG	Male Nonsmoker	1.24	1.61
$PM_{2.5}$ (25 µg/m^3)	Six Cities	All	1.36[a]; 1.38[b]	2.94[a]; 3.73[b]
		Male Nonsmoker	1.21[a]	0.81[a]
	ACS (50 cities)	All	1.17	4.35
		Male Nonsmoker	1.25	1.96
SO_4 = (15 µg/m^3)	Six Cities	All	1.50[a]; 1.57[b]	2.94[a]; 3.67[b]
		Male Nonsmoker	1.35	0.81[a]
	ACS (151 cities)	All	1.11	5.11
		Male Nonsmoker	1.1	1.59
	AHSMOG	Male Nonsmoker	1.28	0.96
Days/yr. with PM_{10} > 100 µg/m^3 (30 days)	AHSMOG	Male Nonsmoker	1.08	2.18
$PM_{10-2.5}$ (25 µg/m^3)	Six Cities	All	1.81[a]; 1.56[b]	2.94[a,c] 1.81[b]
		Male Nonsmoker	1.43[a]	0.81[a]

[a]Method 1 compares Portage versus Steubenville (Table 3, Dockery et al., 1993).
[b]Method 2 is based on ecologic regression models (Table 12-18, U.S. Environmental Protection Agency, 1996a).
[c]Method 1 not recommended for $PM_{10-2.5}$ analysis, due to high concentration in Topeka.

at California sites (where sulfate levels are typically low) found significant effects in males for PM_{10} 100 µg/m^3 exceedances and a marginal effect of mean PM_{10}, but no PM effects for females or with sulfates. On balance, the overall results shown in Tables 8-14 and 8-15 suggest statistically significant relationships between long-term exposures to PM_{10}, $PM_{2.5}$, and/or sulfates and excess total and cause-specific cardiopulmonary mortality.

The semi-individual long-term PM exposure studies conducted to date collectively appear to confirm earlier cross-sectional study indications that the fine mass component of PM_{10} (and

TABLE 8-15. COMPARISON OF CARDIOPULMONARY MORTALITY RELATIVE RISK ESTIMATES AND T-STATISTICS FOR PARTICULATE MATTER COMPONENTS IN THREE PROSPECTIVE COHORT STUDIES

PM Index	Study	Subgroup	Relative Risk	t Statistic
PM_{10} (50 µg/m^3)	Six Cities	All	1.744[a]	2.94[a]
	AHSMOG	Male Nonsmoker	1.219	1.12
		Male Non-CRC[c]	1.537	2.369
$PM_{2.5}$ (25 µg/m^3)	Six Cities	All	1.527[a]	2.94[a]
	ACS (50 cities)	All	1.317	4.699
		Male	1.245	3.061
		Male Nonsmoker	1.245	1.466
SO_4= (15 µg/m^3)	Six Cities	All	1.743[a]	2.94[a]
	ACS (151 cities)	All	1.19	5.47
		Male	1.147	3.412
		Male Nonsmoker	1.205	2.233
	AHSMOG	Male Nonsmoker	1.279	0.072
		Male Non.-CRC[c]	1.219	0.357
Days/yr. with PM_{10} > 100 (30 days)	AHSMOG	Male Nonsmoker	1.082	1.31
		Male Non.-CRC[c]	1.188	2.37
$PM_{10-2.5}$ (25 µg/m^3)	Six Cities	All	2.251[a]	2.94[a,b]

[a]Method 1 compares Portage versus Steubenville (Table 3, Dockery et al., 1993).
[b]Method 1 not recommended for $PM_{10-2.5}$ analysis due to high concentration in Topeka.
[c]Male non. - CRC = AHSMOG subjects who died of any contributing non-malignant respiratory cause.

usually especially its sulfate constituent) are more strongly correlated with mortality than is the coarse $PM_{10-2.5}$ component. However, the greater precision of $PM_{2.5}$ population exposure measurement (both analytical and spatial) relative to $PM_{10-2.5}$ makes conclusions regarding their relative contributions to observed PM_{10}-related associations less certain than if the effect of their relative errors of measurement could be addressed.

8.2.3.3.2 Lipfert and Morris (2002): An Ecological Study

Although reasons were identified for preferring to use prospective cohort studies to assess the long-term exposure effects of particles and gases, additional useful information may still be derived from ecological studies, particularly by repeated cross-sectional studies that may provide another tool for examining changes in air-pollution-attributable mortality over time. Lipfert and Morris (2002) carried out cross-sectional regressions for five time periods using published data on mortality, air pollution, climate, and socio-demographic factors using county- level data. Data were available for TSP and gaseous co-pollutants as far back as 1960 and for $PM_{2.5}$, PM_{15}, and $SO_4^{=}$ from the inhalable particular network (IPN). Attributable mortality at ages 45+ for 1979-1981 was reported to be associated with 1960-64 TSP, less strongly with 1970-1974 TSP, but not with concurrent (1979-1981) TSP. Attributable mortality for ages 45+in 1979-1981 was associated with $PM_{2.5}$ and SO_4^{-2} but not with PM_{15} for 1979-1984. However, SO_4^{-2} for most intervals from 1960-64 up to 1979-1981 was associated with mortality for most ages. Concurrent SO_2 (1979-1981) was associated with mortality, but much less for earlier years.

Pollution-attributable mortality in 1989-91 was no longer significantly associated with TSP, but remained significantly associated with $PM_{2.5}$ and SO_4^{-2} for ages 45+ for most time intervals: 1979-84 and 1999 for $PM_{2.5}$; 1970-74, 1979-81, 1979-84 for fine); and 1982-88 for SO_4^{-2}. Pollution-attributable mortality in 1995-1997 had little association with present or previous $PM_{2.5}$ and PM_{10}, but a reasonably consistent and positive relationship to SO_4^{-2}. There appeared to be a systematic decrease in the TSP, IPN, $PM_{2.5}$, and PM_{10} effects from the 1960s to the 1990s and in the AIRS and IPN SO_4^{-2} effect over time, but an increase in the AIRS $PM_{2.5}$ effect and in the NO_2 and peak O_3 effects.

One of the journal editors (Ayres, 2002) notes that this study uses some other ecological variables that might improve the model. Two of the ecological variables, vehicle miles of travel per square mile per year by gasoline (VMTG) and diesel (VMTD) vehicles, respectively, in a county (also used in Janssen et al., 2002) are likely to have important associations with air pollution. As noted earlier, some ambient pollutants associated with fuel combustion have higher concentrations near main roads, such as $PM_{10-2.5}$ (EC if from diesel exhaust) , NO_2, and CO; whereas other pollutants (such as O_3) may have higher concentrations away from major highways. Similarly, some models employed included the percentage of air conditioning in a county, a factor that may well be correlated with greater secondary aerosol formation in warmer temperatures and is likely associated with diminished exposure to air pollution, resulting in smaller acute health effects per µg/m^3 of PM pollution (Janssen et al, 2002). Given these potentially confounding terms in this study's model, it is not surprising that the authors find somewhat lower percentage increases in mortality per µg/m^3 of PM than in the above-discussed cohort studies.

8.2.3.3.3 Mortality and Chronic Exposure to Traffic-Related Ambient PM

Although not a study of PM mass, a recent study of the potential mortality effects of long-term exposure to PM air pollution conducted in the Netherlands gives insight into the potential role of long-term effects of PM from traffic origins in the PM mass-mortality association. Hoek et al (2002) aimed to assess the relation between traffic-related air pollution and mortality in participants of the Netherlands Cohort study on Diet and Cancer (NLCS), an ongoing study. They investigated a random sample of 5000 middle-aged people (aged 55-69 years) from the full cohort of the NLCS study during 1986 to 1994. Long-term exposure to traffic-related air pollutants (using black smoke, BS, and nitrogen dioxide, NO_2, as indicators) was estimated for participants' 1986 home address. The authors noted that, in the Netherlands, black smoke is primarily derived from diesel emissions, while NO_2 is from all motorized vehicles. The authors did not consider tracers for other sources of PM, however, so this study did not investigate or preclude effects from other PM source categories. This long-term study is unique in that it examined within metropolitan area small-scale variations in exposures. Exposure was characterized with the measured regional and urban background concentration, as well as using an indicator variable for living near major roads. The association between exposure to air pollution and (cause specific) mortality was assessed with Cox's proportional hazards models, with adjustment for potential confounders. Cardiopulmonary mortality was associated with living near a major road (relative risk 1.95, 95% CI 1.09-3.52), and with background plus local BS (1.71, 1.10-2.67), but not as significantly with the estimated ambient background BS concentration (1.34, 0.68-2.64) or background plus local NO2 (1.81, 0.98-3.34). The relative risk for living near a major road was 1.41 (0.94-2.12) for total deaths. The fact that BS exposure was statistically significantly associated with cardio-pulmonary deaths, but not NO_2, suggests a greater role for diesel particles in the reported associations with living near major roads than for traffic in general. Non-cardiopulmonary, non-lung cancer deaths were unrelated to air pollution

(1.03, 0.54-1.96 for living near a major road); but, discussing the lung cancer results, the authors noted that "the number of cases was small in our study, leading to wide CIs." The authors considered the potential role of residual confounding factors, finding that the unadjusted effects estimates were consistently similar to the effects after adjustment for confounders, and concluding that residual confounding was very unlikely to account for the association between living near a major road and mortality. The authors conclude that long-term exposure to traffic-related air pollution may shorten life expectancy, but note that the local scale PM is mostly characterized by fresh emissions high in ultrafines, while the (more weakly associated) background aerosol is more aged. These differences in ambient PM characteristics may therefore account for the apparent local traffic PM toxicity, rather than its specific source.

8.2.3.4 Recent PM-Mortality Intervention Studies

Although numerous studies have reported short-term associations between PM indices and mortality, a question remains whether a reduction in PM actually leads to a reduction in the deaths that are attributable to PM. This question is important in terms of "accountability" from the regulatory point of view, but it is also a scientific question that demands the validity of the statistical models and their underlying assumptions used to estimate the excess mortality due to PM. The opportunities to address this question are rare, however. There had not been a PM-mortality intervention study (or a study designed as such) published at the time of the 1996 PM CD. However, in Pope et al.'s (1992) analysis of daily mortality and PM_{10} in Utah Valley, the study period did contain the 13-month steel mill closure mentioned above, and the authors noted that the excess deaths estimated for the period when the mill was open, based on the PM_{10} slope obtained from the entire study period (~4.5 years), was 2.3% (for 15 $\mu g/m^3$ PM_{10} difference), as compared to the actual excess average deaths for that period, 3.2%. Thus, the study did suggest some internal consistency between the intervention period and the rest of the study period. There are two new mortality intervention studies that examined: (1) the impact of the ban on coal sale in Dublin, Ireland (Clancy et al., 2002); and (2) the impact of the regulation to use fuel oil with low sulfur content in Hong Kong (Hedley et al., 2002). These regulations were enforced in very short time frame such that they provided opportunities to observe any change in mortality rate before and after the intervention. These studies are reviewed in the following paragraphs.

Clancy et al. (2002) examined the impact of the ban on coal sales that took place in September 1990 in the city of Dublin, Ireland. They assessed the ban's impact on mortality by conducting Poisson regression of the standardized mortality rate during 72 months before and after the ban on coal sales (13 years total study period), adjusting for temperature on the same day and previous days, mean relative humidity and previous days, day-of-week, respiratory epidemics, and directly standardized deaths rates in the rest of Ireland. The impact of the ban was estimated by an indicator variable of the post-ban period. They also reported means of Black Smoke (BS), SO_2, temperature and relative humidity before and after the ban by season, as well as age-standardized deaths rates before and after the ban by seasons. A substantial reduction (35.6 µg/m^3 reduction, or 70% for all seasons) in BS, especially for winter season (63.8 µg/m^3 reduction) was observed. The reduction for SO_2 was less (34% reduction). The post-ban means of age-standardized mortality rates were significantly lower for total (non-accidental), cardiovascular, and respiratory categories for all seasons combined and especially for winter season. In contrast, the mean of the other mortality categories slightly increased for spring and fall (but decreased for summer). The Poisson regression results with adjustments for time-varying covariates showed significant reductions in age-standardized mortality rate for total (−5.7% [−7.2, −4.1]), cardiovascular (−10.3% [−12.6, −8.0]), and respiratory (−15.5% [−19.1, - 11.6]) mortality, but not mortality for other causes (1.7% [−0.7, 4.2]). The results without adjustments for other time-varying covariates showed larger reductions.

Clancy et al. compares their mortality reduction estimates to the expected reduction from APHEA 1 study (Katsouyanni et al., 1997). They noted that the BS mortality regression coefficient from APHEA 1 results would have translated to only 2.1% reduction in total deaths had they been applied to the Dublin data where a reduction of 35.6 µg/m^3 was observed, compared to 5.7% that Clancy and colleagues estimated for the intervention period in their analysis. They also noted that the actual reduction (~3.2% when the PM_{10} average was 15 µg/m^3 lower than the period when the mill was operating) in average deaths during the steel mill closure in Utah Valley as noted by Pope et al. (1992) would have translated to 8.0% had it been applied to the BS reduction in the Dublin data (assuming BS ≈ PM_{10}), which was the same as their unadjusted estimate (8.0%). It should be noted, however, that the reduction estimate in Clancy et al.'s study is the "average" reduction comparing the two 6-yr periods before and after the ban of coal sales. In contrast, most time-series studies, including APHEA, estimate excess mortality risk in response to a short-term change, usually a single day or a few days. As discussed in section 8.4.5, there is some suggestive evidence that risk estimates based on a single- or a few-day exposures may underestimate the possible multi-day effects. The apparent lack of the evidence for "harvesting" (see section 8.4.9.1) further suggests that the excess risk (or reduction) estimates based on the prevailing time-series study design may not predict longer-term effects. Therefore, a comparison of the estimate of reduction in mortality due to the intervention and a predicted reduction from the time-series studies is not straightforward, and it is not surprising that Clancy et al.'s estimate of mortality reduction was larger than predicted based on PM coefficients derived from most time-series studies. Nevertheless, at least qualitatively, Clancy et al.'s study provides suggestive evidence that a substantial reduction in PM leads to a reduction in mortality.

Hedley et al. (2002) assessed the impact of the restriction to use low sulfur (not more than 0.5%) fuel oil, implemented in July 1990, on mortality rate in Hong Kong. Changes in trends in deaths were estimated using Poisson regression of monthly mortality rate between 1985 and 1995, adjusting for trends, seasonal cycles (by sine/cosine terms), temperature, and relative humidity, with stratification by the two five-year pre- and post-intervention periods. They also estimated a measure of warm to cool season change in death rates relative to the mean by fitting monthly deaths as a function of sine and cosine terms for each of the five years after the intervention and by cause (total, respiratory, cardiovascular, neoplasms, and others) and by age groups (all ages, age 15-64, age 65 and older). Interestingly, while SO_2 did decease substantially (~ 50%), PM_{10} levels did not change at all after the intervention. Even sulfate level, while reported to be lower by ~ 20% for the first 2 years after the intervention, were unchanged five years after the intervention, apparently due to regional influences. O_3 showed an increase trend during study period. The seasonal mortality analysis results show that the apparent reduction in seasonal deaths rate occurred only in the first winter, and it was followed by a rebound (i.e., higher than expected) in the following winter. This pattern was seen for total, respiratory, and cardiovascular categories. Based on the Poisson regression of the monthly mortality data analysis, the average annual trend in death rate significantly declined after the intervention for all cause (2.1%), respiratory (3.9%), and cardiovascular causes (2.0%). Hedley et al. also estimated expected average gain in life expectancy per year due to the lower SO_2 level to be 20 days for females and 41 days for males.

Interpreting Hedley et al.'s results is complicated by the upward trend in mortality due to the increase in population size and aging. The result suggests that such an upward trend is less steep after the introduction of low sulfur fuel. While their Poisson regression model of monthly deaths does adjust for trend and seasonal cycles, residual confounding and/or correlation is still possible between the fitted trend and the two stratified periods of pre- and post-intervention. Also, the regression model does not specifically address the influence of influenza epidemics. Since the magnitude of influenza epidemics can change from year to year, the included sine/cosine terms will not fit the year-to-year variation. This issue also applies to the analysis of warm to cool season change in death rates. The most prominent feature of the time-series plot (or the fitted annual cycle of monthly deaths) presented in Hedley et al.'s paper is the lack of winter peak for respiratory and all cause mortality in the year following the intervention. Much could be made out of this lack of peak, but no discussion of potential impact of (a lack of) influenza epidemics is provided. These issues make the interpretation of the estimated decline in upward trend of mortality rate or the apparent lack of winter peak difficult. In any case, since the intervention did not result in the reduction of PM (PM_{10} and in this case), this study did not provide direct information on the impact of PM intervention.

Clancy et al.'s study and Hedley et al.'s study share a similar situation in which regulations caused a sudden reduction in PM and/or SO_2. Both studies estimated reductions in mortality rate before and after the intervention (6-year periods in Clancy et al. study, and 5-year periods in Hedley et al. study). Both studies attempted to adjust for unmeasured secular changes in social or other environmental system that can affect the trend in mortality rate by direct standardization or in the regression models. The challenge of these analyses is that, unlike regular time-series mortality analyses in which only the associations in short-term fluctuations are estimated by filtering out the longer-wave fluctuations, the parameter that is being estimated is in the longer-wave length where effective sample size of "events" can be small. For example, the number of influenza epidemics in these data is "small", and yet their magnitude can vary substantially from year to year, making their influence on the average statistics of long-wave events possibly large. Furthermore, because the regular short-term daily time-series studies specifically filter out these long-wave events, the PM risk coefficients derived from the daily time-series studies may not be directly compared to the estimated mortality reductions from these intervention studies. Clearly, there is uncertainty between mortality risk estimates that are derived from cohort studies (that may be capturing the very long-term effects) and the mortality risk estimates derived from daily time-series studies. These intervention studies appear to capture the risk (reduction) in a time scale that is in between these two types of studies. Thus, despite the limitations, the intervention studies are important not only for validating the PM risk derived from time-series studies, but also as a research method to investigate the time scale of PM health effects.

In summary, a quantitative comparison of the risk reduction in intervention studies and that estimated from time-series studies is difficult at this time, but Clancy et al.'s intervention study does suggest evidence of mortality reduction in response to reduced levels of PM. Hedley et al.'s intervention study also present an unique case where SO_2 levels declined substantially but PM levels did not, but the interpretation of their results is more difficult because of the lack of information on the influence of influenza epidemics.

There are also two morbidity studies that examined the intervention issue. These are Pope's (1989) study of children's respiratory admissions in Utah Valley before and after a steel mill closure due to strike, and Friedman et al.'s study (2001) to examine the impact of traffic control during the Atlanta Olympics on asthma ED visits and hospitalizations. These studies reported reductions in air pollution levels during or after the intervention and provided evidence of associated reductions in adverse health outcomes.

8.2.3.5 Ambient PM Impacts on Fetal and/or Early Postnatal Development/Mortality

Some older cross-sectional mortality studies reviewed in the 1996 PM AQCD suggested that the young may represent a susceptible sub-population for PM-related mortality. For example, Lave and Seskin (1977) found mortality among those 0-14 years of age to be significantly associated with TSP. More recently, Bobak and Leon (1992) studied neonatal (ages < 1 mo) and post-neonatal mortality (ages 1-12 mo) in the Czech Republic and reported significant and robust associations between post-neonatal mortality and PM_{10}, even after considering other pollutants. Post-neonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM_{10} remained significant in simultaneous regressions. The exposure duration was longer than a few days, but shorter than in the adult prospective cohort studies. Thus, the limited available studies reviewed in the 1996 PM AQCD were highly suggestive of an association between ambient PM concentrations and infant mortality, especially among post-neonatal infants.

More recent studies since the 1996 PM AQCD have focused specifically on ambient PM relationships to (a) intrauterine mortality and morbidity and (b) early post neonatal mortality. In a study by Pereira et al. (1998) of intrauterine (pre-natal) mortality during one year (1991-1992) in Brazil, PM_{10} was not found to be a significant predictor, but involvement of CO was suggested by an association between increased carboxyhemoglobin (CoHb) in fetal blood and ambient CO levels on the day of delivery measured in a separate study. Another study (Dejmek et al., 1999) evaluated possible impacts of ambient PM_{10} and $PM_{2.5}$ exposure (monitored by EPA-developed VAPS methods) during pregnancy on intrauterine growth retardation (IUGR) risk in the highly polluted Teplice District of Northern Bohemia in the Czech Republic during three years (1993-1996). Mean levels of pollutants (PM, NO_2, SO_2) were calculated for each month of gestation and three concentration intervals (low, medium, high) were derived for each pollutant. Preliminary analyses found significant associations of IUGR with SO_2 and PM_{10} early in pregnancy but not with NO_2. Odds ratios for IUGR for PM_{10} and $PM_{2.5}$ levels were determined by logistic regressions for each month during gestation, after adjusting for potential confounding factors (e.g., smoking, alcohol consumption during pregnancy, etc.). Definition of an IUGR birth was any one for which the birth weight fell below the 10^{th} percentile by gender and age for live births in the Czech Republic (1992-93). The ORs for IUGR were significantly related to PM_{10} during the first month of gestation: that is, as compared to low PM_{10}, the medium level PM_{10} OR = 1.47 (CI 0.99-2.16), and the high level PM_{10} OR = 1.85 (CI 1.29-2.66). $PM_{2.5}$ levels were highly correlated with PM_{10} (r = 0.98) and manifested similar patterns (OR = 1.16, CI 0.08-0.69 for medium $PM_{2.5}$ level; OR = 1.68, CI 1.18-2.40 for high $PM_{2.5}$ level). These results suggest effects of PM exposures (probably including fine particles such as sulfates, acid aerosols, and PAHs in the Teplice ambient mix) early in pregnancy (circa embryo implantation) on fetal growth and development.

Results indicating likely early post-natal PM exposure effects on neonatal infant mortality have emerged from other new studies. Woodruff et al. (1997), for example, used cross-sectional methods to evaluate possible association of post-neonatal mortality with ambient PM_{10} pollution. This study involved an analysis of a cohort of circa 4 million infants born during 1989-1991 in 86 U.S. metropolitan statistical areas (MSAs). Data from the National Center for Health Statistics-linked birth/infant death records were combined at the MSA level with PM_{10} data from EPA's Aerometric database. Infants were categorized as having high, medium, or low exposures based on tertiles of PM_{10} averaged over the first 2 postnatal months. Relationships between this early neonatal PM_{10} exposure and total and cause-specific post-neonatal mortality rates (from 1 mo to 1 y of age) were examined using logistic regression analyses, adjusting for demographic and environmental factors. Overall post-neonatal mortality rates per 1,000 live births were 3.1 among infants in areas with low PM_{10} exposures, 3.5 among infants with medium PM_{10} exposures, and 3.7 among highly PM exposed infants. After adjustment for covariates, the OR and 95% confidence intervals for total post-neonatal mortality for the high versus the low exposure group was 1.10 (CI = 1.04-1.16). For normal birth weight infants, high PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI = 1.05-1.85) and sudden infant death syndrome (OR = 1.26, CI = 1.14-1.39). Among low birth weight babies, high PM_{10} exposure was positively (but not significantly) associated with mortality from respiratory causes (OR = 1.18, CI = 0.86-1.61). However, other pollutants (e.g., CO) were not considered as possible confounders, and this lack of consideration of other air pollutants as potential confounders in this new study reduces the certainty that PM is the specific causal outdoor air pollutant in this case.

The basic findings from Woodruff et al. (1997) appear to be bolstered by a more recent follow-up study by Bobak and Leon (1999), who conducted a matched population-based case-control study covering all births registered in the Czech Republic from 1989 to 1991 that were linked to death records. They used conditional logistic regression to estimate the effects of suspended particles and nitrogen oxides on risk of death in the neonatal and early post-neonatal period, controlling for maternal socioeconomic status and birth weight, birth length, and gestational age. The effects of all pollutants were strongest in the post-neonatal period and specific for respiratory causes. Only PM showed a consistent association when all pollutants were entered in one model. Thus, in this study, it appears that long-term exposure to PM is the air pollutant metric most strongly associated with excess post-neonatal deaths.

Lipfert et al. (2000c) have reported a study using a modeling approach similar to that of Woodruff et al. (1997), but using annual-average PM_{10} air quality data for one year (1990) instead of PM_{10} averaged over the first two postnatal months during 1989-1991. The quantitative relationship between the individual risk of infant mortality did not differ among infant categories (by age, by birthweight, or by cause), but PM_{10} risks for SIDs deaths were higher for babies of smoking mothers. SO_4^{-2} was a strong negative predictor of SIDs mortality for all age and birth weight categories. The authors (a) noted difficulties in ascribing the reported PM_{10} and SO_4^{-2} associations to effects of the PM pollutants per se versus the results possibly reflecting interrelationships between the air pollution indices, a strong well-established East-West gradient in U.S. SIDS cases, and/or underlying sociodemographic factors (e.g., the socioeconomic or education level of parents) and (b) hypothesized that a parallel gradient in use of wood burning in fireplaces or woodstoves and consequent indoor wood smoke exposure might explain the observed cross-sectional study results. It is also possible that the differences in SO_4 and $PM_{2.5}$ results found from those of PM_{10} in this work may indicate a role of the coarse fraction of the PM_{10} in the Lipfert et al. (2000c) and Woodruff et al. (1997) results.

Chay and Greenstone (2001a,b) also conducted a study of changes in annual air pollution and infant mortality over time (rather than spatially) in the U.S. for the period 1981-1982. These studies used sharp, differential air quality changes across sites attributable to geographic variation in the effects of the 1981-1982 recession to estimate the relationship between PM air pollution and infant mortality. During the narrow period of these two years, there was substantial variation across counties in changes in particulate (TSP) pollution and these differential pollution reductions appeared to be independent of changes in numerous socioeconomic and health care factors that may be related to infant mortality. The authors found that a 1 ug/m^3 reduction in TSP resulted in about 4-8 fewer infant deaths per 100,000 live births at the county level (a 0.35-0.45 elasticity), the estimates being remarkably stable across a variety of specifications. The estimated effects in this study were driven almost entirely by fewer deaths occurring within one month and one day of birth (i.e., neonatal), suggesting that fetal exposure to pollution (via the mother) may have adverse health consequences. Findings of the population reductions in infant birth weight in this study provide evidence consistent with the infant mortality effects found, suggestive of a causal relationship between PM exposure and infant mortality.

The study by Loomis et al. (1999) of infant mortality in Mexico City during 1993-1995 adds additional interesting information pointing towards likely fine particle effects on infant mortality. That is, in Mexico City (where mean 24-h $PM_{2.5}$ = 27.4 $\mu g/m^3$), infant mortality was found to be associated with $PM_{2.5}$, NO_2, and O_3 in single pollutant GAM Poisson models, but much less consistently with NO_2 and O_3 than $PM_{2.5}$ in multipollutant models. The estimated excess risk for $PM_{2.5}$-related infant mortality lagged 3-5 days was 18.2% (CI = 6.4-30.7) per

25 µg/m^3 $PM_{2.5}$. The extent to which such a notable increased risk for infant mortality might be extrapolated to U.S. situations is not clear, however, due to possible differences in prenatal maternal or early postnatal infant nutritional status.

8.2.3.6 Salient Points Derived from Analyses of Chronic Particulate Matter Exposure Mortality Effects

A review of the studies summarized in the previous PM AQCD (U.S. Environmental Protection Agency, 1996a) indicates that past epidemiologic studies of chronic PM exposures collectively indicate increases in mortality to be associated with long-term exposure to airborne particles of ambient origins. The PM effect size estimates for total mortality from these studies also indicate that a substantial portion of these deaths reflected cumulative PM effects above and beyond those exerted by acute exposure events.

The recent HEI-sponsored reanalyses of the ACS and Harvard Six-Cities studies (Krewski et al., 2000) “replicated the original results, and tested those results against alternative risk models and analytic approaches without substantively altering the original findings of an association between indicators of particulate matter air pollution and mortality.” Several questions, including the questions (1-4) posed at the outset of this Section (8.2.3) were investigated by the Krewski et al. (2000) sensitivity analyses for the Six City and ACS studies data sets. Key results emerging from the HEI reanalyses and other new chronic PM mortality studies are as follow:

(1) A much larger number of confounding variables and effects modifiers were considered in the Reanalysis Study than in the original Six City and ACS studies. The only significant air pollutant other than $PM_{2.5}$ and SO_4 in the ACS study was SO_2, which greatly decreased the $PM_{2.5}$ and sulfate effects when included as a co-pollutant (Krewski et al., 2000, Part II, Tables 34-38). A similar reduction in particle effects occurred in any multi-pollutant model with SO_2. The most important new effects modifier was education. The AHSMOG study suggested that other metrics for air pollution, and other personal covariates such as time spent outdoors and consumption of anti-oxidant vitamins, might be useful. Both individual-level covariates and ecological-level covariates shown in (Krewski et al., 2000, Part II, Table 33) were evaluated, including whether or not the observations are independent or spatially correlated.

(2) Specific attribution of excess long-term mortality to any specific particle component or gaseous pollutant was refined in the reanalysis of the ACS study. Both $PM_{2.5}$ and sulfate were

significantly associated with excess total mortality and cardiopulmonary mortality and to about the same extent whether the air pollution data were mean or median long-term concentrations or whether based on original investigator or Reanalysis Team data. The association of mortality with PM_{15} was much smaller, though still significant; and the associations with the coarse fraction ($PM_{15-2.5}$) or TSP were even smaller and not significant. The lung cancer effect was significant only for sulfate with the original investigator data or for new investigators with regional sulfate artifact adjustment for the 1980-1981 data (Krewski et al., 2000, Part II, Table 31). Associations of mortality with long-term mean concentrations of criteria gaseous co-pollutants were generally non-significant except for SO_2 (Krewski et al., 2000, Part II, Tables 32, 34-38), which was highly significant, and for cardiopulmonary disease with warm-season ozone. However, the regional association of SO_2 with SO_4 and SO_2 with $PM_{2.5}$ was very high; and the effects of the separate pollutants could not be distinguished. Krewski et al. (2000, p. 234) concluded that, "Collectively, our reanalyses suggest that mortality may be associated with more than one component of the complex mix of ambient air pollutants in urban areas of the United States." In the most recent extension of the ACS study, Pope et al. (2002) confirmed the strong association with SO_2 but found little evidence of effects for long-term exposures to other gaseous pollutants.

(3) The extensive temporal data on air pollution concentrations over time in the Six City Study allowed the Reanalysis Team to evaluate time scales for mortality for long-term exposure to a much greater extent than reported in Dockery et al. (1993). The first approach was to estimate the log-hazard ratio as a function of follow up time using a flexible spline-function model (Krewski et al., 2000, Part II, Figures 2 and 3). The results for both SO_4^{-2} and $PM_{2.5}$ suggest very similar relationships, with larger risk after initial exposure decreasing to 0 after about 4 or 5 years, and a large increase in risk at about 10 years follow-up time.

The analyses of the ACS Study proceeded somewhat differently, with less temporal data but many more cities. Flexible spline regression models for $PM_{2.5}$ and sulfate as function of estimated cumulative exposure (not defined) were very nonlinear and showed quite different relationships (Krewski et al., 2000, Part II, Figures 10 and 11). The $PM_{2.5}$ relationship shows the mortality log-hazard ratio increasing up to about 15 $\mu g/m^3$ and relatively flat above about 22 $\mu g/m^3$, then increasing again. The sulfate relationship is almost piecewise linear, with a low near- zero slope below about 11 $\mu g/m^3$ and a steep increase above that concentration.

A third approach evaluated several time-dependent $PM_{2.5}$ exposure indicators in the Six City Study: (a) constant (at the mean) over the entire follow-up period; (b) annual mean within each of the 13 years of the study; (c) city-specific mean concentration for the earliest years of the study (i.e., very long-term effect); (d) exposure estimate in 2 years preceding death; (e) exposure estimate in 3 to 5 years preceding death; and (f) exposure estimate > 5 years preceding death. The time-dependent estimates (a-e) for mortality risk are generally similar and statistically significant (Krewski et al., 2000, Part II, Table 53), with RR of 1.14 to 1.19 per 24.5 $\mu g/m^3$ being much lower than the risk of 1.31 estimated for exposure at the constant mean for the period. Thus, it is highly likely the duration and time patterns of long-term exposure affect the risk of mortality; and further study of this question (along with that of mortality displacement from short-term exposures) would improve estimates of life-years lost from PM exposure.

(4) The Reanalysis Study also advanced our understanding of the shape of the relationship between mortality and PM. Again using flexible spline modeling, Krewski et al. (2000, Part II, Figure 6) found a visually near-linear relationship between all-cause and cardiopulmonary mortality residuals and mean sulfate concentrations, near-linear between cardiopulmonary mortality and mean $PM_{2.5}$, but a somewhat nonlinear relationship between all-cause mortality residuals and mean $PM_{2.5}$ concentrations that flattens above about 20 $\mu g/m^3$. The confidence bands around the fitted curves are very wide, however, neither requiring a linear relationship nor precluding a nonlinear relationship if suggested by reanalyses. An investigation of the mortality relationship for other indicators may be useful in identifying a threshold, if one exists, for chronic PM exposures.

(5) With regard to the role of various PM constituents in the PM-mortality association, past cross-sectional studies have generally found the fine particle component, as indicated either by $PM_{2.5}$ or sulfates, to be the PM constituent most consistently associated with mortality. While relative measurement errors of various PM indicators must be further evaluated as a possible source of bias in these estimate comparisons, the Six-Cities and AHSMOG prospective semi-individual studies both indicate that the fine mass components of PM are more strongly associated with mortality effects of chronic PM exposure than are coarse fraction indicators.

(6) The spatial regression methods suggested that part of the relation between sulfate and mortality was probably due to some unobserved variable or group of confounding variables.

In particular, they found that the sulfate-associated effect drops from a relative risk of 1.25 with the Independent Cities Model, to 1.19 with the Regional Adjustment Model, but that all models continued to show an association between elevated risks of mortality and exposure to airborne sulfate.

8.3 MORBIDITY EFFECTS OF PARTICULATE MATTER EXPOSURE

This effects of ambient PM on morbidity endpoints are assessed below in several subsections: (a) cardiovascular morbidity effects of acute ambient PM exposure; (b) effects of short-term PM exposure on the incidence of respiratory and other medical visits and hospital admissions; and (c) short- and long-term PM exposure effects on lung function and respiratory symptoms in asthmatics and non-asthmatics.

8.3.1 Cardiovascular Effects Associated with Acute Ambient Particulate Matter Exposure

8.3.1.1 Introduction

Very little information specifically addressing cardiovascular morbidity effects of acute PM exposure existed at the time of the 1996 PM AQCD. Since that time, a significantly expanded body of literature has emerged, both on the ecologic relationship between ambient particles and cardiovascular hospital admissions and associations of PM exposures with changes in various physiological and/or biochemical measures. The latter studies are particularly important in that they are suggestive of possible mechanisms underlying PM cardiovascular effects. However, it should be noted that the mechanistic interpretation of the cardiovascular physiology results observed to date (some of which are conflicting) remain unclear.

This section begins with a brief summary of key findings from the 1996 PM AQCD regarding acute cardiovascular effects of PM. Next, key new studies are reviewed in the two categories noted above, i.e., ecologic time-series studies and individual-level studies of physiological measures of cardiac function and/or biochemical measures in blood as they relate to ambient pollution. This is followed by discussion of several issues of importance for interpreting the available data, including identification of potentially susceptible sub-populations, roles of environmental co-factors such as weather and other air pollutants, temporal lags in the relationship between exposure and outcome, and the relative importance of various size-classified PM components (e.g., $PM_{2.5}$, PM_{10}, $PM_{10-2.5}$).

8.3.1.2 Summary of Key Findings on Cardiovascular Morbidity from the 1996 Particulate Matter Air Quality Criteria Document

Just two studies were available for review in the 1996 PM AQCD that provided results for acute cardiovascular (CVD) morbidity outcomes (Schwartz and Morris, 1995; Burnett et al., 1995). Both studies were of ecologic time-series design and used standard statistical methods. Analyzing four years of data on the ≥ 65 year old Medicare population in Detroit, MI, Schwartz and Morris (1995) reported significant associations between ischemic heart disease admissions and PM_{10}, controlling for environmental covariates. Based on an analysis of admissions data from 168 hospitals throughout Ontario, Canada, Burnett et al. (1995) reported significant associations between fine particle sulfate concentrations, as well as other air pollutants, and daily cardiovascular admissions. The relative risk due to sulfate particles was slightly larger for respiratory than for cardiovascular hospital admissions. The 1996 PM AQCD concluded on the basis of these studies that: "There is a suggestion of a relationship to heart disease, but the results are based on only two studies, and the estimated effects are smaller than those for other endpoints" (U.S. Environmental Protection Agency, 1996a, p. 12-100). The PM AQCD also stated that acute effects on CVD admissions had been demonstrated for elderly populations (i.e., ≥ 65), but that insufficient data existed to assess relative effects on younger populations.

When viewed alongside the more extensive literature on acute CVD mortality that was available at the time, the evidence from ecologic time-series studies reviewed in the 1996 PM AQCD was consistent with acute health risks of PM being larger for cardiovascular and respiratory causes than for other causes. Given the tendency for end-stage disease states to include both respiratory and cardiovascular impairment, and the associated diagnostic overlap that often exists, it was not possible on the basis of these studies alone to determine which of the two organ systems, if either, was more critically affected.

8.3.1.3 New Particulate Matter-Cardiovascular Morbidity Studies

8.3.1.3.1 Acute Hospital Admission Studies

Salient methodological features and results of newly available studies that examine associations between daily measures of ambient PM and daily hospital admissions for cardiovascular disease are summarized in Table 8B-1 (see Appendix 8B). As discussed earlier in Sections 8.1.4 and 8.2.2, many studies since 1996 used GAM with default convergence criteria. Several of those studies have been reanalyzed by original investigators using GAM with more stringent convergence criteria and GLM with parametric smooths, such as natural splines (NS) or penalized splines (PN). Again, since the extent of possible bias in PM effect-size estimates caused by the default criteria setting in the GAM models is difficult to estimate for individual studies, the discussion here focuses mainly on the studies that either did not use GAM Poisson models or those GAM studies which have been reanalyzed using more stringent convergence criteria and/or alternative approaches. Newly available U.S. and Canadian studies on relationships between short-term PM exposure and hospital admissions or emergency visits that meet these criteria are summarized in Table 8-16, along with a few non-North American studies. Reanalyses studies are indicated in Table 8-16 by indentation of the reference citation to the pertinent short communication in the HEI Special Report (HEI, 2003). The table is organized by first summarizing single-pollutant (PM only) analyses and then multi-pollutant (PM + one or more copollutant) analyses for U.S. and non-U.S. studies.

Of particular importance is the NMMAPS multi-city study (Samet et al., 2000a,b; Zanobetti et al., 2000a), as reanalyzed (Zanobetti and Schwartz, 2003b), which provides evidence for significant PM effects on cardiovascular-related hospital admissions and visits, using a variety of statistical models. These results are supported by another multi-city study (Schwartz, 1999) which, however, has not been reanalyzed with alternative statistical models. Numerous other studies, carried out by individual investigators in a variety of locales, present a more varied picture, especially when gaseous co-pollutants have been analyzed in multipollutant models. Most CVD hospital admissions studies reported to date have used PM_{10} as the main particle measure due to the wide availability of ambient PM_{10} monitoring data. However, results from these studies may also be relevant to an assessment of $PM_{2.5}$ health effects because $PM_{2.5}$ is known to represent 50% or more of PM_{10} in most locations, especially in urban areas typically studied epidemiologically.

A substantial body of new results has emerged from analyses of daily emergency-only CVD hospital admissions in persons 65 and older in relation to PM_{10} in 14 cities from the NMMAPS multi-city study (Samet et al., 2000a,b). The cities studied included Birmingham, AL; Boulder, CO; Canton, OH; Chicago, IL; Colorado Springs, CO; Detroit, MI; Minneapolis/

TABLE 8-16. SUMMARY OF STUDIES OF PM_{10}, $PM_{10\text{-}2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in µg/m³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 µg/m³ PM_{10} or 25 µg/m³ $PM_{2.5}$*, $PM_{10\text{-}2.5}$**
U.S. Results Without Co-pollutants						
Samet et al. (2000a,b) 14 Cities	Total CVD admissions ≥ 65 yrs	PM_{10} Means: 24.4-45.3	none	0 day	Default GAM	5.5% (4.7, 6.2)
Zanobetti and Schwartz, (2003b) 14 Cities		PM_{10} Means: 24.4-45.3		0-1 day	Default GAM Strict GAM GLM NS GLM PS	5.9% (5.1-6.7) 4.95% (3.95-5.95) 4.8% (3.55-6.0) 5.0% (4.0-5.95)
Lippmann et al., 2000 Detroit (Wayne County), MI	Ischemic heart disease ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10\text{-}2.5}$: 13 (7)	none	2 day	Default GAM Default GAM Default GAM	8.9% (0.5-18.0) 4.3% (−1.4-10.4)* 10.5% (2.75-18.9)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	8.0% (−0.3-17.1) 6.2% (−2.0-15.0)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	3.65% (−2.05-9.7)* 3.0% (−2.7-9.0)*
		$PM_{10\text{-}2.5}$: 1 3 (7)			Strict GAM GLM NS	10.2% (2.4-18.6)** 8.1% (0.4-16.4)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Dysrhythmias ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10\text{-}2.5}$: 13 (7)	none	1 day 1 day* 0 day**	Default GAM Default GAM Default GAM	2.9% (−10.8-18.8) 3.2% (−6.5-14.0)* 0.2% (−12.2-14.4)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	2.8% (−10.9-18.7) 2.0% (−11.7-17.7)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	3.2% (−6.6-14.0)* 2.6% (−7.1-13.3)*
		$PM_{10\text{-}2.5}$: 13 (7)			Strict GAM GLM NS	0.1% (−12.4-14.4)** 0.0% (−12.5-14.3)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Heart Failure ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10\text{-}2.5}$: 13 (7)	none	0 day 1 day* 0 day**	Default GAM Default GAM Default GAM	9.7% (0.15-20.2) 9.1% (2.4-16.2)* 5.2% (−3.25-14.4)**
Ito 2003 Detroit (Wayne County), MI		PM_{10}: 31(19)			Strict GAM GLM NS	9.2% (−0.3-19.6) 8.4% (−1.0-18.7)
		$PM_{2.5}$: 18 (11)			Strict GAM GLM NS	8.0% (1.4-15.0)* 6.8% (0.3-13.8)*
		$PM_{10\text{-}2.5}$: 13 (7)			Strict GAM GLM NS	4.4% (−4.0-13.5)** 4.9% (−3.55-14.1)**
Morris and Naumova (1998) Chicago, IL	Congestive heart failure ≥ 65 yrs	PM_{10}: 41 (23)	none	0 day	GAM not used	3.9% (1.0-6.9)

TABLE 8-16 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in μg/m³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 μg/m³ PM_{10} or 25 μg/m³ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results Without Co-pollutants (cont'd)						
Linn et al. (2000) Los Angeles, CA	Total CVD admissions ≥ 30 yrs	PM_{10}: 45 (18)	none	0 day	GAM not used	3.25% (2.04, 4.47)
Moolgavkar (2000b) Cook County, IL	Total CVD admissions ≥ 65 yrs	PM_{10}: 35‡ (22)	none	0 day	Default GAM	4.2% (3.0, 5.5)
Moolgavkar (2003) Cook County, IL					Strict GAM_{100df} GLM NS_{100df}	4.05% (2.9-5.2) 4.25% (3.0-5.5)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admissions ≥ 65 yrs	PM_{10}: 44‡ (26) $PM_{2.5}$: 22‡ (16)	none	0 day	Default GAM Default GAM	3.2% (1.2, 5.3) 4.3% (2.5, 6.1)*
Moolgavkar (2003) Los Angeles County, CA		PM_{10}: 44‡ (26)			Strict GAM_{30df} Strict GAM_{100df} GLM NS_{100df}	3.35% (1.2-5.5) 2.7% (0.6-4.8) 2.75% (0.1-5.4)
		$PM_{2.5}$: 22‡ (16)			Strict GAM_{30df} Strict GAM_{100df} GLM $nspline_{100df}$	3.95% (2.2-5.7)* 2.9% (1.2-4.6)* 3.15% (1.1-5.2)*
Tolbert et al., (2000a) Atlanta, GA 1993-1998	Total CVD emerg. dept. visits, ≥ 16 yrs	Period 1 PM_{10}: 30.1, 12.4	none	0-2 day avg.	GAM not used	−8.2% (p=0.002)
Tolbert et al., (2000a) Atlanta, GA 1998-1999	Total CVD emerg. dept. visits, ≥ 16 yrs	Period 2 PM_{10}: 29.1, 12.0 $PM_{2.5}$: 19.4, 9.4 $PM_{10-2.5}$: 9.4, 4.5	none	0-2 day avg.	GAM not used	5.1% (−7.9, 19.9) 6.1% (−3.1, 16.2)* 17.6% (−4.6, 45.0)**
U.S. Results With Co-pollutants						
Lippmann et al., 2000 Detroit (Wayne County), MI	Ischemic heart disease ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	2 day	Default GAM Default GAM Default GAM	8.5% (-0.45-18.3) 3.7% (-2.4-10.3)* 10.1% (2.25-18.6)**
Lippmann et al., 2000 Detroit (Wayne County), MI	Dysrhythmias ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	1 day 1 day 0 day	Default GAM Default GAM Default GAM	−1.3% (−15.5-15.4) 0.55% (−9.7-12.0)* −1.0% (−13.4-13.05)**

TABLE 8-16 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome measure	Mean PM levels (IQR) in μg/m³	Co-pollutants analyzed with PM	Lag structure	Method	Effect measures standardized to 50 μg/m³ PM_{10} or 25 μg/m³ $PM_{2.5}$*, $PM_{10-2.5}$**
U.S. Results With Co-pollutants (cont'd)						
Lippmann et al., 2000 Detroit (Wayne County), MI	Heart Failure ≥ 65 yrs	PM_{10}: 31(19) $PM_{2.5}$: 18 (11) $PM_{10-2.5}$: 13 (7)	CO	0 day 1 day 0 day	Default GAM Default GAM Default GAM	7.5% (−2.6-18.7) 8.9% (2.2-16.1)* 3.9% (−4.7-13.2)**
Morris and Naumova (1998) Chicago, IL	Congestive heart failure ≥ 65 yrs	PM_{10}: 41, 23	CO, NO_2, SO_2, O_3	0 day	GAM not used	2% (−1-6)
Moolgavkar (2000b) Cook County, IL	Total CVD admissions ≥ 65 yrs	PM_{10}: 35, 22	NO_2	0 day	Default GAM	1.8% (0.4, 3.2)
Moolgavkar (2003) Cook County, IL		PM_{10}: 35, 22	CO		Strict GAM_{100df} GLM NS_{100df}	2.95% (1.7-4.2) 3.1% (1.8-4.4)
Moolgavkar (2000b) Los Angeles County, CA	Total CVD admissions ≥ 65 yrs	PM_{10}: 44‡ (26) $PM_{2.5}$: 22‡ (16)	CO	0 day	Default GAM Default GAM	−1.8% (−4.4, 0.9) 0.8% (−1.3, 2.9)*
Moolgavkar (2003) Los Angeles County, CA		PM_{10}			Strict GAM_{100df} GLM NS_{100df}	−1.3% (−3.8-1.2) −1.1% (-4.2-2.0)
		$PM_{2.5}$			Strict GAM_{100df} GLM NS_{100df}	1.0% (−1.1-3.3)* 1.45% (−1.1-4.0)*
Non-U.S. Results Without Co-pollutants						
Burnett et al., (1997a) Toronto, Canada	Total CVD admissions all ages	PM_{10}: 28, 22 $PM_{2.5}$: 17, 15 $PM_{10-2.5}$: 12, 7	none	1-4 day avg.	GAM not used	12.1% (1.4, 23.8) 7.2% (−0.6, 15.6)* 20.5% (8.2, 34.1)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	PM_{10}: 14.0, 9.0 $PM_{2.5}$: 8.5, 5.9	none	1-3 day avg.	GAM not used	29.3% (p=0.003) 14.4% (p = 0.055)*
Atkinson et al. (1999b) Greater London, England	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: 28.5, 90-10 %tile range: 30.7	none	0 day	GAM not used	2.5% (−0.2, 5.3)
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admissions ≥ 65 yrs	PM_{10}: 20.7, 8.4	none	1-3 day avg.	GAM not used	12.4% (4.6, 20.9)
Wong et al. (1999a) Hong Kong	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: Median 45.0, IQR 34.8	none	0-2 day avg.	GAM not used	4.1% (1.3, 6.9)

TABLE 8-16 (cont'd). SUMMARY OF STUDIES OF PM_{10}, $PM_{10-2.5}$, OR $PM_{2.5}$ EFFECTS ON TOTAL CVD HOSPITAL ADMISSIONS AND EMERGENCY VISITS

Reference citation, location, etc.	Outcome Measure	Mean PM levels (IQR) in $\mu g/m^3$	Co-pollutants Analyzed with PM	Lag Structure	Method	Effect measures standardized to 50 $\mu g/m^3$ PM_{10} or 25 $\mu g/m^3$ $PM_{2.5}$*, $PM_{10-2.5}$**
Non-U.S. Results With Co-pollutants						
Burnett et al., (1997a) Toronto, Canada	Total CVD admissions all ages	PM_{10}: 28, IQR 22	O_3, NO_2, SO_2, CO	1-4 day avg.	GAM not used	−1.4% (−12.5, 11.2)
		$PM_{2.5}$: 17, 15				−1.6% (−10.5, 8.2)*
		$PM_{10-2.5}$: 12, 7				12.1% (−1.9, 28.2)**
Stieb et al. (2000) Saint John, Canada	Total CVD emerg. dept. visits, all ages	PM_{10}: 14.0, 9.0	CO, H_2S, NO_2, O_3, SO_2, total reduced sulfur	1-3 day avg.	GAM not used	PM_{10} not significant; no quantitative results presented
Atkinson et al. (1999b) Greater London, England	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: 28.5, 90-10 %tile range: 30.7	NO_2, O_3, SO_2, CO	0 day	GAM not used	PM_{10} not significant; no quantitative results presented
Prescott et al. (1998) Edinburgh, Scotland	Total CVD admissions ≥ 65 yrs	PM_{10}: 20.7, 8.4	SO_2, NO_2, O_3, CO	1-3 day avg.	GAM not used	PM_{10} effect robust; no quantitative results presented
Wong et al. (1999a) Hong Kong	Total emerg. CVD admissions ≥ 65 yrs	PM_{10}: Median 45.0, IQR 34.8	NO_2, O_3, SO_2	0-2 day avg.	GAM not used	PM_{10} effect robust; no quantitative results presented

*$PM_{2.5}$ entries, **$PM_{10-2.5}$. All others relate to PM_{10}; ‡Median.

St. Paul, MN; Nashville, TN; New Haven, CT; Pittsburgh, PA; Provo/Orem, UT; Seattle, WA; Spokane, WA; and Youngstown, OH. The range of years studied encompassed 1985-1994, although this varied by city. Covariates included SO_2, NO_2, O_3, and CO; however these were not analyzed directly as regression covariates. Individual cities were analyzed first by Poisson regression methods on PM_{10} for lags from 0 to 5 days. An overall PM_{10} risk estimate was then computed by taking the inverse-variance weighted mean of the city-specific risk estimates. The city-specific risk estimates for PM_{10} were also examined for correlations with omitted covariates, including other pollutants. No relationship was observed between city-specific risk estimates and measures of socioeconomic status, including percent living in poverty, percent non-white, and percent with college educations. The overall weighted mean risk estimate for PM_{10} was greatest for lag 0 and for the mean of lags 0-1. For example, the mean risk estimate for the mean of lags 0-1 was a 5.9% increase in CVD admissions per 50 µg/m^3 PM_{10} (95% CI: 5.1 - 6.7). The mean risk was larger in a subgroup of data where PM_{10} was less than 50 µg/m^3, suggesting the lack of a threshold. A weakness of this study was its failure to report multipollutant results. The authors argued that confounding by co-pollutants was not present because the city-specific risk estimates did not correlate with city-specific regressions of PM_{10} on co-pollutant levels. However, the validity of this method for identifying meaningful confounding by co-pollutants at the daily time-series level has not been demonstrated. Thus, it is not possible to conclude from these results alone that the observed PM_{10} associations were independent of co-pollutants.

The Samet et al. (2000a,b) reports used GAM LOESS smoothing to control for time and weather covariates. Data from the 14 city NMMAPs analysis of CVD hospital admissions were reanalyzed recently (Zanobetti and Schwartz, 2003b) using three alternative control methods. A small decrease in overall effects was observed as compared with the original study results. Whereas the original 14 city pooled analysis yielded a 5.9% increase in CVD admissions per 50 µg/m^3 increase in mean lags 0 and 1 day PM_{10} (95% CI: 5.1-6.7%), the reanalysis reported 4.95% (3.95-5.95%), 4.8% (3.55-6.0%), and 5.0 (4.0-5.95%) when reanalyzed by GAM with stringent convergence criteria, GLM with natural spline, and GLM with penalized spline, respectively. On the basis of these results, no change is warranted with regard to the overall conclusions for the original published study.

Zanobetti et al. (2000a) reanalyzed a subset of 10 cities from among the 14 evaluated by Samet et al. (2000a,b). The same basic pattern of results obtained by Samet et al. (2000a,b) were found, with strongest PM_{10} associations on lag 0 day, smaller effects on lag 1 and 2, and none at longer lags. The cross-city weighted mean estimate at 0 day lag was excess risk = 5.6% (95% CI 4.7, 6.4) per 50 µg/m^3 PM_{10} increment. The 0-1 day lag average excess CVD risk = 6.2% (95% CI 5.4, 7.0) per 50 µg/m^3 PM_{10} increment. Effect-size estimates increased when data were restricted to days with PM_{10} < 50 µg/m^3. As before, no evidence of gaseous (CO, O_3, SO_2) co-pollutant modification of PM effects was seen in the second stage analyses. Again, however, co-pollutants were not tested as independent explanatory variables in the regression analysis. Like the larger NMMAPS morbidity analyses reported by Samet et al. (2000a,b), this sub-study utilized the GAM function in SPlus. These 10 cities were among the 14 cities that Zanobetti and Schwartz (2003b) recently reanalyzed using alternative statistical methods, and the results discussed above would thus apply in general here.

Janssen et al. (2002), in further analyses of the data set examined above by Samet et al. (2000a,b), evaluated whether differences in prevalence in air conditioning (AC) and/or the contribution of different sources to total PM_{10} emissions could partially explain the observed variability in exposure-effect relations in the 14 cities. Cities were characterized and analyzed as either winter or nonwinter peaking for the AC analyses. Data on the prevalence of AC from the 1993 American Housing Survey of the United States Census Bureau (1995) were used to calculate the percentage of homes with central AC for each metropolitan area. Data on PM_{10} emissions by source category were obtained by county from the U.S. EPA emissions and air quality data web site (U.S. Environmental Protection Agency, 2000a). In an analysis of all 14 cities, central AC was not strongly associated with PM_{10} coefficients. However, separate analysis for nonwinter-peaking and winter-peaking PM_{10} cities yielded coefficients for CVD-related hospital admissions that decreased significantly with increased percentage of central AC for both groups of cities. There were also significant positive relationships between CVD effects and PM_{10} percent emissions from highways or from diesel vehicles, suggesting that mobile source particles may have more potent cardiovascular effects than other particle types. For both analyses, similar though weaker, patterns were found for hospitalization for COPD and pneumonia. The authors note that the stronger relationship for hospital admission rates for CVD over COPD and pneumonia may relate to the 10 times higher CVD hospital admissions rate (which would result in a more precise estimate). However, no co-pollutant analyses were reported. The ecologic nature and limited sample size also indicate the need for further study. Because Janssen et al.'s analysis utilized the GAM function in SPlus, Zanobetti et al. (2003b) reanalyzed the main findings from this study using alternative methods for controlling time and weather covariates. While the main conclusions of the study were not significantly altered, some changes in results are worth noting. The effect of air conditioning remained significant for the non-winter PM_{10}-peaking cities. The significance of highway vehicles and diesels on PM_{10} effect sizes remained significant, as did oil combustion. However, the effect of air conditioning use on PM_{10} effect estimates was less pronounced and no longer statistically significant at $p < 0.05$ for the winter PM_{10}-peaking cities using natural splines or penalized splines, in comparison to the original Janssen et al. GAM analysis.

Schwartz (1999) extended the analytical approach he had used in Tucson (described below) to eight more U.S. metropolitan areas, limiting analyses to a single county in each location to enhance the representativeness of the air pollution data. The locations analyzed were Chicago, IL; Colorado Springs, CO; New Haven, CT; Minneapolis, MN; St. Paul, MN; Seattle, WA; Spokane, WA; and Tacoma, WA. Again, the analyses focused on total cardiovascular (CVD) hospital admissions among persons ≥ 65 years old. In univariate regressions, remarkably consistent PM_{10} associations with CVD admissions were found across the eight locations, with a 50 μg/m^3 increase in PM_{10} associated with 3.6 to 8.6% increases in admissions. The univariate eight-county pooled PM_{10} effect was 5.0% (CI 3.7-6.4), similar to the 6.1 % effect per 50 μg/m^3 observed in the previous Tucson analysis. In a bivariate model that included CO, the pooled PM_{10} effect size diminished somewhat to 3.8% (CI 2.0-5.5) and the CO association with CVD admissions was generally robust to inclusion of PM_{10} in the model. The Schwartz 1999 paper used GAM LOESS smoothing with default convergence criteria to control for time and weather covariates. Although no direct reanalyses of this study using alternative statistical methods have been reported, six of the eight cities included in Schwartz (1999) were included in the NMMAPS reanalyses (Zanobetti et al., 2003; Zanobetti and Schwartz, 2003b).

Turning to some examples of independent single-city analyses, PM_{10} associations with CVD hospitalizations were also examined in a study by Schwartz (1997), which analyzed three years of daily data for Tucson, AZ linking total CVD hospital admissions for persons ≥65 years old with PM_{10}, CO, O_3, and NO_2. As was the above case in Chicago, only one site monitored daily PM_{10}, whereas multiple sites did so for gaseous pollutants (O_3, NO_2, CO). Both PM_{10} and CO were independently (i.e., robustly) associated with CVD-related admissions; but O_3 and NO_2 were not. The percent effect of a 50 μg/m^3 increase in PM_{10} changed only slightly from 6.07 (CI 1.12-11.27) to 5.22 (CI 0.17 - 10.54) when CO was included in the model along with PM_{10}. The Schwartz 1997 paper utilized GAM smoothing to control for time and weather covariates. To date, no revised results have been reported using alternative statistical methods.

Morris and Naumova (1998) reported results for PM_{10}, as well as for O_3, NO_2, and SO_2, in an analysis of four years of congestive heart failure data among people ≥ 65 years old in Chicago, IL. As many as eight monitoring sites were available for calculating daily gaseous pollutant concentrations; however, only one site in Chicago monitored daily PM_{10}. Only same-day results were presented, based on an initial exploratory analysis showing strongest effects for same-day pollution exposure (i.e., lag 0). Associations between hospitalizations and PM_{10} were observed in univariate regressions (3.9% [1.0, 6.9] per 50 μg/m^3 PM_{10} increase), but these diminished somewhat in a multi-pollutant model (2.0%, [−1.4, 5.4]). Strong, robust associations were seen between CO and congestive heart failure admissions. These results seem to suggest a more robust association with CO than with PM_{10}. However, the observed differences might also be due in part to differential exposure misclassification for PM_{10} (monitored at one site) as compared with CO (eight sites). This study did not use GAM functions to control for time and weather covariates.

In a study designed to compare the effects of multiple PM indices, Lippmann et al. (2000) analyzed associations between PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$ and various categories of CVD hospital admissions (only emergency and urgent admissions) among the elderly (65+ yr) in Detroit on 344 days in the period 1992-1994. While no consistent differences were observed in the relative risks for the alternative PM indices, many of the associations involving PM were significant: (a) ischemic heart disease (IHD) in relation to PM indices (i.e., 8.9% [0.5, 18.0] per 50 µg PM_{10}); 10.5% (2.8, 18.9) per 25 µg/m^3 $PM_{10-2.5}$; and 4.3% (−1.4, 10.4) per 25 µg/m^3 $PM_{2.5}$ (all at lag 2d); and (b) heart failure (i.e., 9.7% [0.2, 20.2] per 50 µg/m^3 PM_{10}); 5.2% (−3.3, 14.4) per 25 µg/m^3 $PM_{10-2.5}$; and 9.1% (2.4, 16.2) per 25 µg/m^3 $PM_{2.5}$ (the first two at lag 0 d and the latter at lag 1 d). No associations with dysrythmias were seen however. The PM effects generally were robust when co-pollutants were added to the model. Results for 2-pollutant models involving CO are given in Table 8-16 above. As discussed earlier with regard to the Lippmann et al. (2000) mortality findings, it is difficult to discern whether the observed associations with coarse fraction particles ($PM_{10-2.5}$) are independently due to such particles or may possibly be attributed to the moderately correlated fine particle ($PM_{2.5}$) fraction in Detroit. In addition, power was limited by the small sample size. Because GAM was used in the analyses reported in Lippmann et al. (2000), Ito (2003) has recently reported reanalyses results for the Detroit study using GAM with more stringent convergence criteria and GLM with natural splines. PM effect sizes diminished somewhat (up to 30%) and sometimes lost significance. However, these changes tended to affect all PM metrics in a similar fashion. Thus, there was no change in basic conclusions for the original Lippmann et al. (2000) study, i.e., that there was no evidence for stronger effects for one size fraction versus others. Ito (2003) also noted that study results were more sensitive to alternative weather models and degree of smoothing (degrees of freedom used for the smoothing function) than to whether or not GAM, with strict convergence criteria, was used.

As part of the ARIES Study, Tolbert et al. (2000a) initially reported preliminary results for multiple PM indices as they relate to daily hospital emergency department (ED) visits for dysrhythmias (DYS) and all CVD categories for persons aged 16 yrs or older, based on analyses of data from 18 of 33 participating hospitals in Atlanta, GA. During Period 1 of the study (1993-1998), PM_{10} from the EPA AIRS database was reported to be negatively associated with CVD visits. In a subsequent one-year period (Aug. 1998-Aug. 1999), when data became available from the Atlanta PM supersite, positive but non-significant associations were seen between CVD and PM_{10} (RR of 5.1% per 50 μg/m^3 PM_{10}) and $PM_{2.5}$ (RR of 6.1% per 25 μg/m^3 $PM_{2.5}$); and significant positive associations were seen with certain fine particle components, i.e., elemental carbon ($p \leq 0.005$) and organic carbon ($p \leq 0.02$), and CO ($p \leq 0.005$). No multi-pollutant results were reported. Study power was limited due to the short data record in Period 2. More complete analyses for January 1993 to August 2000 data from all participating hospitals have recently been reported (Metzger et al., in press) to show that, using an a priori 3-day morning average in single-pollutant GLM analyses, CVD visits were associated with $PM_{2.5}$, organic carbon, elemental carbon, oxygenated hydrocarbons, CO, and NO_2 (but not with O_3 or SO_2). Secondary analyses suggested that these associations were strongest for same day air pollutant levels.

In an analysis of 1992-1995 Los Angeles data, Linn et al. (2000) also found that PM_{10}, CO, and NO_2 were all significantly associated with increased CVD admissions in single-pollutant models among persons aged 30 yr and older. Associations generally appeared to be stronger for CO than for PM_{10}. No PM_{10} results were presented with co-pollutants in the model. Neither Tolbert et al. nor Linn et al. reported any key findings based on GAM analyses.

Lastly, Moolgavkar (2000b) analyzed PM_{10}, CO, NO_2, O_3, SO_2 and limited $PM_{2.5}$ data in relation to daily total cardiovascular (CVD) and total cerebrovascular (CrD) admissions for persons aged ≥65 from three urban counties (Cook, IL; Los Angeles, CA; Maricopa, AZ) in the period 1987-1995. Of particular note was the availability of $PM_{2.5}$ data in LA, though only every sixth day. Consistent with most studies, in univariate regressions, PM_{10} (and $PM_{2.5}$ in LA) were associated at some lags with CVD admissions in Cook and LA counties, but not in Maricopa county. However, in two-pollutant models in Cook and LA counties, the PM risk estimates diminished substantially and/or were rendered non-significant, whereas co-pollutant (CO or NO_2) risk estimates were less affected. These results suggest that gaseous pollutants, with the exception of O_3, may have been more strongly associated with CVD hospitalizations than was PM. These findings were based on an analysis that used GAM functions for time and weather controls. Moolgavkar (2003) reported results of a reanalysis using improved GAM convergence criteria and GLM with natural splines (nspline) and a range of degrees of freedom (30 versus 100) for the smooth function of time. Results were not very sensitive to the use of default versus improved GAM or splines (Table 8-16) but did appear to be more sensitive to degrees of freedom. The nspline results were given only with 100 degrees of freedom. This is an unusually large number, especially for $PM_{2.5}$, where data were available only every sixth day over a nine year period.

The above analyses of daily PM_{10} and CO in U.S. cities, overall, indicate that elevated concentrations of both PM_{10} and CO may enhance risk of CVD-related morbidity leading to increased ED visits or hospitalizations. The Lippmann results appear to implicate both $PM_{2.5}$ and $PM_{10-2.5}$ in increased hospital admissions for some categories of CVD among the elderly.

8.3.1.3.2 Studies in Non-U.S. Cities

Four separate analyses of hospitalization data in Canada have been reported by Burnett and coworkers since 1995 (Burnett et al., 1995, 1997a,c, 1999). A variety of locations, outcomes, PM exposure metrics, and analytical approaches were used, which hinders somewhat the ability to draw broad conclusions across the full group of studies. The first study (Burnett et al., 1995), reviewed briefly in the 1996 PM AQCD, analyzed six years of data from 168 hospitals in Ontario, CN. Respiratory and CVD hospital admissions were analyzed in relation to sulfate and O_3 concentrations. Sulfate lagged one day was associated with CVD admissions, with an effect of 2.8% (CI 1.8-3.8) increase per 13 $\mu g/m^3$ SO_4^{-2} without O_3 in the model and 3.3% (CI 1.7-4.8) with O_3 included. When CVD admissions were split out into sub-categories, larger associations were seen between sulfates and coronary artery disease and heart failure than for cardiac dysrhythmias. Sulfate associations with total admissions were larger for the elderly $\geq$ 65 yr old (3.5% per 13 $\mu g/m^3$) than for those < 65 yr old (2.5% per 13 $\mu g/m^3$). There was little evidence for seasonal differences in sulfate associations.

Burnett et al. (1997c) analyzed daily congestive heart failure hospitalizations in relation to CO and other air pollutants (O_3, NO_2, SO_2, CoH) in ten large Canadian cities as a replication of an earlier U.S. study by Morris et al. (1995). The Burnett Canadian study expanded upon the previous work both by its size (11 years of data for each of 10 large cities) and by including a measure of PM air pollution (coefficient of haze, CoH); whereas no PM data were included in the earlier Morris et al. study. The Burnett study was restricted to the population $\geq$ 65 years old. The authors noted that all pollutants except O_3 were correlated, making it difficult to separate them statistically. CoH, CO, and NO_2 measured on the same day as admission (i.e., lag 0) were all strongly associated with congestive heart failure admissions in univariate models. In multi-pollutant models, CO remained a strong predictor, but CoH did not (no gravimetric PM measures were used).

The roles played by size-selected gravimetric and chemically-speciated particle metrics as predictors of CVD hospitalizations were explored in analyses of data from metropolitan Toronto for the summers of 1992-1994 (Burnett et al., 1997a). The analyses used dichotomous sampler ($PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$), hydrogen ion, and sulfate data collected at a central site as well as O_3, NO_2, SO_2, CO, and CoH data collected at multiple sites in Toronto. Hospital admissions categories included total cardiovascular (i.e., the sum of ischemic heart disease, cardiac dysrhythmias, and heart failure) and total respiratory-related admissions. Model specification with respect to pollution lags was completely data-driven, with all lags and averaging times out to 4 days prior to admission evaluated in exploratory analyses and "best" metrics chosen on the basis of maximal t-statistics. The relative risks of CVD admissions were positive and generally statistically significant for all pollutants analyzed in univariate regressions, but especially so for O_3, NO_2, CoH, and $PM_{10-2.5}$ (i.e., regression t-statistics > 3). Associations for gaseous pollutants were generally robust to inclusion of PM covariates, whereas the PM indices (aside from CoH) were not robust to inclusion of multiple gaseous pollutants. In particular, $PM_{2.5}$ was not a robust predictor of CVD admissions in multi-pollutant models: whereas an 25 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 7.2% increase (t = 1.8) in CVD admissions in a univariate model, the effect was reduced to −1.6% (t = 0.3) in a model that included O_3, NO_2, and SO_2. CoH, like CO and NO_2, is generally thought of as a measure of primary motor-vehicle emissions during the non-heating season. The authors concluded that "particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory diseases in this study beyond that attributable to climate and gaseous air pollution."

Burnett et al. (1999) later reported results of a more extensive attempt to explore cause-specific hospitalizations for persons of all ages in relation to a large suite of gaseous and PM air pollutant measures, using 15 years of Toronto data. Cardiovascular admissions were split out into separate categories for analysis: dysrhythmias, heart failure, and ischemic heart disease. Burnett et al. selected only those admissions to acute care treatment hospitals that were considered an emergency or urgent. The analyses also examined several respiratory causes, as well as cerebrovascular and diseases of the peripheral circulation; the latter categories were included because they should show PM associations if one mechanism of PM action is related to increased plasma viscosity, as suggested by Peters et al. (1997a). The PM metrics analyzed were $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$ estimated from daily TSP and TSP sulfate data, based on a regression analysis for dichotomous sampling data that were available every sixth day during an eight-year subset of the full study period. This use of estimated rather than measured PM components limits interpretation of the reported PM results, i.e., in general, use of estimated PM exposure metrics should tend to increase exposure measurement error and thereby tend to decrease effects estimates. Model specification for lags was again data-driven, based on maximal t-statistics. Although some statistically significant associations with one or another PM metric were found in univariate models, there were no significant PM associations with any of the three CVD hospitalization outcomes in multi-pollutant models. For example, whereas an 25 $\mu g/m^3$ increase in estimated $PM_{2.5}$ was associated with a 8.05% increase (t-statistic = 6.08) in ischemic heart disease admissions in a univariate analysis, the $PM_{2.5}$ association was reduced to 2.25% (n.s.) when NO_2 and SO_2 were included in the model. The gaseous pollutants dominated most regressions. There also were no associations between PM and cerebral or peripheral vascular disease admissions.

The Burnett et al. studies provide some of the most extensive results for PM in conjunction with multiple gaseous pollutants, but the inconsistent use of alternative PM metrics in the various analyses confuses the picture. A general finding appears to be lack of robustness of associations between cardiovascular outcomes and PM in multi-pollutant analyses. This was seen for CoH in the analysis of 10 Canadian cities (Burnett et al., 1997c), for $PM_{2.5}$ and PM_{10} in the analysis of summer data in Toronto (Burnett et al., 1997a), and for linear combinations of TSP and sulfates (i.e., estimated $PM_{2.5}$, PM_{10}, and $PM_{10-2.5}$) in the analysis of 15 years of data in Toronto (Burnett et al., 1999). One exception was the association reported between CVD admissions to 168 Ontario hospitals and sulfate concentrations (Burnett et al., 1995), where the sulfate association was robust to the inclusion of O_3. Also, although gravimetric PM variables were not robust predictors in the Toronto summer analysis, CoH was (Burnett et al., 1997a), perhaps reflecting the influence of primary motor vehicle emissions. This contrasts, however, with CoH's lack of robustness in the 10-city analysis (Burnett et al., 1997c).

Stieb et al. studied all-age acute cardiac emergency room visits in relation to a rich set of pollution covariates in Saint John, Canada for the period 1992-1996. Daily data were available on $PM_{2.5}$, PM_{10}, fine fraction hydrogen and sulfate ions, CoH, CO, H_2S, NO_2, O_3, SO_2, and total reduced sulfur. In a multi-pollutant model, neither PM_{10} nor $PM_{2.5}$ were significantly related to total cardiac ED visits, though O_3 and SO_2 were.

The APHEA II (Le Tertre et al., 2002) project examined the association between PM_{10} and hospital admissions for cardiac causes in eight European cities. They found a significant effect of PM_{10} (0.5%; 0.2, 0.8) on admission for cardiac causes (all ages) and cardiac causes (0.7%; 0.4, 1.0) and ischemic heart disease (0.8%; 0.3, 1.2) for people over 65 years, with the effect of PM_{10} per unit of pollution being half that found in the United States. PM_{10} did not seem to be confounded by O_3 or SO_2. The PM_{10} effect was reduced when CO was incorporated in the regression model and eliminated when controlling for NO_2. In contrast to PM_{10}, black smoke was robustly associated with CVD hospital admissions when co-pollutants were introduced into the model. This led the authors to suggest that diesel PM may be especially important. GAM functions were used in the original analysis. In a recent reanalysis using GAM with stringent convergence criteria and GLM with either natural or penalized splines, no marked changes from original results were observed (Le Tertre et al., 2003).

Several additional non-U.S. studies, mainly in the U.K., have also been published since the 1996 PM AQCD. Most of these studies evaluated co-pollutant effects along with those of PM. Interpretation is hindered somewhat, however, by the failure to report quantitative results for PM_{10} in the presence of co-pollutants. In univariate models, Atkinson et al. (1999b) reported PM associations for persons aged $<$ 65 yr and for persons aged $\geq$ 65 yr. Significant associations were reported for both ambient PM_{10} and black smoke (BS), as well as all other co-pollutants, with daily admissions for total cardiovascular disease and ischemic heart disease for 1992-1994 in London, UK, using standard time-series regression methods. In two-pollutant models, the associations with PM_{10}, NO_2, SO_2, and CO were moderated by the presence of BS in the model, but the BS association was robust to co-pollutants. Interpretation is hampered somewhat by the lack of quantitative results for two-pollutant models.

In another U.K. study, associations with PM_{10}, and to a lesser extent BS, SO_2, and CO, were reported for analyses of daily emergency hospital admissions for cardiovascular diseases from 1992-1995 for Edinburgh, UK (Prescott et al., 1998). No associations were observed for NO_2 and O_3. Significant PM_{10} associations for CVD admissions were present only in persons < 65 yrs old. The authors reported that the PM_{10} associations were unaffected by inclusion of other pollutants; however, results were not shown. On the other hand, no associations between PM_{10} and daily ischemic heart disease admissions were observed by Wordley and colleagues (1997) in an analysis of two years of daily data from Birmingham, UK. However, PM_{10} was associated with respiratory admissions and cardiovascular mortality during the same study period. This inconsistency of results across causes and outcomes is difficult to interpret, but may relate in part to the relatively short time-series analyzed. The authors stated that gaseous pollutants did not have significant associations with health outcomes independent of PM, but no results were presented for models involving gaseous pollutants.

A study in Hong Kong by Wong et al. (1999a) found associations between CVD admissions and PM_{10}, SO_2, NO_2, and O_3 in univariate models, but did not examine multi-pollutant models. In models including PM_{10} and dichotomous variables for gaseous pollutants (high versus low concentration), the PM_{10} effects remained relatively stable. Ye and colleagues analyzed a 16 year record of daily emergency hospital visits for July and August in Tokyo among persons age 65 and older (Ye et al., 2001). In addition to PM_{10}, the study included NO_2, O_3, SO_2, and CO. Models were built using an objective significance criterion for variable inclusion. NO_2 was the only pollutant significantly associated with angina, cardiac insufficiency, and myocardial infarction hospital visits.

8.3.1.3.3 Summary of Salient Findings for Acute PM Exposure Effects on CVD Hospital Admissions

The ecologic time-series studies reviewed here add substantially to the body of evidence on acute CVD morbidity effects of PM and co-pollutants. Two U.S. multi-city studies offer the strongest current evidence for effects of PM_{10} on acute CVD hospital admissions, but uncertainties regarding the possible role of co-pollutants in the larger of the two studies hinders interpretation with respect to independent PM_{10} effects. Among single-city studies carried out in the U.S. and elsewhere by a variety of investigators (see Table 8-16), less consistent evidence for PM effects is seen. Of particular importance is the possible roles of co-pollutants (e.g., CO) as confounders of the PM effect. Among 13 independent studies that included gravimetrically-measured PM_{10} and co-pollutants, three reported PM effects that appeared to be independent of co-pollutants (Schwartz, 1997; Lippmann et al., 2000; Prescott et al., 1998); eight reported no significant PM_{10} effects after inclusion of co-pollutants (Morris and Naumova, 1998; Moolgavkar, 2000b; Tolbert et al., 2000a; Burnett et al., 1997a; Steib et al., 2000; Atkinson et al., 1999b; Wordley et al. (1997); Morgan et al., 1998; Ye et al., 2001); and two studies were unclear regarding independent PM effects (Linn et al., 2000; Wong et al., 1999a). In a recent quantitative review of published results from 12 studies on airborne particles and hospital admissions for cardiovascular disease, Morris (2001) noted that adjustment for co-pollutants consistently reduced the PM_{10} effect, with reductions ranging from 10 to 320% across studies. Thus, although several studies do appear to provide evidence for PM effects on CVD hospital admissions independent of co-pollutant effects, a number of other studies examining co-pollutants did not find results indicative of independent PM_{10} effects on CVD hospital admissions

With respect to particle size, only a handful of studies have examined the relative effects of different particle indicators (Lippmann et al., 2000; Burnett et al., 1997a; Tolbert et al., 2000a; Steib et al., 2000; Moolgavkar, 2000b). Perhaps due to statistical power issues, no clear picture has emerged as to particle-size fraction(s) most associated with acute CVD effects.

As discussed above, several studies originally based on statistical analyses involving the SPlus GAM function have reported new results using alternative statistical methods. The reanalyses yielded some slightly reduced effect estimates and/or increased confidence intervals or little or no change resulted in other cases. Thus, based on these new results, the overall conclusions from the cardiovascular hospitalization studies remain the same.

Because hospitalization can be viewed as likely reflecting some of the same pathophysiologic mechanisms that may be responsible for acute mortality following PM exposure, it is of interest to assess the coherence between the morbidity results reviewed here and the mortality results reviewed in Section 8.2.2 (Borja-Aburto et al., 1997, 1998; Braga et al., 2001; Goldberg et al., 2000; Gouveia and Fletcher, 2000; Hoek et al., 2001; Kwon et al., 2001; Michelozzi et al., 1998; Morgan et al., 1998; Pönkä et al., 1998; Schwartz et al., 1996a; Simpson et al., 1997; Wordley et al., 1997; Zeghnoun et al., 2001; Zmirou et al., 1998). The mortality studies reported significant associations between acute CVD mortality and measures of ambient

PM, though the PM metrics used and the relative risk estimates obtained varied across studies. The PM measurement methods included gravimetrically analyzed filter samples (TSP, PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$), beta gauge (particle attenuation of beta radiation), nephelometry (light scattering), and black smoke (filter reflectance). Where tested, PM associations with acute CVD mortality appeared to be generally more robust to inclusion of gaseous covariates than was the case for acute hospitalization studies (Borja-Aburto et al., 1997, 1998; Morgan et al., 1998; Wordley et al., 1997; Zmirou et al., 1998). Three studies (Braga et al., 2001; Goldberg et al., 2000; Hoek et al., 2001), as noted in Section 8.2.2, provide data indicating that some specific CVD causes of mortality (such as heart failure) were more strongly associated with air pollution than total CVD mortality; but it was noted that ischemic heart disease (which contributes about half of all CVD deaths) was the strongest contributor to the association between air pollution and cardiovascular mortality. The above-noted results for acute CVD mortality are qualitatively consistent with those reviewed earlier in this section for hospital admissions.

Figure 8-10 illustrates PM_{10} excess risk estimates for single-pollutant models derived from selected U.S. studies of PM_{10} exposure and total CVD hospital admissions, standardized to a 50 $\mu g/m^3$ exposure to PM_{10} as shown in Table 8-16. Results are shown both for studies yielding pooled outcomes for multiple U.S. cities and for studies of single U.S. cities. The Zanobetti and Schwartz (2003b) and Samet et al. (2000a) pooled cross-city results for 14 U.S. cities provide the most precise estimate for relationships of U.S. ambient PM_{10} exposure to increased risk for CVD hospitalization. That estimate, and those derived from most other studies depicted in Figure 8-10, generally appear to confirm likely excess risk of CVD-related hospital admissions for U.S. cities in the range of 3-9% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$ 65 yr). Other individual-city results (see Table 8-16) from Detroit are also indicative of excess risk for ischemic heart disease in the range of approximately 3.0 and 8.1% per 25 $\mu g/m^3$ of $PM_{2.5}$ or $PM_{10-2.5}$, respectively, and for heart failure of 6.8% and 4.9% excess risk per 25 $\mu g/m^3$ of $PM_{2.5}$ and $PM_{10-2.5}$, respectively. However, the extent to which PM affects CVD-hospitalization risks independently of, or together with other co-pollutants (such as CO), remains to be further resolved.

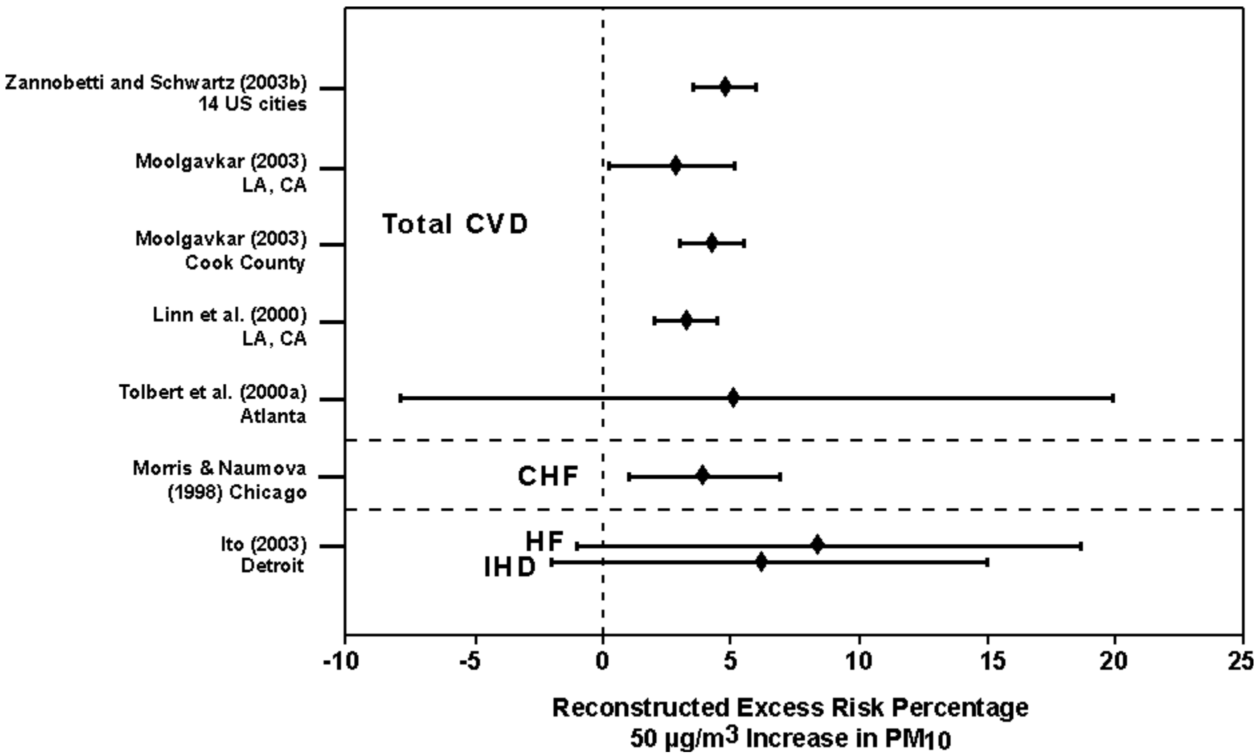

Figure 8-10. Acute cardiovascular hospitalizations and particulate matter exposure excess risk estimates derived from selected U.S. PM_{10} studies based on single-pollutant models. Both multi-pollutant models and $PM_{2.5}$ and $PM_{10-2.5}$ results are shown in Table 8-16. CVD = cardiovascular disease. CHF = congestive heart failure. HF = heart failure. IHD = ischemic heart disease.

8.3.1.3.4 Individual-Level Studies of Cardiovascular Physiology

Several new studies have evaluated longitudinal associations between ambient PM and physiologic measures of cardiovascular function or biochemical changes in the blood that may be associated with cardiac risks. In contrast to the ecologic time-series studies discussed above, these studies measure outcomes and most covariates at the individual level, making it possible to draw conclusions regarding individual risks, as well as to explore mechanistic hypotheses. Heterogeneity of responses across individuals, and across subgroups defined on the basis of age, sex, pre-existing health status, etc., also can be assessed, in principle. While exposure assessment remains largely ecologic (i.e., the entire population is usually assigned the same exposure value on a given day), exposure is generally well characterized in the small, spatially-clustered study populations. The recent studies fall into two broad classes: (1) those addressing cardiac rhythm or adverse events and (2) those addressing blood characteristics. While significant uncertainty still exists regarding the interpretation of results from these new studies, the varied responses that have been reported to be associated with ambient PM and co-pollutants are of much interest in regard to mechanistic hypotheses concerning pathophysiologic processes potentially underlying CVD-related mortality/morbidity effects discussed in preceding sections.

Cardiac Physiology and Adverse Cardiac Events

Alterations in heart rate and/or rhythm have been hypothesized as reflecting pathophysiologic changes that may be possible mechanisms by which ambient PM exposures may exert acute effects on human health. Decreased heart rate variability, in particular, has been identified as a predictor of increased cardiovascular morbidity and mortality. Several independent studies have recently reported temporal associations between PM exposures and various measures of heart beat rhythm in panels of elderly subjects (Liao et al., 1999; Pope et al., 1999a,b,c; Dockery et al., 1999; Peters et al., 1999a, 2000a; Gold et al. 2000; Creason et al., 2001). Changes in blood pressure may also reflect increases in CVD risks (Linn et al., 1999; Ibald-Mulli et al., 2001). Finally, one important new study (Peters et al., 2001a) has linked acute (2- and 24-h) ambient $PM_{2.5}$ and PM_{10} concentrations with increased risk of myocardial infarction in subsequent hours and days.

Liao et al. (1999) studied 26 elderly subjects (age 65-89 years; 73% female) over three consecutive weeks at a retirement center in metropolitan Baltimore, 18 of whom were classified as “compromised” based on previous cardiovascular conditions (e.g., hypertension). Daily six-minute resting electrocardiogram (ECG) data were collected, and time intervals between sequential R-R intervals recorded. A Fourier transform was applied to the R-R interval data to separate its variance into two major components: low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.40 Hz). The standard deviation of all normal-to-normal (N–N; also designated R-R) heartbeat intervals (SDNN) was computed as a time-domain outcome variable. $PM_{2.5}$ was monitored indoors by TEOM and outdoors by dichotomous sampler. Outdoor $PM_{2.5}$ levels ranged from 8.0 to 32.2 $\mu g/m^3$ (mean = 16.1 $\mu g/m^3$). Regression analyses controlled for inter-subject differences in average variability, allowing each subject to serve as his/her own control. Consistent associations were seen between increases in $PM_{2.5}$ levels (both indoors and outdoors) and decreases in all three outcome variables (LF, HF, SDNN), with associations being stronger for the 18 “compromised” subjects. The short time interval (6 min per day) of measurement for these parameters hampers interpretation of the possible medical significance of the reported positive results, longer or several measurements per day allowing for clearer indications of likely underlying perturbation of CV function.

Creason et al. (2001) reported results of a subsequent study using similar methods among 56 elderly residents of a retirement center in Baltimore County, MD. The 11 men and 45 women ranged in age from 72 to 97 years and were all Caucasian. Associations between ambient $PM_{2.5}$ and decreased HRV were not statistically significant at $p < 0.05$. When two episodic $PM_{2.5}$ days with rainfall were excluded from the 24-day data set, trends associating decreased HRV and $PM_{2.5}$ were present, but did not meet significance at $p < 0.05$. There was no evidence of effects among subsets of subjects with compromised health status as observed previously in the study by Liao et al. (1999). No results were presented for pollutants other than $PM_{2.5}$.

Pope and colleagues (1999c), using ambulatory ECG monitoring, studied HRV and PM_{10} in a panel of six elderly subjects (69-89 years, 5/6 male) and one 23-year old male subject, all compromised by some form of heart disease. SDNN, SDANN, and r-MSSD were used as measures of HRV based on 48-hr holter readings. Daily gravimetric PM_{10} data from three sites in the study area ranged from ~10 $\mu g/m^3$ to 130 $\mu g/m^3$ during the study, with high levels occurring only during the first half of the 1.5 month study period. No co-pollutants (e.g., O_3, CO, NO_2, etc.) were studied. Regression analyses with subject-specific intercepts were performed, with and without control for daily barometric pressure and mean heart rate. Same-day and previous-day ambient PM_{10} were negatively associated with SDNN and SDANN; and the results were unaffected by inclusion of covariates. Heart rate, as well as r-MSSD, were both positively, but less strongly, associated with PM_{10}. No co-pollutants were studied. The specific heart rate variability findings (i.e., PM associations with decreased SDANN and SDNN and increased r-MSSD) make it difficult to interpret the results or their cardiac health significance. The decreased SDANN and SDNN suggests decreased sympathetic activity, whereas the r-MSSD increase suggests increase parasympathetic (vagal) input to the heart (which is likely protective in terms of risk of ischemic related arrhythmia, but might increase the risk of atrial arrhythmia). These specific HRV findings do not allow clear conclusions as to how PM may be affecting cardiac functioning.

The Pope et al. (1999c) study discussed above was nested within a larger cohort of 90 subjects who participated in a study of heart rate and oxygen saturation in the Utah Valley (Dockery et al., 1999; Pope et al., 1999b). The investigators hypothesized that decreases in oxygen saturation might occur as a result of PM exposure, and that this could be a risk factor for adverse cardiac outcomes. The study was carried out in winter months (mid-November through mid-March), when frequent inversions lead to fine particle episodes. PM_{10} levels at the three nearest sites averaged from 35 to 43 $\mu g/m^3$ during the study, and daily 24-h levels ranged from 5 to 147 $\mu g/m^3$. Two populations were studied: 52 retired Brigham Young University faculty/staff and their spouses, and 38 retirement home residents. Oxygen saturation (SpO_2) and heart rate (HR) were measured once or twice daily by an optical sensor applied to a finger. In regression analyses controlling for inter-individual differences in mean levels, SpO_2 was not associated with PM_{10}, but was highly associated with barometric pressure. In contrast, HR association with PM_{10} significantly increased but significantly decreased with barometric pressure in joint regressions. Including CO in the regressions did not change these basic findings. This was the first study of this type to examine the interrelationships among physiologic measures (i.e., SpO_2 and HR), barometric pressure, and PM_{10}. The profound physiological effects of barometric pressure noted here highlight the importance of carefully controlling for barometric pressure effects in studies of cardiac physiology.

Gold and colleagues (2000) obtained somewhat different results in a study of heart rate variability among 21 active elderly subjects, aged 53-87 yr, in a Boston residential community. Resting, standing, exercising, and recovering ECG measurements were performed weekly using a standardized protocol on each subject, which involved 25 min/week of continuous Holter ECG monitoring. Two time-domain measures were extracted: SDNN and r-MSSD (see above for definitions). Heart rate also was analyzed as an outcome. Continuous PM_{10} and $PM_{2.5}$ monitoring was conducted by TEOM at a site 6 km from the study site and PM data were corrected for the loss of semivolatile mass. Data on CO, O_3, NO_2, SO_2, temperature and relative humidity were available from nearby sites. Outcomes were regressed on $PM_{2.5}$ levels in the 0-24 hour period prior to ECG testing, with and without control for HR and temperature. As for the other studies discussed above, declines in SDNN were associated with $PM_{2.5}$ levels, in this case averaged over 4 hours. These associations reached statistical significance at the $p < 0.05$ level only when all testing periods (i.e., resting, standing, exercise) were combined.

In contrast to the above studies, both HR and r-MSSD here were negatively associated with $PM_{2.5}$ levels (i.e., lower HR and r-MSSD) when $PM_{2.5}$ was elevated. These associations were statistically significant overall, as well as for several of the individual testing periods, and were unaffected by covariate control. Gold et al. (2003) subsequently reported reanalyses involving temperature with either a GAM function with stringent convergence criteria or a GLM with natural splines, with no substantial changes in results being reported. The negative associations between $PM_{2.5}$ and decreases in both HR and r-MSSD are puzzling, given that decreased HR is indicative of increased parasympathetic tone whereas decreased r-MSSD is reflective of decreased parasympathetic modulation of heart function. This discrepancy raises the possibility that one or another or both of the observed outcomes may be due to chance.

Evidence for decreased HRV in response to $PM_{2.5}$ exposures comes from several other recent studies. Magari et al. (2001) found significant decreases in SDNN of 1.4% (95% CI = 2.1 to −0.6) per 100 ug/m^3 3-hr mean $PM_{2.5}$ in young healthy Boston area boilermakers studied during non-work periods. Another study of 40 boilermakers (including the 20 studied above) analyzed data collected during both work and non-work periods (Magari et al., 2002). That study found a significant 2.7% decrease in SDNN and a 1.0% increase in HR for every 100 µg/m^3 increase in 4-hr moving average of estimated $PM_{2.5}$. The larger effect size for the non-work PM exposure study may reflect differing health effects of ambient versus occupational PM composition. These studies are suggestive of PM-related HRV effects in young healthy adults, but use of estimated $PM_{2.5}$ based on light scattering precludes firm quantitative interpretation of exposure levels.

Peters et al. (1999a) reported HR results from a retrospective analysis of data collected as part of the MONICA (monitoring of trends and determinants in cardiovascular disease) study in Augsburg, Germany. Analyses focused on 2,681 men and women aged 25-64 years who had valid ECG measurements taken in winter 1984-1985 and again in winter 1987-1988. Ambient pollution variables included TSP, SO_2, and CO. The earlier winter included a 10-day episode with unusually high levels of SO_2 and TSP, but not of CO. Pollution effects were analyzed in two ways: dichotomously comparing the episode and non-episode periods, and continuously using regression analysis. However, it is unclear from the report as to what extent the analyses reflect between-subject versus within-subject effects. A statistically significant increase in mean heart rate was seen during the episode period versus other periods, controlling for cardiovascular risk factors and meteorology. Larger effects were seen in women. In single-pollutant regression analyses, all three pollutants were associated with increased HR. More recently, Ibald-Mulli et al. (2001) reported similar findings from a study of blood pressure among 2607 men and women aged 25-64 years in the MONICA study. Systolic blood pressure increased on average during an episode of elevated TSP and SO_2, but the effect disappeared after controlling for meteorological parameters (e.g., temperature and barometric pressure). However, when TSP and SO_2 were analyzed as continuous variables, both were associated with elevated systolic blood pressure, controlling for meteorological variables. In two-pollutant models, TSP was more robust than SO_2, and the TSP association was greater in subgroups of subjects with elevated blood viscosity and heart rates.

Linn et al. (1999) reported associations between both diastolic and systolic blood pressure and PM_{10} in a panel study of 30 Los Angeles residents with severe COPD. The relationship was not observed when inside-home PM levels were used in the analyses. Also, no relationship was found between PM levels and heart rate or arrhythmias, based on 48 hours of holter data.

In a retrospective study, Peters and colleagues (2000a) examined incidence of cardiac arrhythmias among 100 patients (mean age 62.2 yr.; 79% male) with implanted cardiovertex defibrillators followed over a three year period. Shocks from cardiovertex defibrillators are frequently used for life-threatening arrhythmias but not always (only ~65-70% are for life-threatening arrhythmias). $PM_{2.5}$ and PM_{10} were measured in South Boston by the TEOM method, along with black carbon, O_3, CO, temperature and relative humidity; SO_2 and NO_2 data were obtained from another site. The 5^{th} percentile, mean, and 95^{th} percentiles of PM_{10} levels were 7.8, 19.3, and 37.0 µg/m^3, respectively. The corresponding $PM_{2.5}$ values were 4.6, 12.7, and 26.6 µg/m^3. Logistic regression was used to analyze events in relation to pollution variables, controlling for between-person differences, seasons, day-of-week, and meteorology in two subgroups: 33 subjects with at least one arrhythmia event and 6 subjects with 10 or more such events. In the larger subgroup, only NO_2 on the previous day, and the mean NO_2 over five days, were significantly associated with arrhythmia incidence. In patients with 10 or more events, the NO_2 associations were stronger. Also, some of the $PM_{2.5}$ and CO lags became significant in this subgroup. Important caveats regarding this study include the fact that the vast majority of cardiovertex defibrillator discharges occurred among a small subset (i.e., 6) of the patients.

Also, potentially important variables, e.g., cardiovascular drug usage and anti-arrhythmia drug changes during follow-up, were not reported.

Checkoway (1999) has reported a Seattle mortality study of PM_{10} levels and cases of patients experiencing out-of-hospital sudden cardiac death (SCD). They used a case-crossover study design in 362 subjects suffering an SCD episode. They evaluated PM levels over the 5 days preceding SCD and compared those levels to levels recorded in the same month and during the same days of the week (Mean PM_{10} level = 31.9 $\mu g/m^3$). They evaluated lags of 0 to 5 days looking for a correlation. These investigators found no correlation between SCD episodes and PM levels even after controlling for multiple confounding variables. They reported an estimated relative risk at a one day lag of 0.87 (95% CI 0.74, 1.01). The HEI (2000) review commentary noted that the authors reported, from their power calculations, that the sample size (362) was not large enough to either find or rule out a relative risk less than 1.5 and that lack of association with PM in this study does not imply that other cardiac or cardiovascular disease outcomes are not associated with PM. These negative findings suggest that PM may not be a risk factor for acute myocardial infarction in previously healthy individuals, or that the pattern and/or mix of PM exposures in Seattle, where woodsmoke may be an important component, may convey lesser risk than observed elsewhere.

An exploratory study of a panel of COPD patients (Brauer et al., 2001) examined several PM indicators in relation to CVD and respiratory health effects. The very low levels of ambient particles (PM_{10} mean = 19 $\mu g/m^3$) and low variability in these levels plus the sample size of 16 limit the conclusions that can be drawn. Still, for cardiovascular endpoints, single-pollutant models indicated that both systolic and diastolic BP decreased with increasing exposure, but this was not statistically significant. Also, 24-h holter monitoring data recorded on 7 separate days for each individual did not show any heart rate variability changes associated with PM levels. The size of the ambient PM_{10} effect estimate for ΔFEV_1 was larger than the effect estimate for ambient $PM_{2.5}$ and personal $PM_{2.5}$ but not statistically significant. This initial effort indicated that ambient PM_{10} consistently had the largest effect estimates, whereas while models using personal exposure measurements did not show larger or more consistently positive effect estimates relative to those models using ambient exposure metrics.

An important study by Peters et al. (2001a) reported associations between onset of myocardial infarction (MI) and ambient PM (either PM_{10} or $PM_{2.5}$) as studied in a cohort of 772 MI patients in Boston, MA. Precise information on the timing of the MI, obtained from patient interviews, was linked with concurrent air quality data measured at a single Boston site. A case crossover design enabled each subject to serve as his/her own control. One strength of this study was its analysis of multiple PM indices and co-pollutants, including real-time $PM_{2.5}$, PM_{10}, the $PM_{10-2.5}$ difference, black carbon, O_3, CO, NO_2, and SO_2. Only $PM_{2.5}$ and PM_{10} were significantly associated with MI risk in models adjusting for season, meteorological parameters, and day of week. Both the mean $PM_{2.5}$ concentration in the previous two hours and in the 24 hours lagged one day were independently associated with MI, with odds ratios of 1.48 (1.09-2.02) for 25 ug/m^3 and 1.62 (1.13-2.34) for 20 ug/m^3, respectively. PM_{10} associations were similar. The non-significant findings for other pollution metrics should be interpreted in the context of potentially differing exposure misclassification errors associated with the single monitoring site.

The above studies present a range of findings regarding possible effects of $PM_{2.5}$ on cardiac rhythm and adverse events. However, the studies offer conflicting results, especially with regard to HRV findings. Several reported PM levels to be associated with decreases in one or more HR variability measured in elderly subjects with preexisting cardiopulmonary disease, although increased r-MSSD (a measure of high-frequency HR variability) was found to be associated with PM elevations in at least one study (Pope et al., 1999a). Several other found no changes related to PM levels (Creason, et al., 2001) or blood pressure (Brauer et al., 2001). Some recent studies have also reported effects in healthy elderly and young adult populations. All those studies which examined HR found associations with PM; most being positive associations; but one (Gold et al., 2000; Gold et al., 2003) reported a negative relationship. Overall, variations in methods used and discrepancies in results obtained across the studies argue for caution in drawing any conclusions yet regarding ambient PM effects on heart rate variability or other ECG measures of cardiovascular parameters.

Viscosity and Other Blood Characteristics

Peters et al. (1997a) state that plasma viscosity, a risk factor for ischemic heart disease, is affected by fibrinogen and other large asymmetrical plasma proteins, e.g., immunoglobulin M and $\propto_2$-macroglobulin. They note that, in a cohort study of elderly men and women, fibrinogen levels were strongly related to inflammatory markers, such as neutrophil count and acute-phase proteins (C-reactive protein and $\propto_1$-antichymotrypsin) and self-reported infections.

Support for a mechanistic hypothesis, relating to enhanced blood viscosity, was suggested by an analysis of plasma viscosity data collected in a population of 3256 German adults in the MONICA study (Peters et al., 1997a). Each subject provided one blood sample during October 1984 to June 1985. An episode of unusually high air pollution levels occurred during a 13 day period while these measurements were being made. Among the 324 persons who provided blood during the episode, there was a statistically significant elevation in plasma viscosity as compared with 2932 persons studied at other times. The odds ratio for plasma viscosity exceeding the 95^{th} percentile was 3.6 (CI 1.6−8.1) among men and 2.3 (CI 1.0−5.3) among women. Analysis of the distribution of blood viscosity data suggested that these findings were driven by changes in the upper tail of the distribution rather than by a general shift in mean viscosity, consistent with the likelihood of a susceptible sub-population.

A prospective cohort study of a subset of male participants from the above-described Augsburg, Germany MONICA study was reported by Peters et al. (2001b). Based on a survey conducted in 1984/85, a sample of 631 randomly selected men (aged 45-64 yr and free of cardiovascular disease at entry) were evaluated in a 3-yr follow-up that examined relationships of air pollution to serum C-reactive protein concentrations. C-reactive protein is a sensitive marker of inflammation, tissue damage, and infections, with acute and chronic infections being related to coronary events. Inflammation is also related to systemic hypercoagulability and onset of acute ischemic syndromes. During the 1985 air pollution episode affecting Augsburg and other areas of Germany, the odds of abnormal increases in serum C-reactive protein (i.e., $\geq 90^{th}$ percentile of pre-episode levels = 5.7 mg/L) tripled; and associated increases in TSP levels of 26 $\mu g/m^3$ (5-day averages) were associated with an odds ratio of 1.37 (95% CI 1.08-1.73) for C-reactive protein levels exceeding the 90^{th} percentile levels in two pollutant models that included SO_2 levels. The estimated odds ratio for a 30 $\mu g/m^3$ increase in the 5-day mean for SO_2 was 1.12 (95% CI 0.92−1.47).

Other studies have examined blood indices in relation to PM pollution in United Kingdom cities. Seaton and colleagues (1999) collected sequential blood samples (up to 12) over an 18 month period in 112 subjects (all over age 60) in Belfast and Edinburgh, UK. Blood samples were analyzed for hemoglobin, packed cell volumes, fibrinogen, blood counts, factor VII, interleuken 6, and C-reactive protein. In a subset of 60 subjects, plasma albumin also was measured. PM_{10} data monitored by TEOM were collected from ambient sites in each city. Personal exposure estimates for three days preceding each blood draw were derived from ambient PM data adjusted by time-activity patterns and I/O penetration factors. No co-pollutants were analyzed. Data were analyzed by analysis of covariance, controlling for city, seasons, temperature, and between-subject differences. Significant changes in several blood indices were associated with either ambient or estimated personal PM_{10} levels. All changes were negative, except for C reactive protein in relation to ambient PM_{10}. Prescott et al. (2000) also investigated factors that might increase susceptibility to PM-related cardiovascular events for a cohort of 1,592 subjects aged 55-74 in Edinburgh, UK. Baseline measurements of blood fibrinogen and blood and plasma viscosity were examined as modifiers of PM effects (indexed by BS) on the incidence of fatal and non-fatal myocardial infarction or stroke. All three blood indices were strong predictors of increased cardiac event risk; but there was no clear evidence of either a main effect of BS, nor interactions between BS and blood indices.

In another European study, Pekkanen and colleagues (2000) analyzed plasma fibrinogen data from a cross-sectional survey of 4,982 male and 2,223 female office workers in relation to same-day and previous three-day PM_{10}, black smoke, NO_2, CO, SO_2, and O_3 concentrations. In the full analysis, NO_2 and CO were significantly associated with fibrinogen levels. When the analysis was restricted to the summer season, NO_2 and CO, as well as PM_{10} and black smoke, showed significant univariate associations.

Schwartz (2001) later reported analyses for possible blood coagulability effects in the United States, finding not only significant associations between PM_{10} exposures and plasma fibrinogen levels a subset of the NHANES III cohort, but also PM_{10} associations with platelet and white cell counts, the PM_{10} associations being robust when O_3, NO_2, or SO_2 were included. CO was not analyzed.

The above findings add support for intriguing hypotheses about possible mechanisms by which PM exposure may be linked to adverse cardiac outcomes. They are interesting in implicating both increased blood viscosity and C-reactive protein, a biological marker of inflammatory responses thought to be predictive of increased risk for serious cardiac events.

8.3.1.4 Issues in the Interpretation of Acute Cardiovascular Effects Studies

Susceptible subpopulations. Because they lack extensive data on individual subject characteristics, hospital admissions studies provide only limited information on susceptibility factors based on stratified analyses. The relative effect sizes for PM-cardiovascular associations (and respiratory) admissions reported in ecologic time-series studies are generally somewhat higher than those for total admissions. This provides some limited support for hypothesizing that acute PM effects operate via cardiopulmonary pathways or that persons with pre-existing cardiopulmonary disease have greater susceptibility to PM, or both. Although there is some data from ecologic time-series studies showing larger PM effects on cardiovascular admissions in adults aged ≥ 65 yr versus younger populations, the differences are neither striking nor consistent. One recent study reported larger CVD hospitalization among persons with current respiratory infections. The individual-level studies of cardiophysiologic function assessed above are suggestive but do not yet fully confirm, that elderly persons with pre-existing cardiopulmonary disease are susceptible to subtle changes in heart rate variability in association with PM exposures. More data are needed before that conclusion can be drawn with confidence. Because younger and healthier populations have not yet been much studied, it is not yet possible to say whether PM will affect their health status or if the elderly are more at risk for PM-related cardiovascular effects.

Role of other environmental factors. The time-series studies published since 1996 have all controlled adequately for weather influences. Thus, it is deemed unlikely that residual confounding by weather accounts for the observed PM associations. With one possible exception (Pope et al., 1999a), the roles of meteorological factors have not been analyzed extensively as yet in the individual-level studies of cardiac function. Thus, the possibility of confounding in such studies cannot yet be fully discounted. Co-pollutants have been analyzed extensively in many recent time-series studies of PM and hospital admissions. In some studies, PM clearly has an independent association after controlling for gaseous co-pollutants. In others, the PM effects are reduced once co-pollutants are added to the model; but this may be in part due to colinearity between PM_{10} and co-pollutants and/or gaseous pollutants (e.g., CO) having independent effects on cardiovascular function.

Temporal patterns of responses following PM exposure. The evidence from recent time-series studies of CVD admissions suggests rather strongly that PM effects tend to be maximal at lag 0, with some carryover to lag 1, with little evidence for important effects beyond lag 1.

Relationship of CVD effects to PM size and chemical composition attributes. Insufficient data exist from the time-series CVD admissions studies or the emerging individual-level studies to provide clear guidance as to which ambient PM components, defined on the basis of size or composition, determine ambient PM CVD effect potency. The epidemiologic studies have been constrained by limited availability of multiple PM metrics. Where multiple metrics exist, they often are highly correlated or are of differential quality due to differences in numbers of monitoring sites and monitoring frequency.

PM effects on blood characteristics related to CVD events. Interesting, though limited, new evidence has also been derived which is highly suggestive of associations between ambient PM and increased blood viscosity, increased serum C-reactive protein, and fibrinogen (both related to increased risks of serious cardiac events).

8.3.2 Effects of Short-Term Particulate Matter Exposure on the Incidence of Respiratory-Related Hospital Admissions and Medical Visits

8.3.2.1 Introduction

Although hospital admissions represent one severe morbidity measure evaluated in regard to PM exposure, hospital emergency department (ED) visits are a notable related outcome. Doctors' visits also represent another related health measure that, although less studied, is still very relevant to assessing air pollution public health impacts. This category of pollution-affected persons can represent a large population, yet one largely unevaluated due to the usual lack of centralized data records for doctors' visits in the United States.

This section evaluates information on epidemiologic associations of ambient PM exposure with both respiratory hospital admissions and medical visits. It intercompares various studies examining size-related PM mass exposure measures (e.g., for PM_{10}, $PM_{2.5}$, etc.) or various PM chemical components vis-à-vis their associations with such health endpoints, and discusses their respective extents of coherence with PM associations across related health effects measures.

In the following discussion, the main focus for quantitative intercomparisons is on studies considering PM metrics that measure mass or a specific mass constituent, i.e., PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, or sulfates (SO_4^{-2}). Study results for other related PM metrics (e.g., BS) are also considered, but only qualitatively, primarily with respect to their relative coherence with studies using mass or composition metrics measured in North America. In order to consider potentially confounding effects of other co-existing pollutants, study results for various PM metrics are presented both for (1) when the PM metric is the only pollutant in the model and (2) the case where a second pollutant (e.g., O_3) is also included. Results from models with more than two pollutants included simultaneously, however, are not used for quantitative estimates of effect size or statistical strength, because of increased likelihood of bias and variance inflation due to multi-collinearity of various pollutants (e.g., see Harris, 1975).

8.3.2.2 Summary of Key Respiratory Hospital Admissions Findings from the 1996 Particulate Matter Air Quality Criteria Document

In the 1996 PM AQCD, both COPD and pneumonia hospitalization studies were found to show moderate, but statistically significant, relative risks in the range of 1.06 to 1.25 (or 6 to 25% excess risk increment) per 50 µg/m^3 PM_{10} increase or its equivalent. Whereas many hospitalizations for respiratory illnesses occur in those > 65 years of age, there were also increased hospitalizations for those < 65 years of age. Several hospitalization studies restricted their analysis by age group, but did not explicitly examine younger age groups. One exception noted was Pope (1991), who reported increased hospitalization for Utah Valley children (0 to 5 yrs) for monthly numbers of admissions in relation to PM_{10} monthly averages, as opposed to daily admissions in relation to daily PM levels used in other studies. Studies examining acute associations between indicators of components of fine particles (e.g., BS; sulfates, $SO_4^{=}$; and acidic aerosols, H^+) and hospital admissions were reported, too, as showing significant relationships. While sulfates were especially predictive of respiratory health effects, it was not clear whether the sulfate-related effects were attributable to their acidity, to the broader effects of associated combustion-related fine particles, or to other factors.

8.3.2.3 New Respiratory-Related Hospital Admissions Studies

New studies appearing since the 1996 PM AQCD have examined various admissions categories, including: total respiratory admissions for all ages and by age; asthma for all ages and by age; chronic obstructive pulmonary disease (COPD) admissions (usually for patients > 64 yrs.), and pneumonia admissions (for patients > 64 yrs.). Table 8B-2, Appendix 8B summarizes salient details regarding the study area, study period, study population, PM indices considered and their concentrations, methods employed, study results, and “bottom-line” PM index percent excess risks per standard PM increment (e.g., 50 μg/m^3 for PM_{10}) for the newer studies.

The percent excess risk (ER) estimates presented in Table 8B-2 are based upon the relative risks (RR’s) provided by the authors, but converted into percent increments per standardized increments used by the U.S. EPA to facilitate direct intercomparisons of results across studies (as discussed in Section 8.1). The ER’s shown in the table are for the most positively significant pollutant coefficient; and the maximum lag model is used to provide estimates of potential pollutant-health effects associations.

Based on information from Dominici et al. (2002) indicating that the default convergence criteria used in the S-Plus function GAM may not guarantee convergence to the best unbiased estimate (as discussed earlier), only those studies that used other statistical algorithms or which have reported reanalyzed S-Plus GAM results are assessed in the text below. However, given the modest effects of this reanalysis on most study results (i.e., while effect estimates are modified somewhat, the study conclusions remain largely unchanged), Table 8B-2 includes all studies and notes those that originally used the S-Plus GAM algorithm, as well as which of those studies have since been reanalyzed with more appropriate methods.

Of most pertinence here are those newly available studies that evaluate associations between one or another ambient PM metric and respiratory hospital admissions in U.S. or Canadian cities, as for PM_{10} mass concentrations are summarized in Table 8-17.

Among numerous new epidemiologic studies of PM_{10} morbidity, many evaluated relatively high PM_{10} levels. However, some did evaluate associations with PM_{10} concentrations ranging to rather low levels. Of note is the fact that associations have been reported by several investigators between acute PM_{10} exposures and total respiratory-related hospital admissions for numerous U.S. cities with annual mean PM_{10} concentrations extending to below 50 μg/m^3. On this account, the results of the NMMAPS multi-city study (Samet et al., 2000a,b) of PM_{10} levels and hospital admissions by persons $\geq$ 65 in 14 U.S. cities are of particular interest. As noted in Table 8-18, this study indicates PM_{10} effects similar to other cities, but with

TABLE 8-17. SUMMARY OF UNITED STATES PM_{10} RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels (ug/m³)	Co-Pollutants Measured	Day Lag	Method	Effect Estimate (95% CL) (% increase per 50 ug/m³)
Schwartz et al. (1996b)	Respiratory	PM_{10} = 43	SO_3	—	Poisson GLM	5.8 (0.5, 11.4)
Samet et al. (2000a,b)*	COPD	PM_{10} = 33	SO_2, O_3, NO_2, CO	1	Default GAM Default GAM	7.4 (5.1, 9.8) 7.5 (5.3, 9.8)
Reanalysis by Zanobetti and Schwartz (2003b)				0-1 0-1 0-1 0-1	Default GAM Strict GAM NS GLM PS GLM	9.4 (5.9, 12.9) 8.8 (4.8, 13.0) 6.8 (2.8, 10.8) 8.0 (4.3, 11.9)
Lippmann et al. (2000)*	COPD	PM_{10} = 31	SO_2, O_3, NO_2, CO, H^+	33	Default GAM Default GAM	No Co Poll: 9.6 (−5.3, 26.8) Co Poll: 1.0 (−15, 20)
Reanalysis by Ito (2003)				3	Default GAM Strict GAM NS GLM	No Co Poll: 9.6 (−5.3, 26.8) No Co Poll: 6.5 (−7.8, 23.0) No Co Poll: 4.6 (−9.4, 20.8)
Moolgavkar (2000c)*	COPD (> 64 yrs) (median)	PM_{10} = 35, Chicago PM_{10} = 44, LA PM_{10} = 41, Phoenix PM_{10} = 44, LA	— — — CO	202	Default GAM: 30df Default GAM: 30df Default GAM: 30df Default GAM: 30df	2.4 (−0.2, 5.11) 6.1 (1.1, 11.3) 6.9 (−4.1, 19.3) 0.6 (−5.1, 6.7) (two poll. model)
Reanalysis by Moolgavkar (2003)	COPD (> 64 yrs)	Chicago		0	Strict GAM: 100df	3.24 (.031, 6.24)
Reanalysis by Moolgavkar (2003)	COPD (all ages)	Los Angeles		222	Strict GAM: 30df Strict GAM: 100df NS GLM: 100df	7.78 (4.32-10.51) 5.52 (2.53-8.59) 5.00 (1.22, 8.91)
Samet et al. (2000a,b)*	Pneumonia	PM_{10} = 33	SO_2, O_3, NO_2, CO	1	Default GAM Default GAM	8.1 (6.5, 9.7) 6.7 (5.3, 8.2)
Reanalysis by Zanobetti and Schwartz (2003b)				0-1 0-1 0-1 0-1	Default GAM Strict GAM NS GLM PS GLM	9.9 (7.4, 12.4) 8.8 (5.9, 11.8) 2.9 (0.2, 5.6) 6.3 (2.5, 10.3)
Lippmann et al. (2000)	Pneumonia	PM_{10} = 31	SO_2, O_3, NO_2, CO, H^+	11	Default GAM Default GAM	No Co Poll: 21.4 (8.2, 36.3) Co Poll: 24 (8.2, 43)
Reanalysis by Ito (2003)	Pneumonia			111	Default GAM Strict GAM NS GLM	No Co Poll: 21.5 (8.3, 36) No Co-Poll: 18.1 (5.3, 32.5) No Co-Poll: 18.6 (5.6, 33.1
Jacobs et al. (1997)	Asthma	PM_{10} = 34	O_3, CO	—	Poisson GLM	6.11 (CI not reported)
Nauenberg and Basu (1999)	Asthma	PM_{10} = 45	O_3	0	Poisson GLM	16.2 (2.0, 30)
Tolbert et al. (2000b)	Asthma	PM_{10} = 39	O_3, NO_X	1	GEE	13.2 (1.2, 26.7)
Sheppard et al. (1999)*	Asthma	PM_{10} = 31	CO, O_3, SO_2	1	Default GAM	13.2 (5.5, 22.6)
Reanalysis by Sheppard (2003)					NS GLM Strict GAM	10.9 (2.8, 19.6) 8.1 (0.1, 16.7)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model

TABLE 8-18. PERCENT INCREASE IN HOSPITAL ADMISSIONS PER 10-µg/m^3 INCREASE IN PM_{10} IN 14 U.S. CITIES (ORIGINAL AND REANALYZED RESULTS)

Constrained lag models (Fixed Effect Estimates)	**% Increase**	**CVD (95% CI)**	**% Increase**	**COPD (95% CI)**	**% Increase**	**Pneumonia (95% CI)**
Original One day mean (lag 0)	1.07	(0.93, 1.22)	1.44	(1.00, 1.89)	1.57	(1.27, 1.87)
Original Previous day mean	0.68	(0.54, 0.81)	1.46	(1.03, 1.88)	1.31	(1.03, 1.58)
Original Two day mean (for lag 0 and 1)	1.17	(1.01, 1.33)	1.98	(1.49, 2.47)	1.98	(1.65, 2.31)
Reanalyzed Two day mean (for lag 0 and 1)	0.99	(0.79, 1.19)	1.71	(0.95, 2.48)	1.98	(1.65, 2.31)
Original PM_{10} < 50 µg/m^3 (two day mean)	1.47	(1.18, 1.76)	2.63	(1.71, 3.55)	2.84	(2.21, 3.48)
Reanalyzed PM_{10} < 50 µg/m^3 (two day mean)	1.32	(0.77, 1.87)	2.21	(1.02, 3.41)	1.06	(0.06, 2.07)
Original Quadratic distributed lag	1.18	(0.96, 1.39)	2.49	(1.78, 3.20)	1.68	(1.25, 2.11)
Reanalyzed Quadratic distributed lag	1.09	(0.81, 1.38)	2.53	(1.20, 3.88)	1.47	(0.86, 2.09)
Unconstrained distributed lag						
Fixed effects estimate	1.19	(0.97, 1.41)	2.45	(1.75, 3.17)	1.9	(1.46, 2.34)
Original Random effects estimate	1.07	(0.67, 1.46)	2.88	(0.19, 5.64)	2.07	(0.94, 3.22)
Reanalyzed Random effects estimate	1.12	(0.84, 1.40)	2.53	(1.21, 3.87)	2.07	(0.94, 3.22)

Source: Samet et al. (2000a,b) and Zanobetti and Schwartz (2003b) reanalyses.

narrower confidence bands, due to its greater power derived by combining multiple cities in the same analysis. This allows significant associations to be identified, despite the fact that many of the cities considered have relatively small populations and that each had mean PM_{10} below 50 µg/m^3. The cities considered and their respective annual mean/daily maximum PM_{10} concentrations (in µg/m^3) are Birmingham (34.8/124.8); Boulder (24.4/125.0); Canton (28.4/94.8); Chicago (36.4/144.7); Colorado Springs (26.9/147.2); Detroit (36.8/133.6); Minneapolis/St Paul (36.8/133.6); Nashville (31.6/128.0); New Haven (29.3/95.4); Pittsburgh (36.0/139.3); Provo/Orem (38.9/241.0); Seattle (31.0/145.9); Spokane (45.3/605.8); and Youngstown (33.1/104.0).

Table 8-18 also shows results of reanalyzing a number of the models considered in original research with the use of models using more stringent convergence requirements than the original default option. These results show that the effect estimates decline somewhat, but that the basic direction of effect and conclusions about the significance of the PM effect on hospital admissions remained unchanged.

Zanobetti and Schwartz (2003b), in their reanalyses, also considered spline models that are thought to better estimate confidence intervals around pollutant effect estimates than the original GAM analyses. With the spline models, confidence intervals usually increased over the original GAM model and the coefficients also decreased somewhat (similar to GAM with more stringent convergence criteria). As for possible co-pollutant confounding, it was reported that “In our previous studies we did not find confounding due to other pollutants. These results are confirmed in this reanalysis by the meta-regression analyses.” Overall, the authors concluded that “the general result is that the association of PM_{10} with hospital admissions remains and in most cases is little changed.”

Janssen et al. (2002) did further analyses for the Samet et al. (2000a,b) 14-city data set examining associations for variable prevalence in air-conditioning (AC) and/or contributions of different sources to total PM_{10}. For COPD and pneumonia, the associations were less significant, but the pattern of association was similar to that for CVD. The Zanobetti and Schwartz (2003b) reanalyses also examined these results, and they stated that “We still found a decreased PM_{10} effect with increasing percentage of home with central AC.”

Moolgavkar (2003) also reanalyzed his earlier GAM analyses of hospital admissions for chronic obstructive pulmonary disease (Moolgavkar, 2000c) Los Angeles (Los Angeles County) and Chicago (Cook County). In his original publication, Moolgavkar found ca. 5.0% excess risk for COPD hospital admissions among the elderly (64+ yr) in Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10\text{-}2.5}$ in one pollutant models; but the magnitudes of the risk estimates dropped by more than half to non-statistically significant levels in two-pollutant models including CO. However, unlike the meta-regression approach to the multiple pollutant issue used by Zanobetti and Schwartz (2003b), simultaneous regression of moderately to highly correlated pollutants can lead to biased pollutant coefficients and commonly results in diminished effect estimates for some or all of the pollutants considered. In the same study, similar magnitudes of excess risk (i.e., in the range of ca. 4 to 7%) were found in one-pollutant models to be associated with $PM_{2.5}$ or $PM_{10\text{-}2.5}$ for other age groups (0-19 yr; 20-64 yr) in Los Angeles, as well.

In his reanalyses of these GAM results using the more stringent convergence criteria, Moolgavkar (2003) combined all three Los Angeles age groups into one analysis, providing greater power, but also complicating before/after comparisons as to the actual effect of using the more stringent convergence criteria on the results. In the Cook County analyses, the author changed other model parameters (i.e., the number of degrees of freedom in the model smooths) at the same time as implementing more stringent convergence criteria; so direct before/after comparisons are not possible for Moolgavkar's (2003) Chicago analyses. Moolgavkar noted that "changes in the convergence criteria and the use of GLM instead of GAM can, but does not always, have substantial impact on the results of the analyses and their interpretation." He also concluded: "Given that different analytic strategies can make substantial differences to the estimates of effects of individual pollutants I do not believe that these numerical estimates are too meaningful. Patterns of association appear to be robust, however. For example, in Los Angeles, with the exception of COPD admissions with which NO_2 appears to show the most robust association, it is clear that CO is the best single index of air pollution associations with health end points, far better than the mass concentration of either PM_{10} or of $PM_{2.5}$. In Cook County the results are not so clear-cut, however, any one of the gases is at least as good an index of air pollution effects on human health as is PM_{10}."

Tolbert et al. (2000b) used generalized estimating equations (GEE), logistic regression, and Baysian models to evaluate associations between emergency department visits for asthma (by those < 17 yrs old) in Atlanta during the summers of 1993 – 1995 (~ 6000 visits for asthma out of ~ 130,000 total visits) and several air pollution variables (PM_{10}, O_3, total oxides of nitrogen). Logistic regression models controlling for temporal and demographic variables gave statistically significant ($p < 0.05$) lag 1 day relative risk estimates of 1.04 per 15 $\mu g/m^3$ 24-h PM_{10} increment and 1.04 per 20 ppb increase in maximum 8-h O_3 levels. In multipollutant models including both PM_{10} and O_3, the terms for each became non-significant due to high collinearity of the two variables ($r^2 = 0.75$). The authors interpreted their findings as suggesting positive associations between pediatric asthma visits and both PM_{10} and O_3. The PM_{10} effects appeared to be stronger for concentrations > 20 $\mu g/m^3$ than below that 24-h value.

Other U.S. studies finding associations of respiratory-related hospital admissions or medical visits with PM_{10} levels extending below 50 µg/m^3 include: Schwartz (1994) in Minneapolis-St. Paul, Minnesota; Schwartz et al. (1996b) in Cleveland; Sheppard et al. (1999) in Seattle; Linn et al. (2000) in Los Angeles; and Nauenberg and Basu (1999) in Los Angeles; in Minneapolis-St. Paul, MN, but not in Birmingham, AL. The excess risk estimates most consistently fall in the range of 5 to 25% per 50 µg/m^3 PM_{10} increment, with those for asthma visits and hospital admissions often being higher than those for COPD and pneumonia admissions.

Similar associations between increased respiratory related hospital admissions/medical visits and low short-term PM_{10} levels were also reported by various investigators for several non-U.S. cities. Wordley et al. (1997), for example, reported positive and significant associations between PM_{10} (mean = 25.6 µg/m^3, max. = 131 µg/m^3) and respiratory admissions in Birmingham, UK using multivariate linear regression methods; and Atkinson et al. (1999b), using Poisson modeling, reported significant increases in hospital admissions for respiratory disease to be associated with PM_{10} (mean = 28.5 µg/m^3) in London, UK. Hagen et al. (2000) and Prescott et al. (1998) also found positive but non-significant associations of hospital admissions and, PM_{10} levels in Drammen, Norway (mean = 16.8 µg/m^3) and Edinburgh, Scotland (mean = 20.7 µg/m^3). Admissions in Drammen considered relatively small populations, limiting statistical power in this study. Petroeschevsky et al. (2001) examined associations between outdoor air pollution and hospital admissions in Brisbane, Australia during 1987-1994 using a light scattering index (BSP) for fine PM. The levels of PM are quite low in this city, relative to most U.S. cities, but BSP was positively and significantly associated with total respiratory admissions, but not for asthma.

8.3.2.3.1 Particulate Matter Mass Fractions and Composition Comparisons

While PM_{10} mass has generally been the metric most often used as the particle pollution index in the U.S. and Canada, some new studies have examined the relative roles of various PM_{10} mass fractions (e.g., $PM_{2.5}$ and $PM_{10-2.5}$) and chemical constituents (such as SO_4^{-2}) contributing to PM-respiratory hospital admissions associations. Several new studies (from among those summarized in Tables 8-19 and 8-20, respectively) report significant associations of increased respiratory-cause medical visits and/or hospital admissions with ambient $PM_{2.5}$

TABLE 8-19. SUMMARY OF UNITED STATES $PM_{2.5}$ RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels ug/m^3	Co-Pollutants Measured	Lag	Method	Effect Estimate (95% CL) (% increase per 25 ug/m^3)
Lippmann et al. (2000)	COPD	$PM_{2.5}$ = 18	SO_2, O_3, NO_2, CO, H+	3 3	Default GAM Default GAM	No Co Poll: 5.5 (−4.7, 16.8) Co Poll: 2.8 (−9.2, 16)
Reanalysis by Ito (2003)	COPD				Default GAM Strict GAM NS GLM	No Co Poll: 5.5 (−4.7, 16.8) No Co Poll: 3.0(−6.9, 13.9) No Co Poll: 0.3(−9.3, 10.9)
Moolgavkar (2000c)*	COPD (> 64 yrs) (median)	$PM_{2.5}$ = 22, LA $PM_{2.5}$ = 22, LA	— CO	2 2	Default GAM Default GAM	5.1 (0.9, 9.4) 2.0 (-2.9, 7.1) Two poll. model
Reanalysis by Moolgavkar (2003)	COPD (all ages)			222	Strict GAM: 30df Strict GAM: 100df NS GLM: 100df	4.69 (2.06, 7.38) 2.87 (0.53, 5.27) 2.59 (-0.29, 5.56)
Lippmann et al. (2000)	Pneumonia	$PM_{2.5}$ = 18	SO_2, O_3, NO_2, CO, H^+	1 1	Default GAM Default GAM	No Co-Poll: 12.5 (3.7, 22.1) Co Poll: 12 (1.7, 23)
Reanalysis by Ito (2003)	Pneumonia				Default GAM Strict GAM NS GLM	No Co-Poll: 12.5 (3.7, 22.1) No Co-Poll: 10.5 (1.8, 19.8) No Co-Poll: 10.1 (1.5, 19.5)
Sheppard et al. (1999)*	Asthma	$PM_{2.5}$ = 16.7	CO, O_3, SO_2	1	Default GAM	8.7 (3.3, 14.3)
Reanalysis by Sheppard (2003)			CO		Default GAM Strict GAM NS GLM Strict GAM NS GLM	No Co-Poll: 8.7 (3.3, 14.3) No Co-Poll: 8.7 (3.2,14.4) No Co-Poll: 6.5 (1.1,12.0) With Co-poll: 6.5 (2.1, 10.9) With Co-poll: 6.5 (2.1, 10.9)
Freidman et al. (2001)	Asthma	$PM_{2.5}$ = (36.7-30.8 decrease)	O_3	3 d. cum	Poisson GEE	1.4 (0.80-2.48)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model.

and/or $PM_{10\text{-}2.5}$ ranging to quite low concentrations. These include the Lippmann et al. (2000) study in Detroit, where all PM metrics (PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, H^+) were positively related to pneumonia and COPD admissions among the elderly (aged 65+ yr) in single pollutant models, with their RR values for pneumonia generally remaining little changed (but with broader confidence intervals) in multipollutant models including one or more gaseous pollutant (e.g., CO, O_3, NO_2, SO_2). However, for COPD admissions, the effect estimates were reduced and became non-significant in multipollutant models including gaseous copollutants. Excess risks

TABLE 8-20. SUMMARY OF UNITED STATES $PM_{10-2.5}$ RESPIRATORY-RELATED HOSPITAL ADMISSION STUDIES

Reference	Outcome Measures	Mean Levels ug/m^3	Co-Pollutants Measured	Lag	Method	Effect Estimates (95% CL) (% increase per 25 ug/m^3)
Moolgavkar (2000c)*	COPD		—	3	Default GAM	5.1% (−0.4, 10.9)
Lippmann et al. (2000)*	COPD	$PM_{10-2.5}$ = 12	SO_2, O_3, NO_2, CO, H+	33	Default GAM Default GAM	No Co-Poll: 9.3 (−4.2, 24.7) Co-Poll: 0.3 (−14, 18)
Reanalysis by Ito (2003)					Default GAM Strict GAM NS GLM	No Co-Poll: 9.3 (−4.2, 24.7) No Co-Poll: 8.7 (−4.8, 24.0) No Co-Poll: 10.8 (−3.1, 26.5)
Lippmann et al. (2000)*	Pneumonia	$PM_{10-2.5}$ = 12	SO_2, O_3, NO_2, CO, H^+	11	Default GAM Default GAM	No Co-Poll: 11.9 (−0.6, 24.4) Co-Poll: 13.9 (0.0, 29.6)
Reanalysis by Ito (2003)				111	Default GAM Strict GAM NS GLM	No Co-Poll: 11.9 (−0.6, 24.4) No Co-Poll: 9.9 (−0.1, 22.0) No Co-Poll: 11.2 (−0.02, 23.6)
Sheppard et al. (1999)*	Asthma	$PM_{10-2.5}$ = 16.2	CO, O_3, SO_2	1	Default GAM	11.1 (2.8, 20.1)
Reanalysis by Sheppard (2003)				11	Strict GAM NS GLM	5.5 (−2.7 11.1) 5.5 (0, 14.0)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model.

for pneumonia admissions in the one pollutant model using default GAM were 13% (3.7, 22) and 12% (−0.6, 24) per 25 µg/m^3 of $PM_{2.5}$ and $PM_{10-2.5}$, respectively; those for COPD admissions were 5.5% (−4.7, 17) and 9.3% (−4.2, 25) per 25 µg/m^3 $PM_{2.5}$ and $PM_{10-2.5}$, respectively.

Lippmann et al. (2000) reported weaker associations with sulfate and acidic components of $PM_{2.5}$ than with $PM_{2.5}$ mass overall, but the acidity levels during this study were very low, being below detection on most study days. In contrast, past studies of sulfates and aerosol acidity associations with respiratory hospital admissions have found stronger sulfate associations when the acidity of those aerosols was higher (e.g., Thurston et al, 1994). As noted by Lippman et al.(2000), “a notable difference between the data of Thurston and colleagues from Toronto and our data is the H^+ levels: the H^+ levels in Toronto were 21.4, 12.6, and 52.3 nmol/m^3 for the summers of 1986, 1987, and 1988, respectively, whereas in our study, the H^+ level averaged only 8.8 nmol/m^3.” Thus, these results are consistent with past studies and biological plausibility, in that sulfates and its associated PM should be less toxic when in a less strongly acidic form, as indeed found in this study.

In order to evaluate the potential influence of the Generalized Additive Model (GAM) convergence specification on the results of the original Detroit data analysis, Ito (2003) re-examined associations between PM components and daily mortality/morbidity by using more stringent GAM convergence criteria, and by applying a Generalized Linear Models (GLM) that approximated the original GAM models. The reanalysis of GAM Poisson models used more stringent convergence criteria, as suggested by Dominici et al. (2002): the convergence precision (epsilon) was set to 10-14 and maximum iteration was set to 1000, for both the local scoring and back-fitting algorithms. The GLM model specification approximated the original GAM models. Natural splines were used for smoothing terms. To model time trend, the same degrees of freedom as the smoothing splines in the GAM models were used, with the default placement of knots. For weather models, to approximate LOESS smoothing with a span of 0.5 in the GAM model, natural splines with degrees of freedom were used. Generally, the GAM models with stringent convergence criteria and GLM models resulted in somewhat smaller estimated relative risks than those reported in the original study, e.g., for respiratory admissions in Table 8-21. It was found that the reductions in the estimated relative risks were not differential across the PM indices. Thus, conclusions of the original study about the relative roles of PM components by size and chemical characteristics remained unaffected.

Lumley and Heagerty (1999) illustrate the effect of reliable variance estimation on data from hospital admissions for respiratory disease on King County, WA for eight years (1987-94), together with air pollution and weather information, using estimating equations and weighted empirical variance estimators. However, their weather controls were relatively crude (i.e., seasonal dummy variables and linear temperature terms). This study is notable for having compared sub-micron PM ($PM_{1.0}$) versus coarse $PM_{10-1.0}$ and for finding significant hospital admission associations only with $PM_{1.0}$. This may suggest that the $PM_{2.5}$ versus PM_{10} separation may not always be sufficient to differentiate submicron fine particle versus coarse-particle toxicities.

Asthma hospital admission studies in various U.S. communities provide additional important new data. Of particular note is a study by Sheppard et al. (1999) which evaluated relationships between measured ambient pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, SO_2, O_3, and CO) and

TABLE 8-21. INTERCOMPARISON OF DETROIT PNEUMONIA HOSPITAL ADMISSION RELATIVE RISKS (± 95% CI below) OF PM INDICES (per 5th-to-95th percentile pollutant increment) FOR VARIOUS MODEL SPECIFICATIONS.*

	Original GAM (default)	GAM (stringent)	GLM
$PM_{2.5}$ (1)	1.185 (1.053, 1.332)	1.154 (1.027, 1.298)	1.149 (1.022, 1.292)
$PM_{10\text{-}2.5}$ (1)	1.114 (1.006, 1.233)	1.095 (0.990, 1.211)	1.107 (1.00, 1.226)
PM_{10} (1)	1.219 (1.084, 1.372)	1.185 (1.054, 1.332)	1.190 (1.057, 1.338)
H^+ (3)	1.060 (1.005, 1.118)	1.049 (0.994, 1.107)	1.049 (0.994, 1.107)
$SO_4^=$ (1)	1.156 (1.050, 1.273)	1.128 (1.025, 1.242)	1.123 (1.020, 1.235)

*The selected lag is indicated in parenthesis next to the pollutant name.

Source: Ito (2003).

non-elderly adult (< 65 years of age) hospital admissions for asthma in Seattle, WA. PM and CO were found to be jointly associated with asthma admissions. An estimated 4 to 5% increase in the rate of asthma hospital admissions (lagged 1 day) was reported to be associated with interquartile range changes in PM indices (19 µg/m^3 for PM_{10}, 11.8 µg/m^3 for $PM_{2.5}$, and 9.3 µg/m^3 for $PM_{10\text{-}2.5}$), equivalent to excess risk rates as follows: 13% (CI = 05-23) per 50 µg/m^3 for PM_{10}; 9% (CI = 3-14) per 25 µg/m^3 $PM_{2.5}$; 11% (CI = 3-20) per 25 µg/m^3 $PM_{10\text{-}2.5}$. Also of note for the same region by the same research team using similar methods is the Norris et al. (1999) study showing associations of low levels of $PM_{2.5}$ (mean = 12 µg/m^3) with markedly increased asthma ED, i.e., excess risk = 44.5% (CI = 21.7-71.4) per 25 µg/m^3 $PM_{2.5}$.

Sheppard (2003) recently conducted a reanalysis of their nonelderly hospital admissions data for asthma in Seattle, WA, to evaluate the effect of the fitting procedure on their previously published analyses. As shown in Figure 8-11, the effect estimates were slightly smaller when more stringent convergence criteria were used with GAM, and there was an additional small reduction in the estimates when GLM with natural splines were used instead. The average reduction in effect estimate between the default and stringent covergence criteria for $PM_{2.5}$, PM_{10}, and $PM_{10\text{-}2.5}$ (coarse) mass averaged 10.7%. The coefficients remained statistically

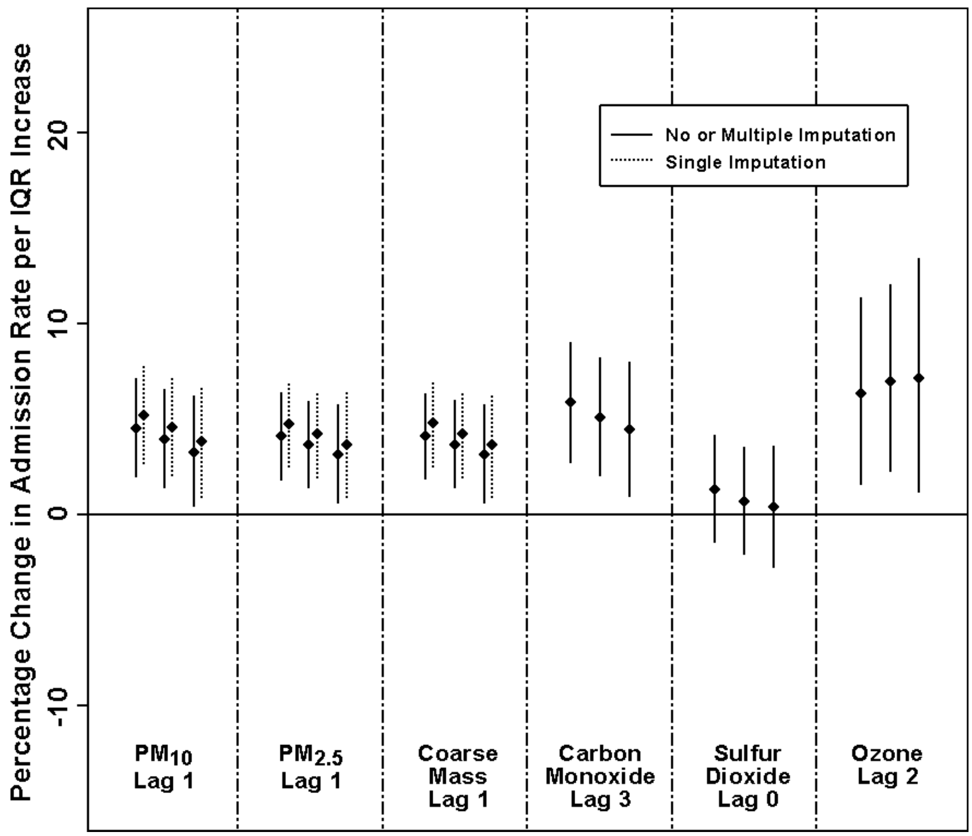

Figure 8-11. Percent change in hospital admission rates and 95% CIs for an IQR increase in pollutants from single-pollutant models for asthma. Poisson regression models are adjusted for time trends (64-df spline), day-of-week, and temperature (4-df spline). The IQR for each pollutant equals: 19 ug/m^3 for PM_{10}, 11.8 ug/m^3 for $PM_{2.5}$, 9.3 ug/m^3 for coarse PM, 20 ppb for O_3, 4.9 ppb for SO_2, and 924 ppb for CO. Triplets of estimates for each pollutant are for the original GAM analysis using smoothing splines, the revised GAM analysis with stricter convergence criteria, and the GLM analysis with natural splines. For pollutants that required imputation (i.e., estimation of missing value) estimates ignoring (single imputation) or adjusting for (multiple imputation) the imputation are shown.

Source: Sheppard (2003).

significant for both $PM_{2.5}$ and PM_{10} but not for coarse mass. Confidence intervals were slightly wider for the GLM model fit. Sheppard concluded that, "Overall the results did not change meaningfully. There were small reductions in estimates using the alternate fitting procedures. I also found that the effect of single imputation (i.e., not adjusting for replacing missing exposure data with an estimate of its expected value) was to bias the effect estimates slightly upward. In this data set this bias is of the same order as the bias from using too liberal convergence criteria in the generalized additive model."

Moolgavkar (2003) also conducted reanalyses of respiratory-related hospital admissions, but for COPD data for all ages in Los Angeles. Using GAM with strict convergence criteria and 30 degrees of freedom (df), an excess risk estimate of 4.7% (CI = 2.1 – 7.4) was obtained per 25 µg/m^3 $PM_{2.5}$ increment. The notable effect of increasing degrees of freedom on modeling results is well illustrated by the excess risk estimate dropping to 2.9% (CI = 0.5 – 5.3) with strict GAM and 100 df or 2.6% (CI = –0.3, 5.6) with NS GLM 100 df.

Burnett et al. (1997a) evaluated the role that the ambient air pollution mix, comprised of gaseous pollutants and PM indexed by various physical and chemical measures, plays in exacerbating daily admissions to hospitals for cardiac diseases and for respiratory diseases (tracheobronchitis, chronic obstructive lung disease, asthma, and pneumonia). They employed daily measures of $PM_{2.5}$ and $PM_{10-2.5}$, aerosol chemistry (sulfates and H+), and gaseous pollutants (O_3, NO_2, SO_2, CO) collected in Toronto, Ontario, Canada, during the summers of 1992, 1993, and 1994. Positive associations were observed for all ambient air pollutants for both respiratory and cardiac diseases. Ozone was the most consistently significant pollutant and least sensitive to adjustment for other gaseous and particulate measures. The PM associations with respiratory hospital admissions were significant for: PM_{10} (RR = 1.11 for 50 µg/m^3; CI = 1.05-1.17); $PM_{2.5}$ (fine) mass (RR = 1.09 for 25 µg/m^3; CI = 1.03-1.14);$PM_{10-2.5}$ (coarse) mass (RR = 1.13 for 25 µg/m^3; CI = 1.05-1.20); sulfate levels (RR = 1.11 for 155 nmoles/m^3 = 15 µg/m^3; CI = 1.06-1.17); and H^+ (RR = 1.40 for 75 nmoles/m^3 = 3.6 µg/m^3, as H_2SO_4; CI = 1.15-1.70). After inclusion of O_3 in the model, the associations with the respiratory hospital admissions remained significant for: PM_{10} (RR = 1.10, CI = 1.04-1.16); fine mass (RR = 1.06; CI = 1.01-1.12); coarse mass (RR = 1.11; CI = 1.04-1.19); sulfate levels (RR = 1.06; CI = 1.0-1.12); and H^+ (RR = 1.25; CI = 1.03-1.53), using the same increments. Of the PM metrics considered here, H^+ yielded the highest RR estimate. Regression models that included all recorded pollutant simultaneously (with high intercorrelations among the pollutants) were also presented.

A recent study by Lin et al. (2002) used both case-crossover and time-series analyses to assess the associations between size-fractionated particulate matter and asthma hospitalization among children 6-12 years old living in Toronto between 1981 and 1993. The authors used exposures averaged over periods varying from 1 to 7 days to assess the effects of particulate matter on asthma hospitalization. Estimates of the relative risk of asthma hospitalization were adjusted for daily weather conditions (maximum and minimum temperatures, and average relative humidity) for an incremental exposure corresponding to the interquartile range in particulate matter. However, direct measurements of PM components were available only every sixth day in this data set, and 5 out of every 6 PM data points in the analysis were based on estimated $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10} data, weakening confidence in these input data. Time-series plots of the $PM_{2.5-10}$ data showed much stronger seasonality in the estimated coarse PM data than in the estimated fine PM mass data. Seasonality was controlled for in the time-series analyses using a 3 month span smooth of the data, rather than the more commonly employed one month or less span. Thus, residual seasonality may have been a factor in this study's $PM_{2.5-10}$ results. Both bidirectional case-crossover and time-series analyses revealed that coarse particulate matter ($PM_{10-2.5}$) averaged over 5-6 days was significantly associated with asthma hospitalization in both males and females. The magnitude of this effect appeared to increase with increasing number of days of exposure averaging for most models, with the relative risk estimates stabilizing at about 6 days. Using a bidirectional case-crossover analysis, the estimated relative risks were 1.14 [95% confidence interval (CI), 1.02, 1.28] for males and 1.18 (95% CI, 1.02, 1.36) for females, for an increment of 8.4 $\mu g/m^3$ in 6-day averages of $PM_{10-2.5}$. The corresponding relative risk estimates were 1.10 and 1.18, respectively, from the time-series analysis. The effect of $PM_{10-2.5}$ remained positive after adjustment for the effects of the gaseous pollutants carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). They did not find significant effects of fine particulate matter ($PM_{2.5}$) or of thoracic particulate matter (PM_{10}) on asthma hospitalizations, except in the unidirectional case-cross-over analyses. Seasonal-specific results were not presented. The paper's discussion ignores previous results by Thurston et al. (1994), which provided results during summers in the same time range (1986-1988) that are in direct conflict with respect to the significance of $PM_{2.5}$. That study used daily direct measurements of size fractionated PM in their analysis of those three summers, finding significant effects for summertime $PM_{2.5}$. Seasonality of data analysis may therefore be a factor in the differences between these two Toronto hospital admissions studies regarding the adverse health effects of fine PM. Overall, this new study suggests that coarse particle mass can also be a risk factor in children's asthma hospital admissions.

There have also been numerous new time-series studies examining associations between air pollution and respiratory-related hospital admissions in Europe, as summarized in Appendix 8B, Table 8B-2, but most of these studies relied primarily on black smoke (BS) as their PM metric. BS is a particle reflectance measure that provides an indicator of PM blackness and is highly correlated with airborne carbonaceous particle concentrations (Bailey and Clayton, 1982). In the U.S., Coefficient of Haze (CoH) is a metric of particle transmittance that similarly most directly represents a metric of particle blackness and ambient elemental carbon levels (Wolff et al., 1983) and has been found to be highly correlated with BS (r = 0.9; Lee et al., 1972). However, the relationship between airborne carbon and total mass of overall aerosol (PM) composition varies over time and from locality to locality, so the BS-mass ratio is less reliable than the BS-carbon relationship (Bailey and Clayton, 1982). This means that the BS-mass relationship is likely to be very different between Europe and the U.S., largely due to differences in local PM source characteristics (e.g., percentages of diesel powered motor vehicles). Therefore, while these European BS-health effects studies may be of qualitative interest for evaluating the PM-health effects associations, they are not as useful for quantitative assessment of PM effects relevant to the U.S.

Probably the most extensive and useful recent European air pollution health effects analyses have been conducted as part of the APHEA multi-city study, which evaluated 15 European cities from 10 different countries with a total population of over 25 million. All studies used a standardized data collection and analysis approach, which included consideration of the same suite of air pollutants (BS, SO_2, NO_2, SO_2, and O_3) and the use of time-series regression addressing seasonal and other long-term patterns; influenza epidemics; day of the week; holidays; weather; and autocorrelation (Katsouyanni et al., 1996). The general coherence of the APHEA results with other results gained under different conditions strengthens the argument for causality in the air pollution-health effects association. In earlier studies, the general use of the less comparable suspended particle (SPM) measures and BS as PM indicators in some of the APHEA locations and analyses lessens the quantitative usefulness of such analyses in evaluating associations between PM and health effects most pertinent to the U.S. situation. However, Atkinson et al. (2001) report results of PM_{10} analyses in a study of eight APHEA cities.

As for other single-city European studies of potential interest here, Hagan et al. (2000) compared the association of PM_{10} and co-pollutants with hospital admissions for respiratory causes in Drammen, Norway during 1994-1997. Respiratory admissions averaged only 2.2 per day; so, the power of this analysis is weaker than studies looking at larger populations and longer time periods. The HEI I.B Multi-city Report modeling approach was employed. While a significant association was found for PM_{10} as a single pollutant, it became non-significant in multiple pollutant models. In two pollutant models, the associations and effect size of pollutants were generally diminished, and when all eight pollutants were considered in the model, all pollutants became non-significant. These results are typical of the problems of analyzing and interpreting the coefficients of multiple pollutant models when the pollutants are even moderately inter-correlated over time. A unique aspect of this work was that benzene was considered in this community strongly affected by traffic pollution. In two pollutant models, benzene was most consistently still associated. The authors conclude that PM is mainly an indicator of air pollution in this city and emissions from vehicles seem most important for health effects. Thompson et al. (2001) report a similar result in Belfast, Northern Ireland, where, after adjusting for multiple pollutants, only the benzene level was independently associated with asthma emergency department (ED) admissions.

8.3.2.4 Key New Respiratory Medical Visits Studies

As discussed above, medical visits include both hospital ED visits and doctors' office visits. As in the past PM AQCD's, most available morbidity studies in Table 8B-3, Appendix 8B and in Table 8-22 below are of ED visits and their associations with air pollution. These studies collectively confirm the results provided in the previous AQCD, indicating a positive and generally statistically significant association between ambient PM levels and increased respiratory-related hospital visits.

Of the medical visit and hospital admissions studies since the 1996 PM AQCD, among the most informative are those that evaluate health effects at levels below previously well-implicated PM concentrations. As for U.S. studies, Tolbert et al. (2000b) reported a significant PM_{10} association with pediatric ED visits in Atlanta where mean PM_{10} = 39 $\mu g/m^3$ and maximum PM_{10} = 105 $\mu g/m^3$. The Lipsett et al. (1997) study of winter air pollution and asthma emergency visits in Santa Clara Co, CA, may provide insight where one of the principal sources of PM_{10} is

TABLE 8-22. SUMMARY OF UNITED STATES PM_{10}, $PM_{2.5}$, AND $PM_{10\text{-}2.5}$ ASTHMA MEDICAL VISIT STUDIES

Reference	Outcome Measures	Mean Levels ($\mu g/m^3$)	Co-Pollutants Measured	Lag	Method	Effect Estimate (95% CL)
PM_{10}						
Choudhury et al. (1997)	Asthma	41.5	Not considered	0	GLM	20.9 (11.8, 30.8)
Lipsett et al. (1997)	Asthma	61.2	NO_2, O_3	2	GLM	34.7 (16, 56.5) at 20 °C
Tolbert et al. (2000b)	Asthma	38.9	O_3	1	GEE	SP 13.2 (1.2, 26.7)
Tolbert et al. (2000a)*	Asthma	29.1	NO_2, O_3, CO, SO_2	0-2	GLM	SP 8.8 (−8.7, 54.4)
$PM_{2.5}$						
Tolbert et al. (2000a)*	Asthma	19.4	NO_2, O_3, CO, SO_2	0-2	GLM	SP 2.3 (−14.8, 22.7)
$PM_{10\text{-}2.5}$						
Tolbert et al. (2000a)*	Asthma	9.39	NO_2, O_3, CO, SO_2	0-2	GLM	SP 21.1 (−18.2, 79.3)

NS = Natural Spline General Linear Model; PS = Penalized Spline General Additive Model; SP = Single Pollutant Model; MP = Multipollutant Model
*Preliminary results based on emergency department visit data from 18 of 33 participating hospitals.

Associations with asthma doctor's visits for children and young adults in London when mean PM_{10} = 28.2 $\mu g/m^3$ and the PM_{10} 90th percentile was only 46.4 $\mu g/m^3$. Overall, then, several new medical visits studies indicate PM-health effects associations at lower $PM_{2.5}$ and PM_{10} levels than demonstrated previously for this health outcome.

residential wood combustion (RWC). Their results demonstrate an association between PM levels and asthma. Also of interest, Delfino et al. (1997) found significant PM_{10} and $PM_{2.5}$ associations for respiratory ED visits among older adults in Montreal when mean PM_{10} = 21.7 $\mu g/m^3$ and mean $PM_{2.5}$ = 12.2 $\mu g/m^3$. Hajat et al. (1999) also reported significant PM_{10}

8.3.2.4.1 Scope of Medical Visit Morbidity Effects

Several newer medical visit studies consider a new endpoint for comparison with ED visits: visits in the primary care setting. In particular, key studies showing PM associations for this health outcome include: the study by Hajat et al. (1999) that evaluated the relationship between air pollution in London, UK; and daily General Practice (GP) doctor consultations for asthma and other lower respiratory disease (LRD); the study by Choudhury et al. (1997) of private asthma medical visits in Anchorage, Alaska; and the study by Ostro et al. (1999b) of daily visits by young children to primary care health clinics in Santiago, Chile for upper or lower respiratory symptoms.

While limited in number, the above studies collectively provide new insight into the fact that there is a broader scope of severe morbidity associated with PM air pollution exposure than previously documented. As the authors of the London study note: "There is less information about the effects of air pollution in general practice consultations but, if they do exist, the public health impact could be considerable because of their large numbers." Indeed, the London study of doctors' GP office visits indicates that the effects of air pollution, including PM, can affect many more people than indicated by hospital admissions alone.

These new studies also provide indications as to the quantitative nature of medical visits effects, relative to those for hospital admissions. In the London case, comparing the number of admissions from the authors' earlier study (Anderson et al., 1996) with those for GP visits in the 1999 study (Hajat et al., 1999) indicates that there are circa 24 asthma GP visits for every asthma hospital admission in that city. Also, comparing the PM_{10} coefficients indicates that the all-ages asthma effect size for the GP visits (although not statistically different) was about 30% larger than that for hospital admissions. Thus, these new studies suggest that looking at only hospital admissions and emergency hospital visit effects may greatly underestimate the overall numbers of respiratory morbidity events due to acute ambient PM exposure.

8.3.2.4.2 Factors Potentially Affecting Respiratory Medical Visit Study Outcomes

Some newly available studies have examined certain factors that might extraneously affect the outcomes of PM-medical visit studies. Stieb et al. (1998a) examined the occurrence of bias and random variability in diagnostic classification of air pollution and daily cardiac or respiratory ED visits, such as for asthma, COPD, respiratory infection, etc. They concluded that there was no evidence of diagnostic bias in relation to daily air pollution levels. Also, Stieb et al. (1998b) reported that for a population of adults visiting an emergency department with cardiac respiratory disease, fixed site sulfate monitors appear to accurately reflect daily variability in average personal exposure to particulate sulfate, whereas acid exposure was not as well represented by fixed site monitors. Another study investigated possible confounding of respiratory visit effects due to pollens and mold spores (Steib et al, 2000). Aeroallergen levels did not influence the results, similar to asthma panel studies described below in Section 8.3.3. In London, Atkinson et al. (1999b) studied the association between the number of daily ED visits to for respiratory complaints and measures of outdoor air pollution for PM_{10}, NO_2, SO_2 and CO. They examined different age groups and reported strongest associations for children for visits for asthma, but were unable to separate PM_{10} and SO_2 effects.

8.3.2.5 Identification of Potential Susceptible Subpopulations

Associations between ambient PM measures and respiratory admissions have been found for all age groups, but older adults and children generally have been indicated by hospital admissions studies to exhibit the most consistent PM-health effects associations. As reported in previous PM AQCDs, numerous studies of older adults (e.g., those 65+ years of age) have related acute PM exposure with an increased incidence of hospital admissions (e.g., see Anderson et al, 1998). However, only a limited number have specifically studied children as a subgroup. Burnett et al. (1994) examined the differences in air pollution-hospital admissions associations as a function of age in Ontario, reporting that the largest percentage increase in admissions was found among infants (neonatal and post-neonatal, one year or less in age).

Further efforts have aimed at identifying and quantifying air pollution effects among potentially especially susceptible sub-populations of the general public. Some new studies have further investigated the hypothesis that the elderly are especially affected by air pollution. Zanobetti et al. (2000a) examined PM_{10} associations with hospital admissions for heart and lung disease in ten U.S. cities, finding an overall association for COPD, pneumonia, and CVD. They found that these results were not significantly modified by poverty rate or minority status in this population of Medicare patients. Ye et al. (2001) examined emergency transports to the hospital. Both PM_{10} and $N0_2$ levels were significantly associated with daily hospital transports for angina, cardiac insufficiency, myocardial infarction, acute and chronic bronchitis, and pneumonia. The pollutant effect sizes were generally found to be greater in men than in women, except those for angina and acute bronchitis, which were the same across genders. Thus, in these various studies, cardiopulmonary hospital visits and admissions among the elderly were seen to be consistently associated with PM levels across numerous locales in the U.S. and abroad, generally without regard to race or income; but sex was sometimes an effect modifier.

Several new studies of children's morbidity also support the indication of air pollution effects among children. Pless-Mulloli et al. (2000) evaluated children's respiratory health and air pollution near opencast coal mining sites in a cohort of nearly 5,000 children aged 1-11 in England. Mean PM levels were not high (mean < 20 μg/m^3 PM_{10}), but statistically significant PM_{10} associations were found with respiratory symptoms. A roughly 5 percent increase of General Practitioner medical visits was also noted, but was not significant. Ilabaca et al. (1999) also found an association between levels of fine PM and ED visits for pneumonia and other respiratory illnesses among children < 15 years in Santiago, Chile, where the levels of $PM_{2.5}$ were very high (mean = 71.3 μg/m^3) during 1995-1996. The authors found it difficult to separate out the effects of various pollutants, but concluded that PM (especially the fine component) is associated with the risk of these respiratory illnesses. Overall, these new studies support past assertions that children, and especially neo-natal infants, are especially susceptible to the health effects of air pollution.

The respiratory-related hospital admissions studies summarized in Appendix 8B reveal that the PM RR's for all children (e.g., 0-18) are not often notably larger than those for adults, but such comparisons of RR's must adjust for differences in baseline risks for each group. For example, if hospital admissions per 100,000 per day for young children are double the rate for adults, then they will have a pollution relative risk (RR) per μg/m^3 that is half that of the adults given the exact same impact on admissions/100,000/μg/m^3/day. Thus, it is important to adjust RR's or Excess Risks (ER's) for each different age groups' baseline, but this information is usually not available (especially regarding the population catchment for each age group in each study). One of the few indications that is notable when comparing children with other age group effect estimates in Table 8B-2 is the higher excess risk estimate for infants (i.e., the group < 1 yr. of age) in the Gouveia and Fletcher (2000) study, an age group that has estimated risk estimate roughly twice as large as for other children or adults.

8.3.2.6 Summary of Salient Findings on Acute Particulate Matter Exposure and Respiratory-Related Hospital Admissions and Medical Visits

The results of new studies discussed above are generally consistent with and supportive of findings presented in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a), with regard to ambient PM associations of short-term exposures with respiratory-related hospital admissions/medical visits. Figure 8-12 summarizes results for maximum excess risk of

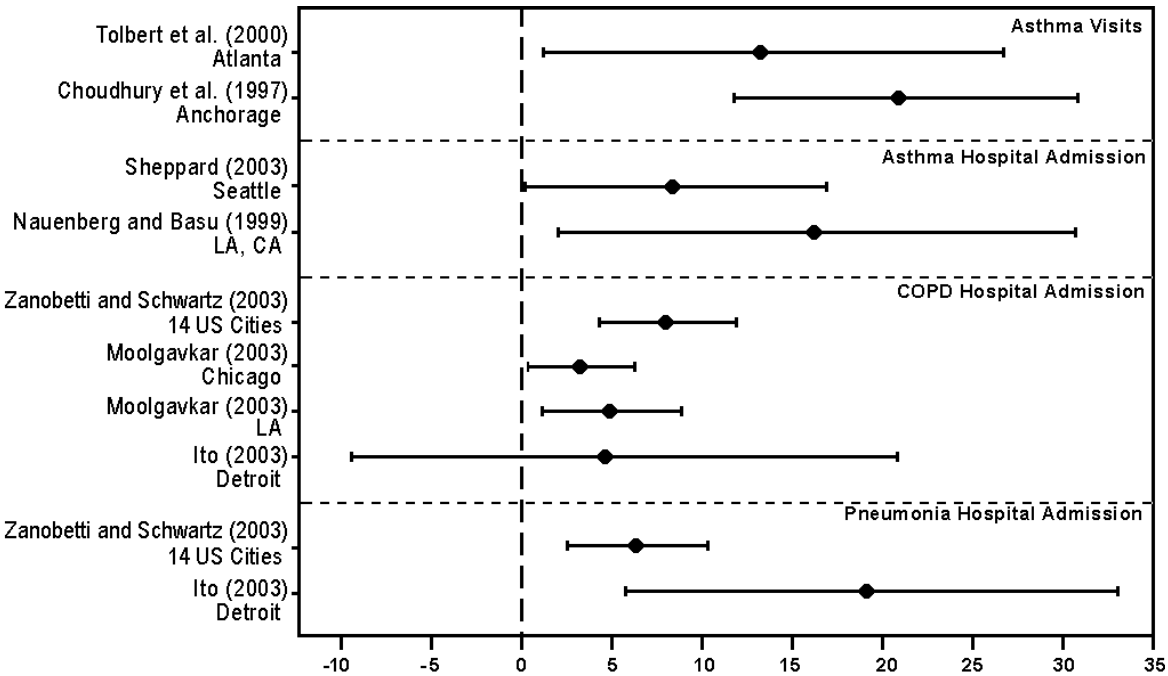

Figure 8-12. Maximum excess risk of respiratory-related hospital admissions and visits per 50 μg/m³ PM_{10} increment in selected studies of U.S. cities based on single-pollutant models.

respiratory-related hospital admission and visits per 50 μg/m³ PM_{10} based on single-pollutant models for selected U.S. cities. The excess risk estimates fall most consistently in the range of 5 to 20% per 50 μg/m³ PM_{10} increments, with those for asthma visits and hospital admissions generally somewhat higher than for COPD and pneumonia hospital admissions. More limited new evidence both (a) substantiates increased risk of respiratory-related hospital admissions due to ambient fine particles ($PM_{2.5}$, $PM_{1.0}$, etc.) and also (b) points towards such admissions being associated with ambient coarse particles ($PM_{10-2.5}$). Excess risk estimates tend to fall in the range of ca. 5.0 to 15.0% per 25 μg/m³ $PM_{2.5}$ or $PM_{10-2.5}$ for overall respiratory admissions or for COPD admissions, whereas larger estimates are found for asthma admissions.

Various new medical visits studies (including non-hospital physician visits) indicate that the use of hospital admissions alone can greatly understate the total clinical morbidity effects of air pollution. Thus, these results support the hypothesis that considering only hospital admissions and ED visit effects may greatly underestimate the numbers of medical visits occurring in a population as a result of acute ambient PM exposure. Those groups identified in these morbidity studies as most strongly affected by PM air pollution are older adults and the very young.

8.3.3 Effects of Particulate Matter Exposure on Lung Function and Respiratory Symptoms

In the 1996 PM AQCD, the available respiratory studies used a wide variety of designs examining pulmonary function and respiratory symptoms in relation to ambient concentrations of PM_{10}. The populations studied included several different subgroups (e.g., children, asthmatics, etc.); and the models used for analysis varied, but did not include GAM use. The pulmonary function studies were suggestive of short-term effects resulting from ambient PM exposure. Peak expiratory flow rates showed decreases in the range of 2 to 5 l/min per 50 µg/m^3 increase in 24-h PM_{10} or its equivalent, with somewhat larger effects in symptomatic groups, e.g., asthmatics. Studies using FEV_1 or FVC as endpoints showed less consistent effects. The chronic pulmonary function studies, less numerous than the acute studies, had inconclusive results.

8.3.3.1 Effects of Short-Term Particulate Matter Exposure on Lung Function and Respiratory Symptoms

The available acute respiratory symptom studies discussed in the 1996 PM AQCD included several different endpoints, but typically presented results for upper respiratory symptoms, lower respiratory symptoms, or cough. These respiratory symptom endpoints had similar general patterns of results. The odds ratios were generally positive, the 95% confidence intervals for about half of the studies being statistically significant (i.e., the lower bound exceeded 1.0).

The earlier studies of morbidity health outcomes of PM exposure on asthmatics were limited in terms of conclusions that could be drawn because of the few available studies on asthmatic subjects. Lebowitz et al. (1987) reported a relationship with TSP exposure and productive cough in a panel of 22 asthmatics but not for peak flow or wheeze. Pope et al. (1991) reported on respiratory symptoms in two panels of Utah Valley asthmatics. The 34 asthmatic school children panel yielded estimated odd ratios of 1.28 (1.06, 1.56) for lower respiratory illness (LRI) and the second panel of 21 subjects aged 8 to 72 for LRI of 1.01 (0.81, 1.27) for exposure to PM_{10}. Ostro et al. (1991) reported no association for $PM_{2.5}$ exposure in a panel of

207 adult asthmatics in Denver; but, for a panel of 83 asthmatic children age 7 to 12 in central Los Angeles, found a relationship of shortness of breath to O_3 and PM_{10}, but could not separate effects of the two pollutants (Ostro et al., 1995). These few studies did not indicate a consistent relationship for PM_{10} exposure and health outcome in asthmatics.

Numerous new studies of short-term PM exposure effects on lung function and respiratory symptoms published since 1996 were identified by an ongoing Medline search. Most of these followed a panel of subjects over one or more time periods and evaluated daily lung function and/or respiratory symptom in relation to changes in ambient PM_{10}, $PM_{10\text{-}2.5}$, and/or $PM_{2.5}$. Some used other measures of airborne particles, e.g. ultrafine PM, TSP, BS, and sulfate fraction of ambient PM. Lung function was usually measured daily, with most studies including forced expiratory volume (FEV), forced vital capacity (FVC) and peak expiratory flow rate (PEF), measured both in the morning and afternoon. Various respiratory symptoms were measured, e.g., cough, phlegm, difficulty breathing, wheeze, and bronchodilator use. Detailed summaries of these studies are presented in Appendix 8B. Data on physical and chemical aspects of ambient PM levels (especially for PM_{10}, $PM_{10\text{-}2.5}$, $PM_{2.5}$, and smaller size fractions) are of particular interest, as are new studies examining health outcome effects and/or exposure measures not much studied in the past.

Specific studies were selected for summarization based on the following criteria:

- Peak flow was used as the primary lung function measurement of interest.
- Cough, phlegm, difficulty breathing, wheeze, and bronchodilator use were summarized as measures of respiratory symptoms when available.
- Quantitative relationships were estimated using PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, and/or smaller PM as independent variables.
- Analyses used in the study were done such that each individual served as their own control.

8.3.3.1.1 Lung Function and Respiratory Symptom Effects in Asthmatic Subjects

Appendix B Tables 8B-4 and 8B-5 summarize salient features of new studies of short-term PM exposure effects on lung function and respiratory symptoms, respectively, in asthmatic subjects; and key quantitative results are summarized in Table 8-23 for PM_{10} and Table 8-24 for $PM_{2.5}$. The peak flow analyses results for asthmatics tend to show small decrements for PM_{10}

TABLE 8-23. SUMMARY OF QUANTITATIVE PFT CHANGES IN ASTHMATICS PER 50 µg/m³ PM_{10} INCREMENT

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/m³ PM_{10}
Asthma Studies					
Pekkanen et al. (1997)	Morning PEFR	14 (10, 23)	NO_2	0 day	−2.71 (−6.57, 1.15)
Gielen et al. (1997)	Morning PEFR	30.5 (16, 60)	Ozone	1 day	1.39 (−0.57, 3.35)
Romieu et al. (1996)	Morning PEFR	166.8 (29, 363)	Ozone	1 day	−4.70 (−7.65, -1.70)
Romieu et al. (1997)	Morning PEFR	(12, 126)	Ozone	1 day	−0.65 (−5.32, 3.97)
Peters et al. (1997a)	Morning PEFR	47 (29, 73)	SO_2, sulfate, H^+	1 day	−0.84 (−1.62, −0.06)
Peters et al. (1997c)	Morning PEFR	55 (?, 71)	SO_2, sulfate, H^+	1 day	−1.30 (−2.36, −0.24)
Gielen et al. (1997)	Morning PEFR	30.5 (16, 60)	Ozone	2 day	0.34 (−1.78, 2.46)
Romieu et al. (1996)	Morning PEFR	166.8 (29, 363)	Ozone	2 day	−4.90 (−8.40, -1.50)
Romieu et al. (1997)	Morning PEFR	(12, 126)	Ozone	2 day	2.47 (−1.75, 6.75)
Gielen et al. (1997)	Evening PEFR	30.5 (16, 60)	Ozone	0 day	−0.30 (−2.24, 1.64)
Romieu et al. (1996)	Evening PEFR	166.8 (29, 363)	Ozone	0 day	−4.80 (−8.00, -1.70)
Romieu et al. (1997)	Evening PEFR	(12, 126)	Ozone	0 day	−1.32 (−6.82, 4.17)
Pekkanen et al. (1997)	Evening PEFR	14 (10, 23)	NO_2	0 day	−0.35 (−4.31, 3.61)
Peters et al. (1996)	Evening PEFR	112	SO_2, sulfate, PSA	0 day	−1.03 (−1.98, −0.08)
Peters et al. (1997a)	Evening PEFR	47 (29, 73)	SO_2, sulfate, H^+	0 day	−0.92 (−1.96, 0.12)
Peters et al. (1997c)	Evening PEFR	55 (?, 71)	SO_2, sulfate, H^+	0 day	−0.37 (−1.82, 1.08)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO_2, SO_2	0 day	−1.10 (−5.20, 3.00)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO_2, SO_2	0 day	−1.66 (−8.26, 4.94)
Gielen et al. (1997)	Evening PEFR	30.5 (16, 60)	Ozone	2 day	−2.32 (−5.36, 0.72)
Romieu et al. (1996)	Evening PEFR	166.8 (29, 363)	Ozone	2 day	−3.65 (−7.20, 0.03)
Romieu et al. (1997)	Evening PEFR	(12, 126)	Ozone	2 day	−0.04 (−4.29, 4.21)
Segala et al. (1998)	Morning PEFR	34.2 (9, 95)	SO_2, NO_2	2 day	−0.62 (−1.52, 0.28)
Pekkanen et al. (1997)	Evening PEFR	14 (10, 23)	NO_2	2 day	0.14 (−6.97, 7.25)

TABLE 8-23 (cont'd). SUMMARY OF QUANTITATIVE PFT CHANGES IN ASTHMATICS PER 50 μg/m³ PM_{10} INCREMENT

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 μg/m³ PM_{10}
Asthma Studies (cont'd)					
Peters et al. (1997c)	Evening PEFR	55 (?, 71)	SO_2, sulfate, H^+	2 day	−2.31 (−4.53, −0.10)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO_2, SO_2	2 day	−1.13 (−4.75, 2.52)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO_2, SO_2	2 day	0.38 (−6.37, 7.13)
Peters et al. (1996)	Evening PEFR	112	SO_2, sulfate, PSA	5 day	−1.12 (−2.13, −0.10)
Peters et al. (1997a)	Evening PEFR	47 (29, 73)	SO_2, sulfate, H^+	1-5 day	−1.34 (−2.83, 0.15)
Timonen & Pekkanen (1997) Urban	Evening PEFR	18 (?, 60)	NO_2, SO_2	1-4 day	−0.73 (−7.90, 6.44)
Timonen & Pekkanen (1997) Suburban	Evening PEFR	13 (?, 37)	NO_2, SO_2	1-4 day	−4.18 (−20.94, 12.58)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO_2, SO_2	1 day	−0.90 (−3.84, 2.04)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO_2, SO_2	2 day	−0.50 (−4.22, 3.22)
Hiltermann et al. (1998)	Ave. AM & PM	39.7 (16, 98)	Ozone, NO_2, SO_2	1-7 day	−2.20 (−10.43, 6.03)
Vedal et al. (1998)	Ave. AM & PM	19.1 (1, 159)	None	1-4 day	−1.35 (−2.70, −.05)

TABLE 8-24. SUMMARY OF PFT CHANGES IN ASTHMATICS PER 25 μg/m³ $PM_{2.5}$ INCREMENT

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 μg/m³ $PM_{2.5}$
Romieu et al. (1996)	Morning PEFR	85.7 (23, 177)	Ozone	1 day	−3.65 (−8.25, 1.90)
Peters et al. (1997c)	Morning PEFR	50.8 (9, 347)	SO_2, sulfate, H^+	1 day	−0.71 (−1.30, 0.12)
Romieu et al. (1996)	Morning PEFR	85.7 (23, 177)	Ozone	2 day	−3.68 (−9.37, 2.00)
Peters et al. (1997c)	Morning PEFR	50.8 (9, 347)	SO_2, sulfate, H^+	1-5 day	−1.19 (−1.18, 0.57)
Romieu et al. (1996)	Evening PEFR	85.7 (23, 177)	Ozone	0 day	−4.27 (−7.12, -0.85)
Peters et al. (1997c)	Evening PEFR	50.8 (9, 347)	SO_2, sulfate, H^+	0 day	−0.75 (−1.66, 0.17)
Romieu et al. (1996)	Evening PEFR	85.7 (23, 177)	Ozone	2 day	−2.55 (−7.84, 2.740
Peters et al. (1997c)	Evening PEFR	50.8 (9, 347)	SO_2, sulfate, H^+	1-5 day	−1.79 (−2.64, -0.95)

and $PM_{2.5}$ as seen in studies by Gielen et al. (1997), Peters et al. (1997b), Romieu et al. (1997), and Pekkanen et al. (1997).

The peak flow analyses results for asthmatics tend to show small decrements for both PM_{10} and $PM_{2.5}$. For PM_{10}, the available point estimates for morning PEF lagged one day showed decreases, but the majority of the studies were not statistically significant (as per Table 8-23 and as shown in Figure 8-13 as an example of PEF outcomes). Lag 1 may be more relevant for morning measurement of asthma outcome from the previous day. The figure presents studies which provided such data. The results were consistent for both AM and PM peak flow analyses. Effects using two- to five-day lags averaged about the same as did the zero to one-day lags, but had wider confidence limits. Similar results were found for the fewer $PM_{2.5}$ studies. Of these, Pekkanen et al. (1997) and Romieu et al. (1996) found similar results for $PM_{2.5}$ and PM_{10}, while the study of Peters et al. (1997c) found slightly larger effects for $PM_{2.5}$.

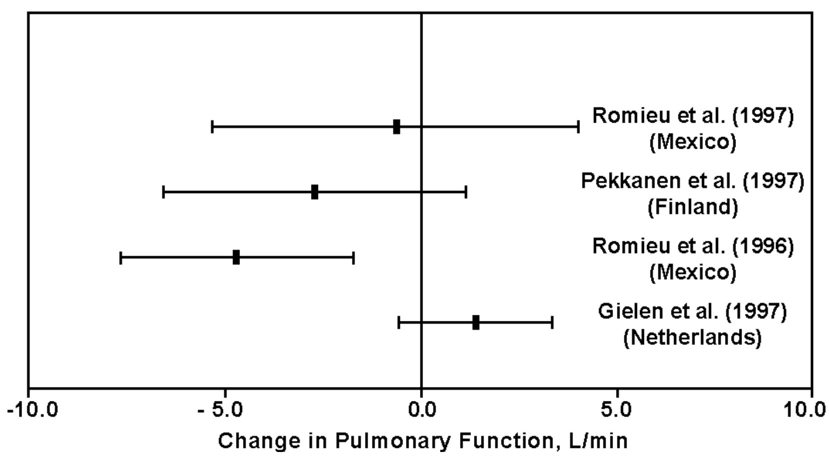

Figure 8-13. Selected acute pulmonary function change studies of asthmatic children. Effect of 50 μg/m³ PM_{10} on morning Peak flow lagged one-day.

Pekkanen et al. (1997) also reported changes in peak flow to be related to several sizes of PM with PN 0.032-0.10 −0.970 (0.502) l(cm³) and $PM_{1.0\text{-}3.2}$ −0.901 (0.536) and PM_{10} −1.13 (0.478) for morning PEF lag 2. Peters et al. (1997c) report that the strongest effects on peak flow were found with ultrafine particles: $PM_{MC\ 0.01\text{-}0.1}$: −1.21 (−2.13, −0.30); $PM_{MC0.01\text{-}2.5}$: −1.01 (−1.92, −0.11); and PM_{10}, −1.30 (−2.36, −0.24). Penttinen et al. (2001) using biweekly spirometry over 6 months on a group of 54 adult asthmatics found that FVC, FEV_1, and spirometric PEFR were inversely, but mostly nonsignificantly-associated with ultra fine particle concentrations. Compared to the effect estimates for self-monitored PEFR, the effect estimates for spirometric PEFR tended to be larger. The strongest associations were observed in the size range of 0.1 to 1 µm. In a further study, von Klot et al. (2002) evaluated 53 adult asthmatics in Erfurt, Germany in the winter of 1996-1997. Relationships were estimated from generalized estimating equations, adjusting for autocorrelation. Asthma symptoms were related to small particles (MC 0.1-0.5, MC 0.01-2.5) and $PM_{2.5\text{-}10}$. The strongest relations were for 14 day mean PM levels, especially for the smaller particles (MC 0.01-2.5).

Overall, then, PM_{10} and $PM_{2.5}$ both appear to affect lung function in asthmatics, but there is only limited evidence for a stronger effect of fine versus coarse fraction particles; nor do ultrafine particles appear to have any notably stronger effect than other larger-diameter fine particles. Also, of the studies provided, few if any analyses were able to clearly separate out the effects of PM_{10} and $PM_{2.5}$ from other pollutants.

The effects of PM_{10} on respiratory symptoms in asthmatics tended to be positive, although they are somewhat less consistent than PM_{10} effects on lung function. Most studies showed increases in cough, phlegm, difficulty breathing, and bronchodilator use, although these increases were generally not statistically significant for PM_{10} (see Tables 8-25, 8-26, 8-27, and 8-28; and, for cough as an example, see Figure 8-14). Vedal et al. (1998) reported that (a) increases in PM_{10} were associated with increased reporting of cough, phlegm production, and sore throat and (b) children with diagnosed asthma are more susceptible to the effects than are other children. Similarly, in the Gielen et al. (1997) study of a panel of children, most of whom had asthma, low levels of PM increased symptoms and medication use. The Peters et al. (1997c) study of asthmatics examined particle effects by size and found that fine particles were associated with increases in cough, of which MC 0.01-2.5 was the best predictor.

Delfino et al. (1998) used an asthma symptom score to evaluate the effects of acute air pollutant exposures. The 1- and 8-hr PM_{10} maximum concentrations had larger effects than the 24-hr mean. Subgroup analyses showed effects of current day PM maxima to be strongest in the 10 more frequently symptomatic children; the odds ratios for adverse symptoms from 90^{th}

TABLE 8-25. SUMMARY OF ASTHMA PM_{10} COUGH STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 $\mu g/m^3$ PM_{10}
Asthma Studies					
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	0 day	1.40 (1.04, 1.88)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	0 day	2.19 (0.77, 6.20)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO_2, SO_2	0 day	0.93 (0.83, 1.04)
Peters et al. (1997c)	OR cough	55 (?, 71)	SO_2, sulfate, H^+	0 day	1.32 (1.16, 1.50)
Peters et al. (1997b)	OR cough	47 (29, 73)	SO_2, sulfate, H^+	0 day	1.01 (0.97, 1.07)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	0 day	1.21 (1.10, 1.33)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	0 day	1.27 (1.16, 1.42)
Vedal et al. (1998)	OR cough	19.1 (1, 159)	None	2 day	1.40 (1.13, 1.73)
Gielen et al. (1997)	OR cough	30.5 (16, 60)	Ozone	2 day	2.19 (0.47, 10.24)
Segala et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO_2, NO_2	2 day	(values not given because not significant)
Neukirch et al. (1998)	OR nocturnal cough	34.2 (9, 95)	SO_2, NO_2	3 day	(values not given because not significant)
Romieu et al. (1996)	OR cough	166.8 (29, 363)	Ozone	2 day	1.27 (1.07, 1.50)
Romieu et al. (1997)	OR cough	(12, 126)	Ozone	2 day	1.00 (0.92, 1.10)
Ostro et al. (2001)	OR cough	47 (11, 119) 24 hr	Ozone, NO_2	3 day	1.32 (1.12, 1.55)
Hiltermann et al. (1998)	OR cough	39.7 (16, 98)	Ozone, NO_2, SO_2	1-7 day	0.94 (0.82, 1.08)
Peters et al. (1997c)	OR cough	55 (?, 71)	SO_2, sulfate, H^+	1-5 day	1.30 (1.09, 1.55)
Peters et al. (1997b)	OR cough	47 (29, 73)	SO_2, sulfate, H^+	1-5 day	1.10 (1.04, 1.17)
Ostro et al. (2001)	OR cough	102 (47, 360) 1 hr max	ozone, NO_2	3 day	1.05 (1.02, 1.18)

TABLE 8-26. SUMMARY OF ASTHMA PM_{10} PHLEGM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m^3	Co-Pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/m^3 PM_{10}
Vedal et al. (1998)	OR phlegm	19.1 (1, 159)	None	0 day	1.28 (0.86, 1.89)
Peters et al. (1997b)	OR phlegm	47 (29, 73)	SO_2, sulfate, H^+	0 day	1.13 (1.04, 1.23)
Romieu et al. (1997)	OR phlegm	(12, 126)	Ozone	0 day	1.05 (0.83, 1.36)
Romieu et al. (1996)	OR phlegm	166.8 (29, 363)	Ozone	0 day	1.21 (1.00, 1.48)
Vedal et al. (1998)	OR phlegm	19.1 (1, 159)	None	2 day	1.40 (1.03, 1.90)
Romieu et al. (1997)	OR phlegm	(12, 126)	Ozone	2 day	1.00 (0.86, 1.16)
Romieu et al. (1996)	OR phlegm	166.8 (29, 363)	Ozone	2 day	1.16 (0.91, 1.49)
Peters et al. (1997b)	OR phlegm	47 (29, 73)	SO_2, sulfate, H^+	1-5 day	1.17 (1.09, 1.27)

TABLE 8-27. SUMMARY OF ASTHMA PM_{10} LOWER RESPIRATORY ILLNESS (LRI) STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range)	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/m^3 PM_{10}
Vedal et al. (1998)	LRI	19.1 (1, 159)	None	0 day	1.10 (0.82, 1.48)
Gielen et al. (1997)	LRI	30.5 (16, 60)	Ozone	0 day	1.26 (0.94, 1.68)
Romieu et al. (1997)	LRI	(12, 126)	Ozone	0 day	1.00 (0.95, 1.05)
Romieu et al. (1996)	LRI	166.8 (29, 363)	Ozone	0 day	1.21 (1.10, 1.42)
Vedal et al. (1998)	LRI	19.1 (1, 159)	None	2 day	1.16 (1.00, 1.34)
Gielen et al. (1997)	LRI	30.5 (16, 60)	Ozone	2 day	1.05 (0.74, 1.48)
Segala et al. (1998)	LRI	34.2 (9, 95)	SO_2, NO_2	2 day	1.66 (0.84, 3.30)
Romieu et al. (1997)	LRI	(12, 126)	Ozone	2 day	1.00 (0.93, 1.08)
Romieu et al. (1996)	LRI	166.8 (29, 363)	Ozone	2 day	1.10 (0.98, 1.24)
Delfino et al. (1998)	LRI	24 h 26 (6, 51) 8-h 43 (23-73) 1-h 57 (30-108)	Ozone Ozone Ozone	0 day 0 day 0 day	1.47 (0.90 - 2.39) 2.17 (1.33 - 3.58) 1.78 (1.25 - 2.53)

TABLE 8-28. SUMMARY OF ASTHMA PM_{10} BRONCHODILATOR USE STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 µg/m³ PM_{10}
Gielen et al. (1997)	OR bronchodilator use	30.5 (16, 60)	Ozone	0 day	0.94 (0.59, 1.50)
Hiltermann et al. (1998)	OR bronchodilator use	39.7 (16, 98)	Ozone, NO_2, SO_2	0 day	1.03 (0.93, 1.15)
Peters et al. (1997b)	OR bronchodilator use	47 (29, 73)	SO_2, sulfate, H^+	0 day	1.06 (0.88, 1.27)
Gielen et al. (1997)	OR bronchodilator use	30.5 (16, 60)	Ozone	2 day	2.90 (1.81, 4.66)
Hiltermann et al. (1998)	OR bronchodilator use	39.7 (16, 98)	Ozone, NO_2, SO_2	1-7 day	1.12 (1.00, 1.25)
Peters et al. (1997b)	OR bronchodilator use	47 (29, 73)	SO_2, sulfate, H^+	1-5 day	1.23 (0.96, 1.58)

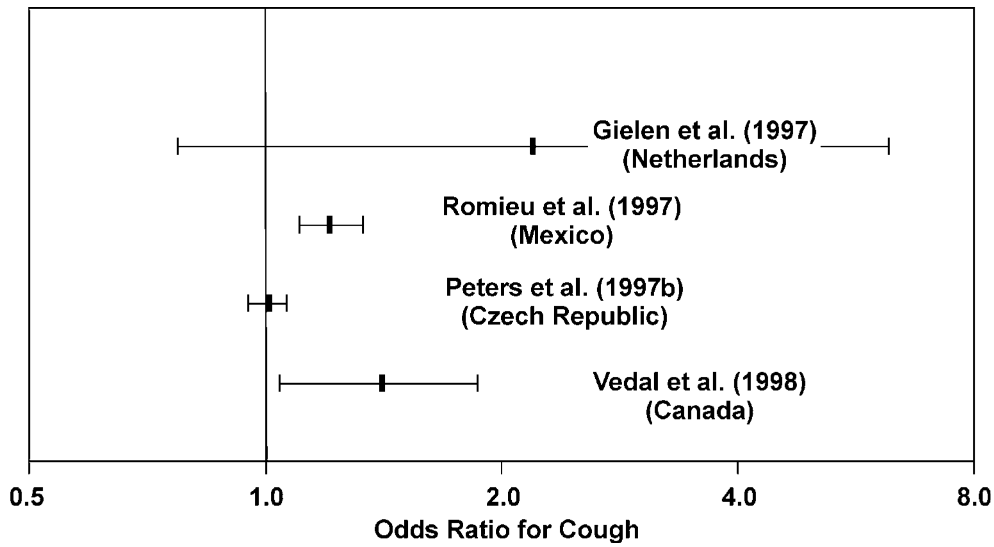

Figure 8-14. Odds ratios with 95% confidence interval for cough per 50-µg/m³ increase in PM_{10} for selected asthmatic children studies at lag 0.

percentile increases were 2.24 (1.46, 3.46), for 1-hr PM_{10}; 1.82 (1.18, 2.8), for 8-hr PM_{10}, and 1.50 (0.80-2.80) for 24-hr PM_{10}. Analyses suggested that effects of O_3 and PM_{10} were largely independent. Delfino et al. (2002) also studied 22 asthmatic children aged 9-19 years in March and April 1996. Relationships were evaluated by use of generalized estimating equations, adjusting for autocorrelation. The endpoint was symptoms interfering with daily activities. This endpoint was associated with PM_{10}, NO_2, and ozone. There was a positive interaction effect of PM_{10} and NO_2 jointly. Both of these studies also reported significant associations with fungal spores, but not pollens; no significant interactions were found between aeroallergens and air pollutants.

Romieu et al. (1996) found children with mild asthma to be more strongly affected by high ambient levels of PM (mean PM_{10} = 166.8 µg/m³) observed in northern Mexico City than in a study (Romieu et al., 1997) conducted in a nearby area with lower PM_{10} levels (mean PM_{10} = 54.2 µg/m³). Yu et al. (2000) reported estimates of odds ratios for asthma symptoms and 10 µg/m³ increments in PM_{10} and $PM_{1.0}$ values of 1.18 (1.05, 1.33) and 1.09 (1.01, 1.18), respectively. Multipollutant models with CO and SO_2 yielded 1.06 (0.95, 1.19) for PM_{10}, and 1.11 (0.98, 1.26) for $PM_{1.0}$, thus showing a lower value for PM_{10} and a loss of significance for both PM_{10} and $PM_{1.0}$. The correlation between CO and $PM_{1.0}$ and PM_{10} was 0.82 and 0.86. Ostro et al. (2001) studied a panel of inner-city African American children using a GEE model with several measures of PM, including PM_{10} (both 24-hour average and 1-hour max.) and $PM_{2.5}$, demonstrating positive associations with daily probability of shortness of breath, wheeze, and cough.

Desqueyroux et al. (2002) studied 60 adult severe asthmatics from November 1995 to November 1996. Relationships were estimated from generalized estimating equations adjusting for autocorrelation. Each asthma exacerbation was confirmed by a physician, and each of the cases were followed for a sufficient length of time to allow investigations of any lagged associations with air pollution. Statistical analysis that accounted for temporal, meteorological, and aerobiological variables and some individual characteristics revealed significant associations between PM_{10}, O_3, and incident asthma attacks. Odds Ratio (OR) for an increase of 10 ug/m^3 of PM_{10} was 1.41; 95% confidence interval (CI) = 1.16; 1.71. PM_{10} was not related to incident asthma attacks using lags of 1 or 2 days; but PM_{10} associations for 3, 4, and 5 day lags were significant. PM_{10} remained significant even after adjusting for other pollutants including O_3, SO_2, and NO_2.

Just et al. (2002) also studied 82 asthmatic children for 3 months during spring and early summer in Paris. Relationships were estimated from generalized estimating equations adjusting for autocorrelation. No significant relationships were found between PM_{13} and lung function or respiratory symptoms. For $PM_{2.5}$ results, see Table 8-29. All showed positive associations (several being clearly significant at $p < 0.05$) between $PM_{2.5}$ and increased cough, phlegm, or LRI.

Of studies that included two indicators for PM (PM_{10}, $PM_{2.5}$) in their analyses, the study of Peters et al. (1997c) found similar effects for the two PM measures, whereas the Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$.

Two asthma studies, both in the United States, examined PM indicators by 1 hr averages as well as by 24 hr averages. The PM_{10} 1 hr outcome was larger than the 24 hr outcome for lower respiratory illness in one study (Delfino et al., 1998) but was lower for cough in the other study (Ostro et al., 2001).

Several of the studies reviewed above (Delfino et al., 1998, 2002; Ostro et al., 2001; Yu et al., 2000; Mortimer et al., 2002; Vedal et al., 1998) that were conducted in the United States

TABLE 8-29. SUMMARY OF ASTHMA $PM_{2.5}$ RESPIRATORY SYMPTOM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 $\mu g/m^3$ $PM_{2.5}$
Peters et al. (1997b)	OR cough	50.8 (9, 347)	SO_2, sulfate, H^+	0 day	1.22 (1.08, 1.38)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	0 day	1.27 (1.08, 1.42)
Tiittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	0 day	1.04 (0.86, 1.20)
Romieu et al. (1996)	OR cough	85.7 (23, 177)	Ozone	2 day	1.16 (0.98, 1.33)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	2 day	1.24 (1.02, 1.51)
Ostro et al. (2001)	OR cough	40.8 (4, 208)	Ozone, NO_2	3 day	1.02 (0.98, 1.06)
Peters et al. (1997b)	OR cough	50.8 (9, 347)	SO_2, sulfate, H^+	1-5 day	1.02 (0.90, 1.17)
Romieu et al. (1996)	OR Phlegm	85.7 (23, 177)	Ozone	0 day	1.21 (0.98, 1.48)
Romieu et al. (1996)	OR Phlegm	85.7 (23, 177)	Ozone	2 day	1.16 (0.99, 1.39)
Romieu et al. (1996)	OR LRI	85.7 (23, 177)	Ozone	0 day	1.21 (1.05, 1.42)
Romieu et al. (1996)	OR LRI	85.7 (23, 177)	Ozone	2 day	1.16 (1.05, 1.42)

and Canada found positive associations between various health endpoints for asthmatics and ambient PM exposure (indexed by PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$). The endpoints included PEF decrements, various individual respiratory symptoms, and combinations of respiratory symptoms. The various endpoints each represent effects on respiratory health.

8.3.3.1.2 Lung Function and Respiratory Symptom Effects in Nonasthmatic Subjects

Results for PM_{10} peak flow analyses in non-asthmatic studies (summarized in Appendix 8B Table 8B-6) were inconsistent, with fewer studies reporting results in the same manner as for the asthmatic studies. Many of the point estimates showed increases rather than decreases (see Table 8-30). The effects on respiratory symptoms in non-asthmatics (see Appendix 8B Table 8B-7) were similar to those in asthmatics. Most studies showed that PM_{10} increases cough, phlegm, difficulty breathing, and bronchodilator use, although these were generally not statistically significant (Table 8-31). Vedal et al. (1998) reported no consistent evidence for adverse health effects in a nonasthmatic control group.

Results of the $PM_{2.5}$ peak flow and symptom analyses in non-asthmatic studies (see Appendix 8B Table 8B-8, Table 8-32) were similar to PM_{10} results discussed above.

Three authors, Schwartz and Neas (2000), Tiittanen et al. (1999) and Neas et al. (1999), used $PM_{10-2.5}$ as a coarse fraction particulate measure (Table 8-33). Schwartz and Neas (2000) found that $PM_{10-2.5}$ was significantly related to cough. Tiittanen found that one day lag of $PM_{10-2.5}$ was related to morning PEF, but there was no effect on evening PEF. Neas et al. found no effects of $PM_{10-2.5}$ on PEF.

The Schwartz and Neas (2000) reanalyses allows comparison of fine and coarse particle effects on healthy school children using two pollutant models of fine and coarse PM. CM was estimated by subtracting $PM_{2.1}$ from PM_{10} data. They report for cough for reanalysis of the Harvard Six City Diary Study in the two PM pollutant model $PM_{2.5}$ OR = 1.07 (0.90, 1.26; per 15 $\mu g/m^3$ increment) and $PM_{10-2.5}$ OR 1.18 (1.04, 1.34; per 8 $\mu g/m^3$ increment) in contrast to lower respiratory symptom results of $PM_{2.5}$ OR 1.29 (1.06, 1.57) and $PM_{10-2.5}$ 1.05 (0.9, 1.23). In the Uniontown reanalysis, peak flow for $PM_{2.1}$ for a 14 $\mu g/m^3$ increment was −0.91 1/m (−1.14, −1.68) and $PM_{10-2.1}$ for 15 $\mu g/m^3$ +1.04 1/m (−1.32, +3.4); for State College $PM_{2.1}$ −0.56 (−1.13, +0.01) and $PM_{10-2.1}$ −0.17 (−2.07, +1.72).

TABLE 8-30. SUMMARY OF NON-ASTHMA PM_{10} PFT STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) μg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 μg/m³ PM_{10}
Gold et al. (1999)	Morning PEFR	51 (23, 878)	Ozone	1 day	−0.20 (−0.47, 0.07)
Tittanen et al. (1999)	Morning PEFR	28 (5, 122)	NO_2, SO_2, CO, ozone	0 day	1.21 (−0.43, 2.85)
Neas et al. (1999)	Morning PEFR	32	Ozone	1-5 day	2.64 (−6.56, 11.83)
Tittanen et al. (1999)	Morning PEFR	28 (5, 122)	NO_2, SO_2, CO, ozone	1-4 day	−1.26 (−5.86, 3.33)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO_2, SO_2	1 day	1.04 (0.95, 1.13)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO_2, SO_2	2 day	1.02 (0.93, 1.11)
Boezen et al. (1999)	OR > 10% AM PEFR Decr.	42 (5, 146)	NO_2, SO_2	1-5 day	1.05 (0.91, 1.21)
Neas et al. (1999)	Morning PEFR	32	Ozone	0 day	−8.16 (−14.81, −1.55)
Harré et al. (1997)	% change in morning PEFR	(not given)	NO_2, SO_2, CO	1 day	0.07 (−0.50, 0.63)
Neas et al. (1999)	Evening PEFR	32	Ozone	0 day	−1.44 (−7.33, 4.44)
Schwartz & Neas (2000) Uniontown	Evening PEFR	(not given)	Sulfate fraction	0 day	−1.52 (−2.80, −0.24)
Schwartz & Neas (2000) State College	Evening PEFR	(not given)	Sulfate fraction	0 day	−0.93 (−1.88, 0.01)
Tittanen et al. (1999)	Evening PEFR	28 (5, 122)	NO_2, SO_2, CO, ozone	0 day	0.72 (−0.63, 1.26)
Tittanen et al. (1999)	Evening PEFR	28 (5, 122)	NO_2, SO_2, CO, ozone	0 day	2.33 (−2.62, 7.28)
Gold et al. (1999)	Evening PEFR	51 (23, 878)	Ozone	0 day	−0.14 (−0.45, 0.17)
Neas et al. (1999)	Evening PEFR	32	Ozone	1-5 day	1.47 (−7.31, 10.22)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO_2, SO_2	0 day	1.17 (1.08, 1.28)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO_2, SO_2	2 day	1.08 (0.99, 1.17)
Boezen et al. (1999)	OR > 10% PM PEFR Decr.	42 (5, 146)	NO_2, SO_2	1-5 day	1.16 (1.02, 1.33)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO_2, SO_2, sulfate	0 day	1.44 (1.02, 2.03)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO_2, SO_2, sulfate	2 day	1.14 (0.83, 1.58)
Van der Zee et al. (1999)	OR > 10% PM PEFR Decr.	34 (?, 106)	NO_2, SO_2, sulfate	1-5 day	1.16 (0.64, 2.10)
Harré et al. (1997)	% change in evening PEFR	(not given)	NO_2, SO_2, CO	1 day	−0.22 (−0.57, 0.16)

TABLE 8-31. SUMMARY OF NON-ASTHMA PM_{10} RESPIRATORY SYMPTOM STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) µg/m³	Co-pollutants Measured	Lag Structure	Effect measures standardized to 50 mg/m³ PM_{10}
Schwartz & Neas (2000)	OR cough – no other symptoms	(not given)	Sulfate fraction	0 day	1.20 (1.07, 1.35)
Boezen et al. (1998)	OR cough	42 (5, 146)	NO_2, SO_2	0 day	1.06 (0.93, 1.21)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO_2, SO_2, sulfate	0 day	1.04 (0.95, 1.14)
Tittanen et al. (1999)	OR cough	28 (5, 122)	NO_2, SO_2, CO, ozone	0 day	1.00 (0.87, 1.16)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO_2, SO_2, sulfate	2 day	0.94 (0.89, 1.06)
Van der Zee et al. (1999) Urban areas	OR cough	34 (?, 106)	NO_2, SO_2, sulfate	1-5 day	0.95 (0.80, 1.13)
Tittanen et al. (1999)	OR cough	28 (5, 122)	NO_2, SO_2, CO, ozone	1-4 day	1.58 (0.87, 2.83)
Boezen et al. (1998)	OR phlegm	42 (5, 146)	NO_2, SO_2	0 day	1.11 (0.91, 1.36)
Tittanen et al. (1999)	OR phlegm	28 (5, 122)	NO_2, SO_2, CO, ozone	2 day	Positive but not significant
Schwartz & Neas (2000)	LRI	(not given)	Sulfate fraction	0 day	
Van der Zee et al. (1999) Urban areas	LRI	34 (?, 106)	NO_2, SO_2, sulfate	0 day	0.98 (0.89, 1.08)
Van der Zee et al. (1999) Urban areas	LRI	34 (?, 106)	NO_2, SO_2, sulfate	2 day	1.01 (0.93, 1.10)

TABLE 8-32. SUMMARY OF NON-ASTHMA $PM_{2.5}$ RESPIRATORY OUTCOME STUDIES

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 $\mu g/m^3$ $PM_{2.5}$
Gold et al. (1999)	Morning PEFR	30.3 (9, 69)	Ozone	1 day	−0.22 (−0.46, 0.01)
Tittanen et al. (1999)	Morning PEFR		NO_2, SO_2, CO, ozone	0 day	1.11 (−0.64, 2.86)
Tittanen et al. (1999)	Morning PEFR		NO_2, SO_2, CO, ozone	1-4 day	−1.93 (−7.00, 3.15)
Neas et al. (1999)	Morning PEFR	24.5 (?, 88)	Ozone	1-5 day	2.64 (−6.56, 11.83)
Schwartz & Neas (2000) Uniontown	Evening PEFR	(not given)	Sulfate fraction	0 day	−1.52 (−2.80, −0.24)
Schwartz & Neas (2000) State College	Evening PEFR	(not given)	Sulfate fraction	0 day	−0.93 (−1.88, 0.01)
Tittanen et al. (1999)	Evening PEFR		NO_2, SO_2, CO, ozone	0 day	0.70 (−0.81, 2.20)
Tittanen et al. (1999)	Evening PEFR		NO_2, SO_2, CO, ozone	0 day	1.52 (−3.91, 6.94)
Gold et al. (1999)	Evening PEFR	30.3 (9, 69)	Ozone	0 day	−0.10 (−0.43, 0.22)
Neas et al. (1999)	Evening PEFR	24.5 (?, 88)	Ozone	1-5 day	1.47 (−7.31, 10.22)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	0 day	1.04 (0.86, 1.20)
Tittanen et al. (1999)	OR cough	15 (3, 55)	NO_2, SO_2, CO, ozone	2 day	1.24 (1.02, 1.51)
Schwartz & Neas (2000)	OR LRS	(not given)	Sulfate fraction	0 day	1.61 (1.19, 2.14)

TABLE 8-33. SUMMARY OF NON-ASTHMA COARSE FRACTION STUDIES OF RESPIRATORY ENDPOINTS

Reference citation, location, etc.	Outcome Measure	Mean Particulate Levels (Range) $\mu g/m^3$	Co-pollutants Measured	Lag Structure	Effect measures standardized to 25 $\mu g/m^3$ $PM_{10-2.5}$
Tittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1 day	−1.26 (−2.71, 0.18)
Neas et al. (1999)	Morning PEFR	8.3	Ozone	1 day	−4.31 (−11.43, 2.75)
Tittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	0.51 (−0.77, 2.16)
Tittanen et al. (1999)	Morning PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	−0.57 (−1.96, 0.81)
Neas et al. (1999)	Morning PEFR	8.3	Ozone	1-5 day	−6.37 (−21.19, 8.44)
Tittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	0 day	0.66 (−0.33, 1.81)
Neas et al. (1999)	Evening PEFR	8.3	Ozone	1 day	1.88 (−4.75, 8.44)
Tittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	0.03 (−1.41, 1.47)
Tittanen et al. (1999)	Evening PEFR	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	2.37 (−1.69, 4.96)
Neas et al. (1999)	Evening PEFR	8.3	Ozone	1-5 day	5.94(−7.00, 18.94)
Tittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	0 day	0.99 (0.87, 1.12)
Tittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	2 day	1.23 (1.06, 1.42)
Tittanen et al. (1999)	OR cough	8 (.2, 67)	NO_2, SO_2, CO, ozone	1-4 day	1.31 (0.81, 2.11)
Schwartz & Neas (2000)	OR cough without other symptoms	(not given)	Sulfate fraction	0 day	1.77 (1.24, 2.55)
Schwartz & Neas (2000)	OR LRS	(not given)	Sulfate fraction	0 day	1.51 (0.94, 4.87)

Coull et al. (2001) reanalyzed data from the Pope et al. (1991) study of PM effects on pulmonary function of children in the Utah Valley, using additive mixed models which allow for assessment of heterogeneity of response or the source of heterogeneity. These additive models describe complex covariate effects on each child's peak expiratory flow while allowing for unexplained population heterogeneity and serial correlation among repeated measurements. The analyses indicate heterogeneity among that population with regard to PM_{10} (i.e., specifically that there are three subjects in the Utah Valley study who exhibited a particularly acute response to PM_{10}). However the limited demographic data available in the Utah Valley Study does not explain the heterogeneity in PM sensitivity among the school children population.

Two studies examined multipollutant models. The Jalaludin et al. (2000) analyses used a multipollutant model that evaluated PM_{10}, O_3, and NO_2. They found in metropolitan Sydney that ambient PM_{10} and O_3 concentrations are poorly correlated (r = 0.13). For PEFR the β (SE) for PM_{10} only was 0.0045 (0.0125), p = 0.72; and for PM_{10} and O_3, 0.0051 (0.0124), p = 0.68. Ozone was also unchanged in the one- and two-pollutant models. Gold et al. (1999) attempted to study the interaction of $PM_{2.5}$ and O_3 on PEF in Mexico City children (age = 8 to 12 yrs). The authors found independent effects of the two pollutants, but the joint effect was slightly less than the sum of the independent effects.

8.3.3.2 Long-Term Particulate Matter Exposure Effects on Lung Function and Respiratory Symptoms

8.3.3.2.1 Summary of 1996 Particulate Matter Air Quality Criteria Document Key Findings

In the 1996 PM AQCD, the available long-term PM exposure-respiratory disease studies were limited in terms of conclusions that could be drawn. At that time, three studies based on a similar type of respiratory symptom questionnaire administered at three different times as part of the Harvard Six-City and 24-City Studies provided data on the relationship of chronic respiratory disease to PM. All three studies suggest a long-term PM exposure effect on chronic respiratory disease. The analysis of chronic cough, chest illness and bronchitis tended to be significantly positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio = 1.66) in the community with the highest particle strong acidity when compared with the least polluted community. Fine particulate sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

Interpretation of such studies requires caution in light of the usual difficulties ascribed to cross-sectional studies. That is, evaluation of PM effects is based on variations in exposure determined by a different number of locations. In the first two studies, there were six locations and, in the third, twenty-four. The results seen in all studies were consistent with a PM gradient, but it was not readily possible to separate out clear effects of PM from other factors or pollutants having the same gradient.

Chronic pulmonary function studies by Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) had good monitoring data and well-conducted standardized pulmonary function testing over many years, but showed no effect for children from airborne particle pollution indexed by TSP, PM_{15}, $PM_{2.5}$ or sulfates. In contrast, the Raizenne et al. (1996) study of U.S. and Canadian children found significant associations between FEV_1 and FVC and acidic particles (H^+). Overall, the available studies provided only limited evidence suggestive of pulmonary lung function decrements being associated with chronic exposure to PM indexed by various measures (TSP, PM_{10}, sulfates, etc.). However, it was noted that cross-sectional studies require very large sample sizes to detect differences because they cannot eliminate person to person variation, which is much larger than the within person variation.

8.3.3.2.2 New Studies of Respiratory Effects of Long-Term Particulate Matter Exposure

Several studies published since 1996 evaluated effects of long-term PM exposure on lung function and respiratory illness (see Appendix 8B, Table 8B-8). The new studies examining PM_{10} and $PM_{2.5}$ in the United States include McConnell et al. (1999), Abbey et al. (1998), Berglund et al. (1999), Peters et al. (1999a,b), and Avol et al. (2001), all of which examined effects in California cohorts but produced variable results. McConnell et al. (1999) noted that, as PM_{10} increased across communities, the bronchitis risk per interquartile range also increased, results consistent with those reported by Dockery et al. (1996). However, the high correlation of PM_{10}, acid, and NO_2 precludes clear attribution of the McConnell et al. bronchitis effects specifically to PM alone. Avol et al. (2001) reported that, for 110 children that moved to other locations as a group, subjects who moved to areas of lower PM_{10} showed increased growth in lung function and subjects who moved to communities with higher PM_{10} showed slowed lung function growth.

Gauderman et al. (2000, 2002) presented results from a study that is both a cohort and a cross-sectional study. This unique design followed two cohorts of southern California children who were fourth graders in 1993 and 1996 respectively. The cohorts, located in 12 communities, were followed for 4 years. A three stage model which allowed for individual slopes, within community covariates, and community-wide air pollution averages, was fitted using SAS Proc MIXED. Pulmonary function measurements included FVC, FEV1, MMEF, and PEFR, all of which gave similar results for both $PM_{2.5}$ and PM_{10}. In the first cohort, PM_{10} showed a significant 1.3% decrease in annual growth rates for a 51.5 µg/m^3 difference in PM_{10}. This difference was only 0.4% in the second cohort; however, the two were not significantly different from each other. The effect for $PM_{2.5}$ was slightly less for a difference of 22.2 µg/m^3. Peters et al. (1999b) studied the prevalence of respiratory symptoms in 12 southern California communities in 1993. To estimate the relationship between symptoms and pollutants a two-stage regression approach was used. The first stage estimated community-specific rates adjusted for individual covariates. The second stage regressed these rates on pollutant averages from 1986 to 1990, finding no significant relationships between respiratory symptoms and average PM_{10} levels.

In a non-U.S. PM_{10} study, Horak et al. (2002) conducted a combined cohort and cross-sectional study similar in design to that of Gauderman et al. (2000). The cohorts were taken from 975 school children in 8 communities in lower Austria between 1994-1997. Relationships were estimated from generalized estimating equations adjusting for autocorrelation. Adjustments were made for sex, atopy, ETS, baseline lung function, height, and site. Growth in FVC and MEF were significantly related to winter PM_{10} levels.

Gehring et al. (2002) enrolled 1,756 newborn children in the Munich area. Individual $PM_{2.5}$ and NO_2 levels were estimated from actual measurements at 40 sites combined with a GIS predictor model. $PM_{2.5}$ levels ranged from 11.9 to 21.9 µg/m^3. The incidence (in the first two years of life) of cough without infection and dry cough at night were related to $PM_{2.5}$ levels. Wheeze, bronchitis, respiratory infections, and runny nose were not related to $PM_{2.5}$ levels.

Other non-U.S. studies examined PM measures such as TSP and BS in European countries. In Germany, Heinrich et al. (2000) reported a cross-sectional survey of children, conducted twice (with the same 971 children included in both surveys). TSP levels decreased between surveys as did the prevalence of all respiratory symptoms (including bronchitis). Also, Krämer et al. (1999) reported a study in six East and West Germany communities, which found decreasing yearly TSP levels to be related to ever-diagnosed bronchitis from 1991-1995. Lastly, Jedrychowski et al. (1999) reported an association between both BS and SO_2 levels in various areas of Krakow, Poland, and slowed lung function growth (FVC and FEV_1).

Leonardi et al. (2000) studied a different health outcome measure as part of the Central European Air Quality and Respiratory Health (CESAR) study. Blood and serum samples were collected from school children ages 9-11 yrs. in each of 17 communities in Central Europe (N = 10 to 61 per city). Numbers of lymphocytes increased as PM concentrations increased across the cities. Regression slopes, adjusted for confounder effects, were largest and statistically significant for $PM_{2.5}$, but small and non-significant for $PM_{10-2.5}$. A similar positive relationship was found between IgG concentration in serum and $PM_{2.5}$ gradient, but not for PM_{10} or $PM_{10-2.5}$. These results tend to suggest a PM effect on immune function more strongly due to ambient fine particle than coarse particle exposure.

8.3.3.2.3 Summary of Long-Term Particulate Matter Exposure Respiratory Effects

The methodology used in the long-term studies varies much more than the methodology in the short-term studies. Some studies reported highly significant results (related to PM) while others reported no significant results. The cross-sectional studies are often confounded, in part, by unexplained differences between geographic regions. The studies that looked for a time trend are also confounded by other conditions that were changing over time. The newer studies that combine the features of cross-sectional and cohort studies provide the best evidence for chronic effects. These studies include Peters et al. (1999b), Gauderman et al. (2000), and Gauderman et al. (2002). The Gauderman studies found significant decreases in lung function growth among So. California school children to be related to PM_{10} levels. However, Peters et al. (1999b) found no relationship between respiratory symptoms and annual average PM_{10} levels in 12 So. California communities.

The cross-sectional studies by Dockery et al. (1996) and Raizenne et al. (1996), assessed before in the previous 1996 PM AQCD, found differences in peak flow and bronchitis rates associated with fine particle acidity.

8.4 INTERPRETIVE ASSESSMENT OF THE EPIDEMIOLOGIC EVIDENCE

8.4.1 Introduction

Numerous PM epidemiology studies assessed in the 1996 PM AQCD implicated ambient PM as a likely contributor to mortality and morbidity effects associated with ambient air pollution exposures. Since preparation of the 1996 PM AQCD, the epidemiologic evidence concerning ambient PM-related health effects has vastly expanded. Past regulatory decisions have been important in the selection of PM indices and evolution of PM epidemiologic literature. That is, the adoption of PM_{10} standards in 1987 and of $PM_{2.5}$ standards in 1997 have generated ambient air concentration databases that have made it possible for research to address many previously unresolved issues regarding possible linkages between airborne PM and human health; and the newly authorized nationwide network of speciation samplers holds promise for further advances regarding identification of the most influential specific components of the ambient air pollution mixture and their sources.

As was discussed in Sections 8.2 and 8.3, numerous new PM epidemiology studies, both of short-term and long-term PM exposure, have yielded findings indicating that statistically significant excess risks for various mortality and/or morbidity endpoints in many U.S. cities and elsewhere are associated with ambient PM indexed by a variety of ambient community monitoring methods. Still, several uncertainties discussed in the 1996 PM AQCD continue to be important in assessing and interpreting the overall PM epidemiology database and its implications for estimating risks associated with exposure to ambient PM concentrations in the United States: (1) potential confounding of PM effects by co-pollutants (especially major gaseous pollutants such as O_3, CO, NO_2, SO_2); (2) the attribution of PM effects to specific PM components (e.g., PM_{10}, $PM_{10\text{-}2.5}$, $PM_{2.5}$, ultrafines, sulfates, metals, etc.) or source-oriented indicators (motor vehicle emissions, vegetative burning, etc.); (3) the temporal relationship between exposure and effect (lags, mortality displacement, etc.); (4) the general shape of exposure-response relationship(s) between PM and/or other pollutants and observed health effects (e.g., potential indications of thresholds for PM effects); (5) the consequences of measurement error; and (6) identification of susceptible population subgroups at special risk for ambient PM health effects. All of these issues are of much importance for characterizing and interpreting ambient PM-health effects associations.

Assessing the above uncertainties in relation to the PM epidemiology data base remains a challenge. The basic issue is that there are an extremely large number of possible models, any of which may turn out to give the best statistical "fit" of a given set of data, and only some of which can be dismissed *a priori* as biologically or physically illogical or impossible, except that putative cause clearly cannot follow effect in time. Most of the models for daily time-series studies are fitted by adjusting for changes over long time intervals and across season, by day of week, weather, and climate. Many of the temporal and weather variable models have been fitted to data using semi-parametric methods such as spline functions or local regression smoothers (LOESS). The goodness of fit of these base models has been evaluated by criteria suitable for generalized linear models (GLM) with Poisson or hyper-Poisson responses (number of events) with a log link function, particularly the Akaike Information Criterion (AIC) and the more conservative Bayes information criterion (BIC), which adjust for the number of parameters estimated from the data. The Poisson over-dispersion index and the auto-correlation of residuals are also often used. It is often assumed, but rarely proven, that the best-fitting models with PM would be models with the largest and most significant PM indices. However, if high correlations between PM and one or more gaseous pollutants emitted from a common source (e.g., motor vehicles) exist in a given area, then disentangling their relative individual partial contributions to observed health effects associations becomes very difficult. There have been very few attempts at broad, systematic investigations of the model selection issue and little reporting of goodness-of-fit criteria among competing models that represent one approach by which to assess or compare models.

Substantial prior knowledge to guide model fitting now exists and an informed modeling strategy can yield a useful set of models as one type of sensitivity analysis. To illustrate, a systemic evaluation of model choice has been carried out by Clyde et al. (2000), using Bayesian Model Averaging for the same Birmingham, AL, data as analyzed by Smith et al. (2000). Several different calibrated information criterion priors were tried in which models with large numbers of parameters are penalized to various degrees. After taking out a baseline trend (estimated using a GLM estimate with a 30-knot thin-plate smoothing spline), 7,860 models were selected for use in model averaging. These included lags 0-3 days of a daily monitor PM_{10}, an area-wide average PM_{10} value with the same lags, temperature (daily extremes and average) lagged 0-2 days, humidity (dewpoint, relative humidity min and max, average specific humidity) lagged 0-2 days, and atmospheric pressure, lagged 0-2 days. The model choice is sensitive to the specification of calibrated information criterion priors, in particular disagreeing as to whether different PM_{10} variables should be included or not. For example, one or another PM_{10} variable is included in all the top 25 Akaike Information Criterion (AIC) models, but only in about 1/3 of the top Bayes Information Criterion (BIC) models. Both approaches give a relative risk estimate of about 1.05, with credibility intervals of (0.94, 1.17) for the AIC prior and (0.99, 1.11) for the BIC prior. A validation study in which randomly selected data were predicted using the different priors favored Bayesian model averaging with BIC prior over model selection (picking the best model) with BIC or any approach with AIC. This type of modeling may represent another type of multi-pollutant modeling approach in addition to more typical hypotheses-driven model construction and interpretation that draws more on external information (e.g., exposure, dosimetric, toxicologic relationships) in specifying models and interpreting their results.

The possibility that an observed effect is "real" (i.e., likely to be found in an independent replication of the study) or merely a statistical artifact is usually characterized by its confidence interval or by its estimated significance level. In most of this document, confidence intervals, or credible intervals for Bayesian analyses, are reported in order to emphasize that the effect size is not known with certainty, but some values are more nearly consistent with the data than effect size values outside the interval. P-values or t-values are implicitly associated with a null hypothesis of no effect. A nominal significance level of $p \leq 0.05$ or 5% (i.e., a 95% confidence interval) is usually used as a guide for the reader, but P-values should not be used as a rigid decision-making tool. If the observed confidence intervals were arrived at by a number of prior model specification searches, eliminating some worse fitting models, the true interval may well be wider.

Given the now extremely large number of published epidemiologic studies of ambient PM associations with health effects in human populations and the considerably wide diversity in applications of even similar statistical approaches (e.g., "time-series analyses" for short-term PM exposure effects), it is neither feasible nor useful here to try to evaluate the methodological soundness of every individual study. Rather, a three-pronged approach is likely to yield useful evaluative information: (1) an overall characterization of evident general commonalities (and/or notable marked differences) among findings from across the body of studies dealing with particular PM exposure indices and types of health outcomes, looking for convergence of evidence regarding types of effects and effect-sizes attributable to ambient PM indices across various methodologically acceptable analyses; (2) thorough, critical assessment of newly published multi-city analyses of PM effects, assuming that greater scientific weight is generally ascribable to their results than those of smaller-sized studies (often of individual cities) yielding presumably less precise effect size estimates; (3) evaluation of albeit at times, less precise, single city results; and (4) evaluation of coherence of the findings among different types of effects and across various geographic locations, as well as with other types of pertinent biological information (e.g., exposure, dosimetry, toxicity, etc.).

In the sections that follow, issues noted above are critically discussed. In addition, given that both the newer multi-city study results and those of newer single-city analyses tend to show evidence of somewhat greater geographical heterogeneity in estimated PM risks across cities and regions than had been seen in studies assessed in the 1996 PM AQCD, the issue of geographical heterogeneity in PM effect estimates is further evaluated here.

First follows a discussion of the GAM issue and a summary of some key findings emerging from the short communications and peer-review commentary recently published by HEI (2003).

8.4.2 GAM Issue and Reanalyses Studies

As discussed earlier, Dominici et al. (2002) reported that the default convergence criteria used in the S-Plus function GAM may not guarantee convergence to the best unbiased estimate in all cases. The actual importance of this effect has only recently begun to be quantified, the results of recent reanalyses of many key studies being especially helpful in this regard; those reanalyses are described in short communicatons published in the HEI (2003b) Special Report. As for the net outcome of these reanalyses efforts, HEI (2003b) summarizes it well, as follows:

> Overall, the revised analyses using GAM with more stringent convergence criteria and iterations and GLM-natural splines resulted in lower estimates, but largely confirmed the effect of exposure to particulate matter on mortality (Burnett and Goldberg, 2003; Dominici et al., 2003; Katsouyanni et al., 2003; Samoli et al. ,2003; Schwartz, 2003b; Zanobetti and Schwartz, 2003a) and morbidity, especially for hospitalizations for cardiovascular and respiratory diseases (Atkinson et al., 2003; Fairley, 2003; Gold et al., 2003; Hoek, 2003; Ito, 2003; Le Tertre et al., 2003; Ostro et al., 2003; Schwartz, 2003a; Sheppard, 2003; Zanobetti and Schwartz, 2003b). As in earlier analyses, the effect was more pronounced among

individuals 65 years of age and older (Fairley; Gold et al.; Goldberg and Burnett; Ito; Le Tertre et al.; Mar et al.; Mooigavkar; Schwartz a). The impact of various sensitivity analyses, when these were performed, differed across the studies. No significant impacts were seen in some (Ostro et al.), whereas in others, alternative modeling of time (Klemm and Mason; Moolgavkar) and weather factors (Goldberg and Burnett; Ito) resulted in substantial changes.

The following discussion evaluates in more detail the nature and extent of potential problems in the various studies that have used the GAM default algorithm, but which have also had their analyses redone using alternative methods unaffected by this convergence issue.

8.4.2.1 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Mortality

Many of the reanalysis studies analyzed associations between PM_{10} and mortality, allowing an examination of the impact of GAM convergence problem on this PM index. Table 8-34 and Figure 8-15 shows the percent excess total non-accidental mortality (unless noted otherwise) risk estimates per 50 µg/m^3 increase in PM_{10} derived from the reanalysis studies for (1) GAM with default convergence criteria; (2) GAM with stringent convergence criteria; and, (3) GLM with natural splines that approximate the original GAM model. The figure shows results only from the studies that used all of the three alternative models for PM_{10}. It can be seen that most, but not all, reanalyses resulted in reductions in PM_{10} risk estimates when more stringent convergence criteria were used in GAM models. Using GLM with natural splines resulted in additional reduction in PM_{10} risk estimates for most, but not all, cases. The extent of reductions in PM_{10} risk estimates in GAM with more stringent convergence criteria or GLM with natural splines was in most cases less than 1% excess deaths per 50 µg/m^3 increase in PM_{10}. Obviously, the relative reduction is greater for the studies that had smaller PM_{10} risk estimates in the original analyses (e.g., NMMAPS U.S. 90 cities analyses). It can also be seen from Figure 8-17 that the extent of reduction in PM_{10} risk estimates is smaller compared to the variability of PM_{10} risk estimates across the studies. Thus, the effect of the GAM convergence problem does not appear, in most cases, to be substantial. Potential factors affecting the heterogeneity of PM_{10} risk estimates across studies are discussed in later sections. Several of the reanalysis reports also analyzed $PM_{2.5}$ and $PM_{10-2.5}$. Generally, the pattern and extent of reductions in mortality risk

TABLE 8-34. PM_{10} EXCESS RISK ESTIMATES FROM REANALYSIS STUDIES FOR TOTAL NON-ACCIDENTAL MORTALITY PER 50 µg/m^3 INCREASE IN PM_{10}

Study	GAM-default	GAM-stringent	GLM
NMMAPS 90-cities; Dominici et al. (2002)	2.1 (1.6, 2.6)	1.4 (0.9, 1.9)	1.1 (0.5, 1.7)
Harvard 6-cities; Klemm and Mason (2003)	4.1 (2.8, 5.4)	3.6 (2.1, 5.0)	2.0 (0.3, 3.8)
US 10 cities; Schwartz (2003b)	3.4 (2.7, 4.1)	3.3 (2.6, 4.1)	2.8 (2.0, 3.6)
8 Canadian cities; Burnett and Goldberg (2003)	4.5 (2.2, 6.7)	3.6 (1.4, 5.8)	2.7 (−0.1, 5.5)
APHEA2; Katsouyanni et al. (2003)	3.5 (2.9, 4.1)	3.3 (2.8, 3.9)	2.1 (1.5, 2.8)
Santa Clara Co.; Fairley (2003)	8.0 (no interval given)	7.8 (2.8, 13.1)	8.3 (2.9, 13.9)
Coachella Valley; Ostro et al. (2003)*	5.6 (1.7, 9.6)	5.5 (1.6, 9.5)	5.1 (1.2, 9.1)
Los Angeles Co.; Moolgavkar (2003)	2.4 (0.5, 4.4)	2.4 (0.5, 4.3)	2.3 (0.1, 4.5)
Cook Co.; Moolgavkar (2003)	2.4 (1.3, 3.5)	2.6 (1.6, 3.6)	2.6 (1.5, 3.7)
Phoenix, AZ; Mar et al. (2003)*	9.9 (1.9, 18.4)	9.7 (1.7, 18.3)	9.5 (0.6, 19.3)
Detroit, ‘85-‘90; Ito (2003)	1.7 (0.2, 3.2)	0.9 (−0.5, 2.4)	0.7 (−0.8, 2.1)
Detroit, ‘92-’94; Ito (2003)	4.4 (−1.0, 10.1)	3.3 (−2.0, 8.9)	3.1 (−2.2, 8.7)
The Netherlands; Hoek (2003)	0.9 (0.1, 1.7)	0.9 (0.2, 1.7)	0.9 (0.1, 1.7)
Erfurt, Germany; Stolzel et al. (2003)	6.4 (0.3, 12.9)	6.2 (0.1, 12.7)	5.3 (−1.8, 12.9)

*Cardiovascular Mortality

estimates were similar to those for PM_{10}. The results and a comparison of $PM_{2.5}$ and $PM_{10\text{-}2.5}$ mortality risk estimates are presented in a later section.

Dominici et al. (2002) also illustrated that GAM models, even with stringent convergence criteria, still result in biased (downward) standard errors of regression coefficients. This was the main reason for the use of GLM with natural splines in the reanalysis studies. As can be seen from Figure 8-15, the 95% confidence bands are somewhat wider for GLM results than for GAM results in some, but not all cases. However, the extent of wider confidence bands is not substantial in most cases (the bias ranged from a few percent to ~15% in most cases). It should be noted that, while a GLM model with natural splines provides correct standard error of regression coefficient, it is not equivalently as flexible as LOESS or smoothing splines. Unlike LOESS or smoothing splines, natural splines fit linearly at both ends of the data span. Natural

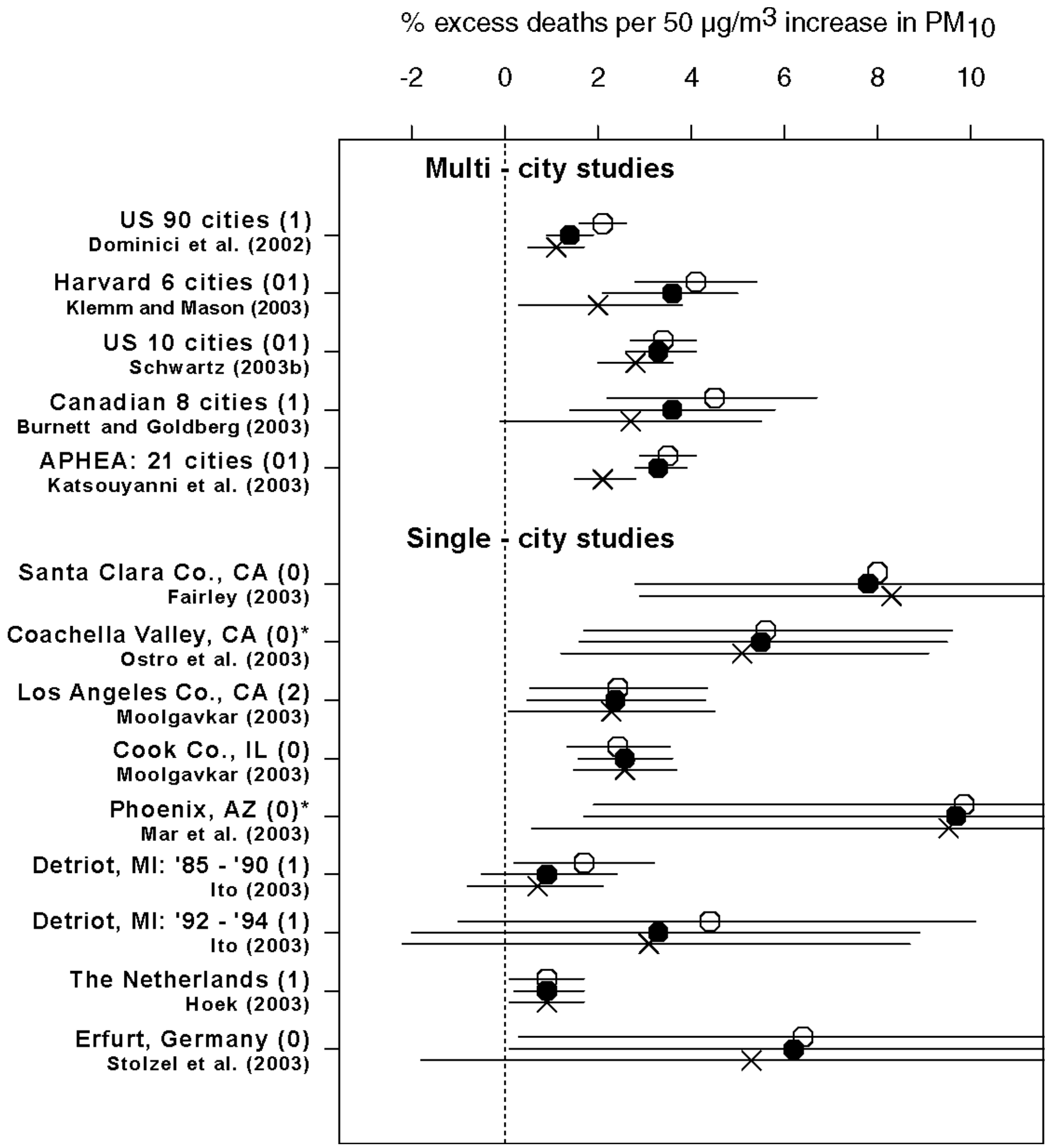

Figure 8-15. PM_{10} excess risk estimates for total non-accidental mortality for numerous locations (and for cardiovascular mortality[*] for Coachella Valley, CA and Phoenix, AZ), using: (1) GAM with default convergence criteria (white circle); (2) GAM with stringent convergence criteria (black circle); and, (3) GLM/natural splines (x) that approximate the original GAM model from the GAM reanalysis studies. The numbers in parenthesis indicate lag days used ("01" is average of 0 and 1 day lags).

splines therefore may not be an ideal model option for temperature effects, for which the slopes are likely non-linear (especially at the higher end). Goldberg and Burnett (2003), in their reanalysis of Montreal data, discussed related issues. In their reanalysis, the originally reported risk estimates of PM indices (CoH, extinction coefficient, predicted $PM_{2.5}$, and sulfate) were greatly attenuated in the GLM model with natural splines. One of the alternative explanations for these results was that the natural spline does not fit the possibly non-linear (threshold) effect of temperature as well as non-parametric smoothers. Hoek (2003), in his reanalysis of the Netherlands data, also showed that, compared to GAM models, GLM/natural spline models resulted in larger deviance, indicating poorer fits. Thus, there are remaining issues regarding the trade-off between GAM/non-parametric smoothers and GLM/parametric smoothers. The GLM/natural splines may produce correct standard errors but cannot guarantee "correct" model specifications. More recently, Dominici et al. (2003) developed and published a GAM routine for SPlus that gives correct standard errors, but it was not developed in time to be used for the GAM reanalysis effects reported on in HEI (2003b).

Three reanalysis reports applied alternative smoothing approaches (e.g., penalized splines) that, as with GLM/natural splines, did not have the problem of biased standard error. These studies were: reanalyses of Harvard six cities data by Schwartz (2003a); reanalysis of 10 US cities data by Schwartz (2003b); and reanalysis of APHEA2 by Katsouyanni et al. (2003). Generally, as with GLM/natural splines, the use of alternative smoothing approaches resulted in smaller PM risk estimates than GAM with stringent convergence criteria. In the re analysis of APHEA2 study, the PM_{10} risk estimates from penalized splines were smaller than those from GAM model, but larger than those from natural splines. Three alternative smoothing approaches (B-splines, penalized splines, and thin-plate splines) used in the reanalysis of Harvard six cities $PM_{2.5}$ data resulted in generally smaller risk estimates than those from natural splines. As was expected, all of these alternative smoothing approaches resulted in standard errors that were comparable to those from natural splines but larger than those from GAM models.

Several of the GAM reanalysis reports included additional sensitivity analyses which provided useful information. These sensitivity analyses included examinations of the effect of changing degrees of freedom for smoothing of temporal trends and weather variables (Dominici et al. [2002]; Ito [2003]; Klemm and Mason [2003]; Moolgavkar [2003]; and Burnett and Goldberg [2003]). In these analyses, changing the degrees of freedom for smoothing of temporal trends or weather effects often resulted in change of PM coefficients to a similar or even greater extent than those caused by the GAM convergence problem. A distinctly less well investigated issue is the effect of the use of different weather model specifications (i.e., how many weather variables and their lags are included). In a limited examination of this issue in the reanalysis of Detroit data (Ito, 2003), a weather model specification similar to that used in the US 90 cities consistently resulted in smaller PM_{10} risk estimates than a weather model similar to that used in Harvard six cities study.

In summary, the results from the GAM reanalysis studies indicate that PM risk estimates from GAM models were often, but not always, reduced when more stringent convergence criteria were used. However, the extent of the reduction was not substantial in most cases. The variability of PM risk estimates due to the model specification, including the number of weather terms and extent of smoothing, is likely larger than the effect of the GAM convergence problem. The extent of downward bias in standard error reported in these data (a few percent to ~15%) also appears not to be very substantial, especially when compared to the range of standard errors across studies due to differences in population size and numbers of days available. Still, the discussions in this chapter focus mainly on the reanalyzed studies or the studies that did not use GAM with default convergence criteria, because the extent of the effect of this problem is not always predictable in each individual study.

8.4.2.2 Impact of Using the More Stringent GAM Model on PM Effect Estimates for Respiratory Hospital Admissions

The NMMAPS multi-city study (Samet et al., 2000a,b) of PM_{10} concentrations and hospital admissions used the default GAM model specification with multiple smooths. To be quantitative in terms of the change that results from the more stringent GAM criteria, Figure 8-16 shows a plot of the respiratory models for which Zanobetti and Schwartz (2003b) provided reanalyses. These results indicate that there was only about a 14% decline in the effect estimates associated with use of the more appropriate stringent convergence requirement. Moreover, it is clear that the two estimates are well within the 95% confidence interval of each other, indicating that the two models are not statistically significantly different from one another.

To examine the potential influence of the GAM convergence specification on the results of the original Detroit data analysis by Lippmann et al. (2000), the associations between PM

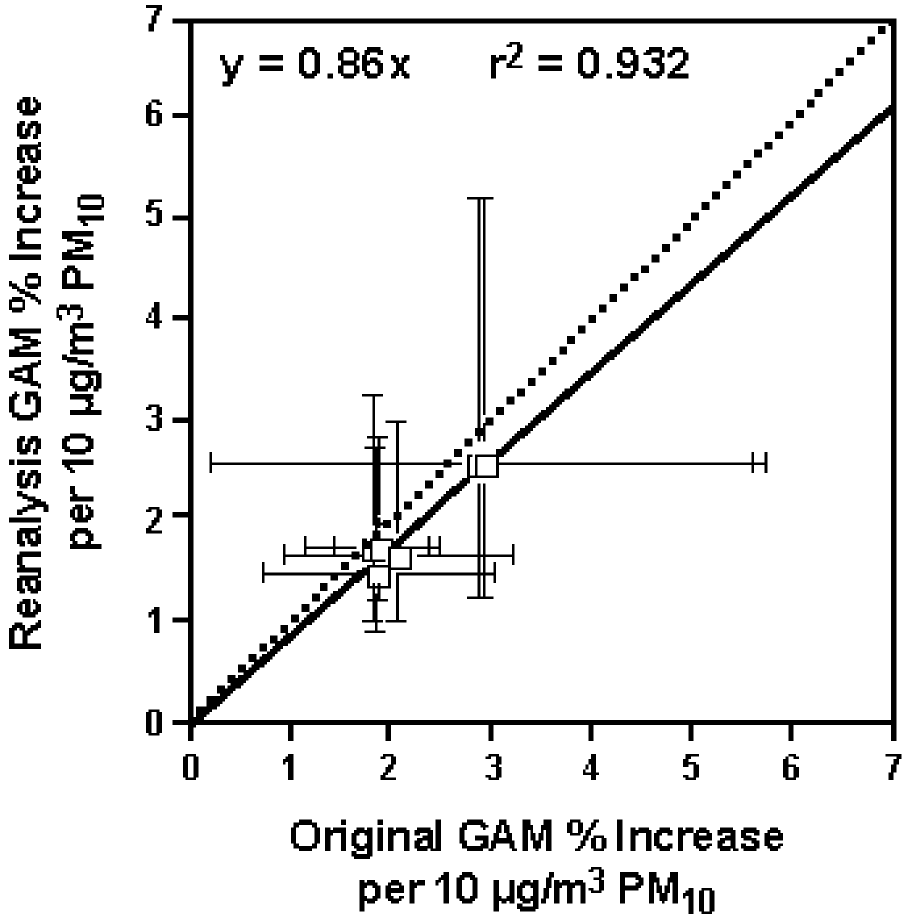

Figure 8-16. Comparison of GAM results for original (default) convergence case versus those from reanalyses with a more stringent convergence criterion (10e-15) for constrained lag respiratory model cases. Note very high overall correlation (r = 0.932) of original default GAM values with reanalysis stringent GAM results and slightly greater divergence from r^2 = 1.0 (dotted line) as excess risk values per 10 µg/m^3 PM_{10} increase.

Source: Derived from Zanobetti and Schwartz (2003b).

components and daily mortality/morbidity were re-examined by Ito using more stringent convergence criteria, as well as by applying a GLM that approximated the original GAM models (Ito, 2003). Generally, the GAM models with stringent convergence criteria and GLM models resulted in somewhat smaller estimated relative risks than those reported in the original study, but the reduction is quite small (averaging 17% less for the stringent GAM case versus default). For COPD, the decrease associated with the more stringent convergence criteria is larger (averaging 30%). Overall, for all types of hospital admissions (including pneumonia, COPD and ischemic heart disease) the effect of the change to the more stringent GAM gave an average decrease of 20 percent, while a switch to the GLM model specification gave an average 29% decrease in estimated PM effect size.

As discussed earlier, Sheppard (2003) recently conducted a reanalysis of their non-elderly hospital admissions data for asthma in Seattle, WA, in order to evaluate the effect of the fitting procedure on their previously published analyses. A lag of 1 day was used for all PM models. As shown in Table 8-35, the results were provided in the manuscript to only one significant figure (to the nearest whole percent), making the calculation of percent changes between models problematic, since the rounding of the effect estimates are nearly of the order of the size of the effect estimate changes. However, it can be seen that the pattern of changes in effects estimates and 95% CI values is similar to that seen in other studies.

TABLE 8-35. COMPARISON OF MAXIMUM SINGLE DAY LAG EFFECT ESTIMATES FOR $PM_{2.5}$, $PM_{2.5-10}$, and PM_{10} FOR SEATTLE ASTHMA HOSPITAL ADMISSIONS BASED ON ORIGINAL GAM ANALYSES USING DEFAULT CONVERGENCE CRITERIA VERSUS REANALYSES USING GAM WITH MORE STRINGENT CONVERGENCE CRITERIA AND GLM

	Original Default GAM Model* % Increase/IQR (95% CI)	Reanalysis Stringent GAM % Increase/IQR (95% CI)	Reanalysis GLM (Natural Spline) % Increase/IQR (95% CI)
$PM_{2.5}$	4 (2, 7)	4 (1, 6)	3 (1, 6)
$PM_{2.5-10}$	4 (1, 7)	2 (0, 5)	2 (−1, 4)
PM_{10}	5 (2, 8)	4 (1, 7)	3 (0, 6)

*$PM_{2.5}$ IQR=11.8 ug/m^3; $PM_{2.5-10}$ IQR = 9.3 ug/m^3; PM_{10} IQR = 19 ug/m^3.

Source: Derived from Sheppard (2003).

Further evidence of the relatively small effect of the default convergence criteria issue in most applications is the recent work by Moolgavkar (2003), in which he reanalyzed his earlier

GAM analyses of hospital admissions for COPD (Moolgavkar, 2000c) for the cities of Los Angeles (Los Angeles County) and Chicago (Cook County). In his original publication, Moolgavkar found ca. 5.0% excess risk for COPD hospital admissions among the elderly (64+ yr) in Los Angeles to be significantly related to both $PM_{2.5}$ and $PM_{10-2.5}$ in one pollutant models. In the same study, similar magnitudes of excess risk (i.e., in the range of ca. 4 to 7%) were found in one-pollutant models to be associated with $PM_{2.5}$ or $PM_{10-2.5}$ for other age groups (0-19 yr; 20-64 yr) in Los Angeles, as well. In his reanalyses of these GAM results using the more stringent convergence criteria, however, Moolgavkar (2003) combined all three Los Angeles age groups into one analysis, providing greater power, but also complicating before/after comparisons as to the actual effect of using the more stringent convergence criteria on the results. In the case of the Cook County analyses, the author changed other model parameters (i.e., the number of degrees of freedom in the model smooths) at the same time as implementing the more stringent convergence criteria, so direct before/after comparisons were not possible for Moolgavkar's Chicago reanalyses.

Therefore, in order to provide a one-to-one comparison for Los Angeles, the original age-specific GAM analyses have been pooled using inverse variance weighting and are presented along with Moolgavkar's (2003) reanalyses results (in terms of a % increase per 10 $\mu g/m^3$ mass increase for both $PM_{2.5}$ and PM_{10}) in Table 8-36. As shown in that table, the Moolgavkar Los Angeles results for all-age COPD admissions for the original and the more stringent convergence criteria GAM cases (using the same degrees of freedom) are very similar, with the effects estimate either decreasing (for $PM_{2.5}$) or increasing (for PM_{10}) very slightly. In those cases where a much larger number of degrees of freedom were used with either the more stringent GAM model or a natural spline GLM model, larger reductions in effects estimates were obtained as compared to the original GAM model. For the same number of degrees of freedom, the natural spline model resulted in either a slightly larger (for $PM_{2.5}$) or a slightly smaller (for PM_{10}) effects estimate than the stringent GAM model. Thus, these reanalysis results indicate that the use of the more stringent GAM convergence criteria results in minimal changes to the size of the PM effect estimates in this case, as compared to those obtained using the default GAM model, whereas the number of degrees of freedom used with either GAM or GLM models can result in much larger changes in the size of the PM effects estimates. More specifically, use of the much

TABLE 8-36. COMPARISON OF LOS ANGELES COPD HOSPITAL ADMISSIONS MAXIMUM SINGLE DAY LAG EFFECT ESTIMATES FOR $PM_{2.5}$ and PM_{10} FROM THE ORIGINAL GAM ANALYSES USING DEFAULT CONVERGENCE CRITERIA VERSUS FOR REANALYSES USING MORE STRINGENT CONVERGENCE CRITERIA AND FOR MODELS SMOOTHED WITH MORE DEGREES OF FREEDOM

	Original Default GAM Model* (30df) % Increase/10 ug/m^3 (95% CI)	Reanalysis Stringent GAM (30df) % Increase/10 ug/m^3 (95% CI)	Reanalysis Stringent GAM (100df) % Increase/10 ug/m^3 (95% CI)	Reanalysis Natural Spline (100df) % Increase/10 ug/m^3 (95% CI)
$PM_{2.5}$	1.90 (0.97-2.84)**	1.85 (0.82-2.89)**	1.38(0.51-2.25)***	1.49(0.41-2.58)***
PM_{10}	1.43 (0.85-2.02)**	1.51 (0.85-2.18)**	1.08 (0.50-1.66)**	0.98 (0.24-1.72)**

*Original GAM estimates derived for "all ages" from original analyses by age subgroups using inverse variance weights.
**For (maximum) lag case = 2 days.
***For (maximum) lag case = 0 days.

Source: Derived from Moolgavkar (2000c) and Moolgavkar (2003).

larger number of degrees of freedom results in a much less efficient estimate of the pollutant effect.

These various reanalyses results therefore confirm that the PM effect estimates generally do decline somewhat when using the more stringent convergence criteria, as compared to the default GAM, with the new estimates being well within the confidence interval of the original estimates. In addition, the effect of using a more stringent convergence criteria was indicated to have less influence on the effect estimate than potential investigator-to-investigator variations in model specifications (e.g., extent of smoothing) can have. Overall, the absolute effect was relatively small, and the basic direction of effect and conclusions regarding the significance of the PM effect on hospital admissions remained unchanged in these analyses when the GAM convergence requirement was made more stringent.

8.4.2.3 HEI Commentaries

The HEI Special Report (2003a,b) presents the HEI Special Panels' reviews of both the Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study, Part II (NMMAPS) and the Revised Analyses of Selected Time-Series Studies, which includes short communication reports presenting results from other revised analyses of original articles and reports. Beyond looking at the results of reanalyses designed specifically to address problems associated with the use of default convergence criteria in the S-Plus GAM function, the reviews also identified issues associated with the sensitivity of study findings to the use of alternative modeling approaches that some investigators employed in their reanalyses. In general, the Special Panels concluded that the original PM effects estimates were more sensitive to the modeling approach used to account for temporal effects and weather variables than to the convergence criteria used in the GAM model.

A modeling issue of particular importance highlighted by HEI (2003b) is the sensitivity of all models (e.g., GAM, GLM-natural splines, GLM-penalized splines) to the degrees of freedom allotted to potentially confounding weather variables and time. The commentary discusses the trade-off involved in selecting the number of degrees of freedom for time and weather variables, while recognizing that there remains no altogether satisfactory way to choose the most appropriate degrees of freedom. For example, in considering the effect of temperature, if the degrees of freedom in the smoothing function for temperature are overly restricted, some actual nonlinear effects of temperature would be falsely ascribed to the pollution variable. To avoid this, the analyst is tempted to afford many degrees of freedom to temperature or other potentially confounding variables. However, if more degrees of freedom are allotted than needed, such that the temperature smooth function is more “wiggly” than the true dose response function, then the result will be a much less efficient estimate of the pollutant effect. This would have the effect of incorrectly ascribing part of the true pollution effect to the temperature variable, which would compromise our ability to detect a true but small pollution effect. The commentary notes that the empirical data cannot determine the optimal trade-off between these conflicting needs, and it is difficult to use an a priori biological or meteorologic knowledge to determine the optimal trade-off. Thus, the Special Panel generally recommends further exploration of the sensitivity of these studies to a wider range of alternative degrees of smoothing and to alternative specifications of weather variables in time-series models.

More specifically, the Specials Panels offered the following conclusions and recommendations:

NMMAPS Revised Analyses

Dominici et al. (2002) conducted a range of revised analyses, applying alternative methods to correct shortcomings in the S-Plus GAM programming. HEI's Special Panel review (HEI, 2003a) of this revised analyses yielded the following conclusions:

- While estimates of effect are quantitatively smaller than those in the original studies, a statistically significant overall effect of PM_{10} on mortality remains, and the qualitative conclusions that were initially drawn from NMMAPS remain unchanged.
- While the alternative approaches used to model temporal effects in the revised NMMAPS analyses addressed the problems of obtaining incorrect effect estimates and standard errors when using the preprogrammed GAMs software, no models can be recommended at this time as being strongly preferred over another for use in this context.
- While formal tests of PM effect across cities did not indicate evidence of heterogeneity because of the generally large individual-city effect standard errors, the power to assess the presence of heterogeneity was low. The possibility of heterogeneity still exists.
- The appropriate degree of control for time in these time-series analyses has not been determined. Thus, the impact of more aggressive control for time should continue to be explored and studies to evaluate bias related to the analytic approach to smoothing and the degree of smoothing should be encouraged.
- Weather continues to be a potential confounder of concern, such that further work should be done on modeling weather-related factors.

Revised Analyses for Other Short Communications

Based on its review, the HEI Special Panel (HEI, 2003b) reached the following conclusions:

- As was the case with the findings of the original studies, the revised findings will continue to help inform regulatory decisions regarding PM.
- The PM effect persisted in the majority of studies, however, the number of studies showing an adverse effect of PM was slightly smaller.

- In some of the large number of studies in which the PM effect persisted, the estimates of PM effect were substantially reduced.
- In the few studies in which further sensitivity analyses were performed, some showed marked sensitivity of the PM effect estimate to the degree of smoothing and/or the specification of weather.
- The use of more appropriate convergence criteria on the estimates of PM effect in the revised analyses produced varied effects across the studies. In some studies, stricter convergence criteria had little impact, and in a few the impact was substantial. No study's conclusions changed in a meaningful way by the use of stricter criteria compared to the original analyses.
- In most studies, parametric smoothing approaches used to obtain correct standard errors of the PM effect estimates produced slightly larger standard errors than the GAM. However, the impact of these larger standard errors on level of statistical significance of the PM effect was minor.
- For the most part, the original PM effect estimates were more sensitive to the method used to account for temporal effects than to changing the convergence criteria.
- Even though the alternative approaches used to model temporal effects in the revised analyses addressed the problems of obtaining incorrect effect estimates and standard errors when using the GAMs software, none can be recommended at this time as being strongly preferred over another for use in this context.
- Neither the appropriate degree of control for time nor the appropriate specification of the effects of weather in these time-series analyses has been determined. This awareness introduces a degree of uncertainty that has not been widely appreciated previously, such that the sensitivity of these studies to a wider range of alternative degrees of smoothing and alternative specifications of weather variables in time-series models should continue to be explored.

8.4.3 Assessment of Confounding by Co-Pollutants

8.4.3.1 Introduction

Airborne particles are found among a complex mixture of atmospheric pollutants, some of which are well measured (such as gaseous criteria co-pollutants O_3, CO, NO_2, SO_2) and others which are not routinely measured. The basic question here is one of determining the extent to which observed health effects can be attributed to airborne particles acting alone or in combination with other air pollutants. Many of the pollutants are closely correlated due to emissions by common sources and dispersion by common meteorological factors, so that it may be difficult to disentangle their effects (as noted in Section 8.1.1), because some are in the pathway of formation of other pollutants (e.g., NO $\rightarrow$ NO_2 $\rightarrow$ NO_3^{-1} $\rightarrow$ Particle Mass).

It is widely accepted that some PM metrics are associated with health effects, and that PM has effects independent of the gaseous co-pollutants. The extent to which ambient gaseous co-pollutants may have health effects independent of PM is important in considering the extent to which health effects attributed to PM may actually be due in part to co-pollutants or to some other environmental factors, and vice versa. EPA produces Air Quality Criteria Documents for four gaseous pollutants: CO, NO_2, SO_2, and O_3 (U.S. Environmental Protection Agency, 1982, 1996b, 2000b). The possible health effects of the gaseous pollutants exerted independently from PM, and in some cases jointly with PM, are discussed in those documents. They are also considered to some extent in this section and elsewhere in this document because they may affect quantitative assessments of the effects of various PM metrics when these other pollutants are also present in the atmosphere. The gaseous pollutants may also be of interest as PM effect modifiers, or through interactions with PM.

Co-pollutant models have received a great deal of attention in the last few years because there now exist improved statistical methods for estimating PM effects by analyses of daily time-series of mortality (Schwartz and Marcus, 1990; Schwartz, 1991) or hospital admissions (Schwartz, 1994) and/or in prospective cohort studies (Dockery et al., 1993). A number of studies using the new methods have not only found significant positive relationships between mortality and one or more PM indicators, but also with one or another of the four gaseous criteria pollutants (O_3, NO_2, CO, SO_2) in daily time-series studies, and between SO_2 and mortality in the reanalyses of two large prospective cohort studies (Krewski et al., 2000). In the daily time-series studies, the estimated PM effect is relatively stable when the co-pollutant is included in the model in some cities, whereas the estimated PM effect in other cities changes substantially when certain co-pollutants are included. In the Krewski et al. (2000) analyses, the estimated effect of $SO_4^{=}$ is greatly decreased when SO_2 is also included as a predictor in a proportional hazards model. Several analyses presented below also discuss models in which multiple particle metrics are present, either with or without gaseous criteria pollutants. These mixtures are encountered in urban air. Included among the studies evaluating both fine and coarse particles are the following ones: Burnett et al. (2000), Chock et al. (2000), Clyde et al. (2000), Fairley (1999), Lippmann et al. (2000), Mar et al.(2000), Cifuentes et al. (2000), and Castillejos et al. (2000).

Some gaseous co-pollutants (e.g., CO, NO_2, and SO_2 may be acting as indicators of distinct emission sources (e.g., motor vehicle exhaust coal- or oil-burning electric power plants, etc.) and/or as indicators of PM from these sources (primary particles and secondary nitrate particles). Concentrations of such gaseous co-pollutants may therefore be correlated with total PM mass or even more strongly correlated with specific PM constituents (due to their emission from a common source). Thus, one or another specific gaseous co-pollutant may serve as an indicator of the day-to-day variation in the contribution of a distinct emission source and to the varying composition of airborne PM. In a model with total PM mass, then, a gaseous co-pollutant may well actually serve as a surrogate for the source-apportioned contribution to ambient air PM. It would be interesting to evaluate models that include both source-relevant particle components and gaseous pollutants derived from common sources (e.g., those attributable to motor vehicles, coal combustion, oil combustion, etc.). The closest approach thus far has been Model II in Burnett et al. (2000), a default GAM analyses.

The role of gaseous pollutants as surrogates for source-apportioned PM may be distinct from confounding. The true health effect may be independently associated with a particular ambient PM constituent that may be more or less toxic than the particle mix as a whole. Thus, a gaseous co-pollutant may give rise to the appearance of confounding in a regression model. By serving as an indicator of the more toxic particles, the gaseous co-pollutant could greatly diminish the coefficient for total particle mass. In such a model, the coefficient for total particle mass would most properly be interpreted an indicator of the other, less-toxic particles.

8.4.3.2 Conceptual Issues in Assessing Confounding

Two main conceptual issues are encountered in evaluating potential confounding: (a) biological plausibility and (b) exposure plausibility. These concerns overlap two of Hill's (1965) suggested criteria for causal inference.

(a) Biological plausibility: It is generally accepted that O_3, NO_2, and SO_2 are associated with diminished pulmonary function and increased respiratory symptoms as well as more serious consequences, and CO exposure has been associated with cardiovascular effects. While one may question whether adverse health effects occur in most healthy people at current exposure to ambient concentrations, there may be susceptible sub-populations for whom one or more ambient gaseous pollutants could perhaps cause health effects at currently encountered ambient exposure levels. Thus, one should not necessarily assume, a priori, that the gaseous co-pollutants at current ambient levels are not associated with respiratory and cardiovascular health effects in susceptible subpopulations. Nor should the converse be assumed without further evaluation. Ambient gaseous co-pollutants can be potential confounders of ambient PM if: (a) the ambient concentrations of particles and gases are correlated; and (b) both the concentrations for PM and for one or another of the gases are correlated with the health outcome.

(b) Exposure plausibility: While most Americans spend most of their time in indoor microenvironments, there is still sufficient personal exposure to O_3 to cause notable respiratory symptoms among sensitive children or adults exercising outdoors when ambient O_3 levels are sufficiently high (hence the declaration of "ozone alert" days). It is also likely that some fraction of ambient CO can contribute to indoor air pollution and total personal CO exposure. Nitrogen dioxide, while reactive, also penetrates indoors; and an ambient pollution component of total personal exposure to NO_2 can be identified among individuals without indoor NO_2 sources but living close to strong outdoor sources such as highways. Thus, there may be some, perhaps many, individuals exposed to elevated concentrations of gaseous criteria pollutants that may be sufficiently high so as (either individually or acting in combination with ambient PM) to contribute to health effects found to be associated with ambient concentrations of PM. Also, some may indirectly contribute to PM exposures via participating in formation of certain ambient PM constituent species, as discussed earlier.

8.4.3.3 Statistical Issues in the Use of Multi-Pollutant Models

Multi-pollutant models may be useful tools for assessing whether the gaseous co-pollutants may be *potential* confounders of PM effects, but cannot determine if in fact they are. Variance inflation and effect size instability can occur in non-confounded multipollutant models as well as in confounded models. Our usual regression diagnostic tools can only determine whether there is a potential for confounding. In PM epidemiology studies, the gaseous pollutants, except ozone, frequently have a high degree of positive linear correlation with PM metrics, a condition known as multi-collinearity; therefore, although multi-colinearity leading to effect size estimate instability and variance inflation are necessary conditions for confounding, they are not sufficient in and of themselves to determine whether confounding exists.

The most commonly used methods include multi-pollutant models in which both the putative causal agent (PM) and one or more putative co-pollutants are used to estimate the health effect of interest. If the effect size estimate for PM is “stable,” then it is often assumed that the effects of confounding are minimal. “Stable” is usually interpreted as meaning that the magnitude of the estimated effect is similar in models with PM alone and in models with PM and one or more co-pollutants, and the statistical significance or width of the confidence interval for the PM effect is similar for all models, with or without co-pollutants. These criteria (usually unquantified) diagnose confounding in a narrow sense, interpreted as synonymous with multi-collinearity, not as a failure of the study design or other forms of model mis-specification.

Beyond the conceptual issues discussed above that arise in assessing confounding, there are a number of technical issues that arise in the use of statistical models. Those issues are discussed below.

(a) Model mis-specification assumes many forms. The omission of predictive regressors (“underfitting”, defined by Chen et al., 2000) may produce biased estimates of the effects of truly predictive regressors that are included in the model. Inclusion of unnecessary or non-predictive regressors along with all truly predictive regressors (“over-fitting”) will produce unbiased estimates of effect, but may increase the estimated standard error of the estimated effect if it is correlated with other predictors. Omitting a truly predictive regressor while including a correlated but non-causal variable (“mis-fitting”) will attribute the effect of the causal regressor to the non-causal regressor. Interaction terms are candidates for omitted regressor variables. It is important to avoid the “mis-fitting” scenario. Assuming that there is a linear relationship when the true concentration-response function is non-linear will produce a biased estimate of the effect size, high or low at different concentrations. One of the most common forms of model mis-specification is to use the wrong set of multi-day lags, which could produce any of the consequences described as “under-fitting” (e.g., using single-day lags when a multi-day or distributed lag model is needed), “over-fitting” (e.g., including a longer span of days than is needed), or “mis-fitting” (e.g., using a limited set of lags while the effects are in fact associated with different set of lags). Different PM metrics and gaseous pollutants may have different lag structures, so that in a multi-pollutant model, forcing both PM and gases to have the same lag structure is likely to yield “mis-fitting.” Finally, classical exposure measurement errors (from use of proxy variables) attenuates (biases) effect size estimates under most assumptions about correlations among the regressors and among their measurement errors (Zeger et al., 2000).

(b) Bias: All of the mis-specifications listed in (c) can bias the effect size estimate except for “over-fitting” and measurement error of Berkson type. The estimates of the standard error of the effect size estimate under “over-fitting” or Berkson error cases are inflated, however; and result in broader confidence intervals than would otherwise occur with a more appropriately specified model and/or one with less Berkson type measurement error.

(c) Estimates of effect size standard errors are usually sensitive to model mis-specification. When all truly predictive regressors are added to an “underfit” model, the uncertainty will almost always be reduced sufficiently that the standard errors of estimated effect size are reduced (“variance deflation”). Adding correlated non-causal variables to “over-fitted” or “mis-fitted” models will further increase the estimated standard errors (“variance inflation”). Variance inflation can occur whenever a covariate is highly correlated with the regressor variable that is presumably the surrogate for the exposure of interest. Confounding with the regressor variable can occur only when the covariate is correlated (a) with the regressor variable proxy for the exposure of interest and (b) with the outcome of interest in the absence of the exposure of interest.

(d) Mis-specification errors may compound each other. If the concentration-response function is nonlinear but there is measurement error in the exposures, then different sub-populations will have greater or smaller risk than assigned by a linear model. Consider the hypothetical case of a "hockey-stick" model with a threshold. If there were no exposure measurement error, then the part of the population with measured concentrations above the threshold would have excess risk, whereas those below would not. If exposures were measured with error, even if the measured concentration were above the threshold, some people would actually have exposures below the threshold and no excess risk. Conversely, if the measured concentration was below the threshold, some people would actually have concentrations above the threshold and would have excess risk. The flattening of a non-linear concentration-response curve by measurement error is a well known phenomenon that may be detected by standard methods (Cakmak et al., 1999).

(e) The question of whether effect size estimates and their standard errors are really significantly different among models is usually not addressed quantitatively. Some authors report various goodness-of-fit criteria such as AIC, BIC, deviance, or over-dispersion index, e.g., (Chock et al., 2000; Clyde et al., 2000), but the practice is not yet so wide-spread as to assist in analyses of secondary data for use in this document. Variance inflation may also happen with a correctly specified model when both pollutants are causal and highly correlated, compared to a model in which only one pollutant is causal and the non-causal pollutant is omitted. The situation where the variance or standard error decreases when an additional variable is added (variance deflation) suggests that the model with the covariate is more nearly correct and that the standard errors of all covariates may decrease. Statistical significance is a concept of limited usefulness in assessing or comparing results of many models from the same data set. Still, it is a familiar criterion, and one addressed here by using a nominal two-sided 5% significance level for all tests and 95% confidence intervals for all estimates, acknowledging their limitations. There is at present no consensus on what clearly constitutes "stability" of a model estimate effect size, e.g., effect sizes that differ by no more than 20% (or some other arbitrary number) from the single-pollutant models. Simple comparison of the overlap of the confidence intervals of the models is not used because the model estimates use the same data, and the confidence intervals for effect size in different models are more-or-less correlated. In analyses with missing days of data for different pollutants, comparisons must also incorporate differences in sample size or degrees of freedom.

In any case, statistical comparisons alone cannot fully resolve questions about either conceptual or statistical issues in confounding via considerations about statistical significance. If the model is mis-specified in any of the numerous ways described above, then effect size estimates and/or their estimated standard errors are likely biased. Statistical assessments alone can determine if the PM metric is too closely correlated with other pollutants to allow for a reasonably accurate quantitative effect size estimate (which is, of course, useful information even if it is concluded that it is not feasible to estimate the separate effects of PM and/or the gaseous co-pollutants). However, no matter what the statistical situation, confounding cannot occur if the gaseous co-pollutant(s) cannot produce the health outcome, or if there is no personal exposure to the gaseous co-pollutant(s), or if that personal exposure is not correlated with their ambient concentrations.

The most commonly used approach to diagnose potential confounding is fitting multi-pollutant models and evaluating the stability of the estimated particle effect sizes against inclusion of co-pollutants. If an additional covariate is added to a baseline model (e.g., with PM alone) and the model predicts the outcome better with the covariate, then the reduction in variance (or deviance for generalized linear or additive models [GLM or GAM]) outweighs the loss of degrees of freedom for variability. Although not always true, it is reasonable to expect a decrease in the estimated asymptotic standard error of the effect size estimate (“variance deflation”), but improved goodness-of-fit may not reduce the standard errors of all parameters in equal proportion because introducing the new covariate modifies the covariate variance-covariance matrix. The weighted inverse covariance matrix provides an exact estimate for standard errors in ordinary linear regression models, and approximately so in GLM or GAM. The effects on other parameter estimates are rarely reported.

“Variance inflation” may occur under several circumstances, including “under-fitting” and “mis-fitting” in which a truly predictive covariate is omitted or replaced by a correlated proxy, and “over-fitting” in which a non-predictive covariate correlated with the PM metric is also included in the model. The potential for over-fitting can be diagnosed by evaluating the eigenvalues of the correlation matrix of the predictors, with very small values identifying near-collinearity. However, the complete covariate correlation matrix is almost never reported, including all weather variables and nonlinear functions entered separately as covariates. Nonetheless, even a correlation matrix among all pollutants would be informative. Furthermore, composite correlation matrices in multi-city studies may conceal important differences among the correlation matrices.

Multi-pollutant models may be sensitive to multi-colinearity (high correlations among particle and gaseous pollutant concentrations) and to so-called “measurement errors”, possibly associated with spatial variability. Combining multi-pollutant models across several cities may not improve the precision of the mean PM effect size estimate combined, if the differences among the cities are as large or larger in the multi-pollutant models as in the single-pollutant PM model. Second-stage regressions have been useful in identifying effect modifiers in the NMMAPS and APHEA 2 studies, but may not, in general, provide a solution to the problem that confounding of effects is a within-city phenomenon. Furthermore, the correlations among pollutants may change from season to season and from place to place, suggesting that confounding as indicated by co-linearity is not always the same.

Three promising alternative approaches versus simple reliance on multi-pollutant modeling have begun to be used to evaluate more fully and definitively the likelihood that exposures to gaseous co-pollutants can account for the ambient PM-health effects associations now having been reported in hundreds of published epidemiology studies. The first is based on evaluation of personal exposures to particles and gases as was done for three panels of participants in Baltimore, MD (Sarnat et al., 2000, 2001). This study (discussed in detail in Chapter 5) directly addresses the premise that if individuals are not exposed to a potential confounder, then there is a lower probability that the potential confounder contributes to the observed effect. The results in this paper support the conclusion that personal exposure to sulfates, fine particles, and PM_{10} are well correlated with their corresponding fixed site ambient concentrations, but the correlations are much lower for $PM_{10\text{-}2.5}$, O_3, and NO_2. There is however a great deal of variation for one of three two-week panels from one season to the next. The sample size is small (N = 56), but did detect marginally significant associations between personal and ambient NO_2 for the personal-ambient correlation, although much lower than for particles. There were, however, some residences in which personal and ambient NO_2 were highly correlated. This has been seen when residences are close to a major road, which was the case for several members in each of the three studied cohorts (i.e, health elderly adults, adults with COPD, and children 9-13 years).

Another promising approach is the use of principal component or factor analysis to determine which combinations of gaseous criteria pollutants and PM size fractions or chemical constituents together cannot be easily disentangled, and which pollutants are substantially independent of the linear combinations of the others. For example, the source-oriented factor analysis study of Mar et al. (2000) produced evidence suggesting independent effects of regional sulfate, motor vehicle-related particles, particles from vegetive burning, and PM_{10-25} for cardiovascular mortality in Phoenix (as discussed in Section 8.2.2.4.3).

There are also now available some recent examples of a third promising approach, i.e., the use of so-called "intervention studies." Particularly interesting evidence for independent effects of ambient PM are beginning to emerge from some such studies, which relate changes (decreases in health risk outcomes) to decreases in airborne particles due to deliberate reductions in emissions from sources that ordinarily contribute to elevated ambient PM levels in a given locale. As described before (Section 8.2.3.4), some health outcome changes occurred in some studies in the presence of low levels of ambient gaseous co-pollutants or little change in at least some of the co-pollutants in the presence of reduced concentrations of PM mass or constituents.

8.4.3.4 Multipollutant Modeling Outcomes

As stated in the introduction to this chapter, ambient PM exists as a component of a complex air pollution mixture that includes other criteria pollutants, as well as many other airborne contaminants that may convey risks to health. Particulate matter is of both primary and secondary origin, and two of the gaseous criteria pollutants (sulfur dioxide and nitrogen dioxide) contribute to the formation of secondary particles. Because of shared sources, concentrations of ambient PM, SO_2, and NO_2 may be correlated to a moderate degree in urban areas. Generally, concentrations of PM and other monitored pollutants are imperfect measures of personal exposures and the extent of measurement error likely varies among the pollutants and also among population subgroups. In interpreting the findings of multi-pollutant models, there are several alternative explanations for observed associations that need to be considered based on the points above as follow:

- An effect estimated for PM reflects a “true effect” of particulate matter (causal interpretation).
- An effect estimated for PM reflects the total effect of the overall air pollution mixture (PM is an indicator of mixture toxicity).
- An effect estimated for PM reflects confounding (at least to a degree) by another pollutant (PM effect is confounded).
- An effect estimated for PM may be modified by levels of other pollutants (there is effect modification).
- An effect estimated for PM may be an underestimate of the true effect because of the inclusion in a model of other criteria air pollutants (SO_2, NO_2, O_3) which are contributors to the PM levels observed. This latter effect can be interpreted as the estimated effect of PM on health not mediated by contributions to PM.

As also stated previously, multi-pollutant modeling is one commonly-used method for assessing potential confounding by co-pollutants. In Figures 8-18 through 8-21, results are presented from studies that were derived from multi-pollutant models, and which either did not use GAM originally or were reanalyzed.

As shown in Figure 8-18, PM effect estimates for total mortality (with PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) from most of the studies do not show much change across the various individual co-pollutants and combinations of co-pollutants that were added to the models [e.g., multi-city studies by Dominici (2003) and Schwartz (2003); single-city studies by Ito (2003), Fairley (2003), and Morgan (1998)]. A notable exception is the study by Moolgavkar (2003) in Cook and Los Angeles counties, in which the PM effect estimates were substantially reduced with the inclusion of CO in the model. On the other hand, in the study in Pittsburgh by Chock et al. (2000), the PM_{10} effect estimates remained little changed or were somewhat increased with the inclusion of CO and the other co-pollutants.

For cardiovascular mortality and morbidity (Figure 8-19), in many cases the PM effect estimates do not show much change when various individual and combinations of co-pollutants were added to the models, although the pattern seems to be somewhat more variable for cardiovascular-related effects than for total mortality. For example, in Toronto, PM effects estimates for cardiovascular hospital admissions for all three PM indicators are appreciably

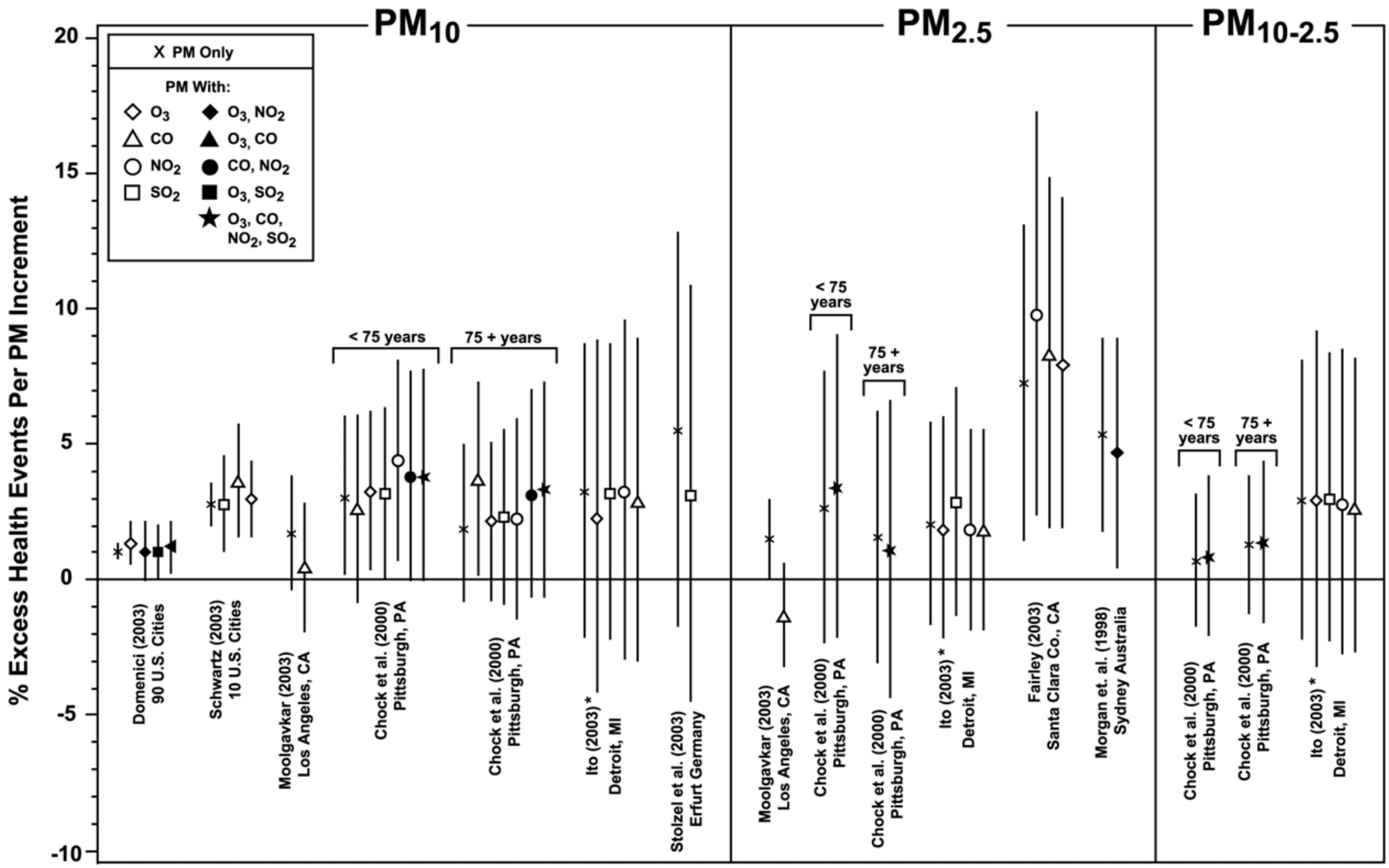

Figure 8-18. Excess risk estimates for total non-accidental mortality in single-pollutant (PM only) and multi-pollutant models. PM increments: 50 µg/m³ for PM_{10} and 25 µg/m³ for $PM_{2.5}$ and $PM_{10\text{-}2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.

*Estimates from multi-pollutant models in Ito (2003) obtained from the author via personal communication (November 25, 2003).

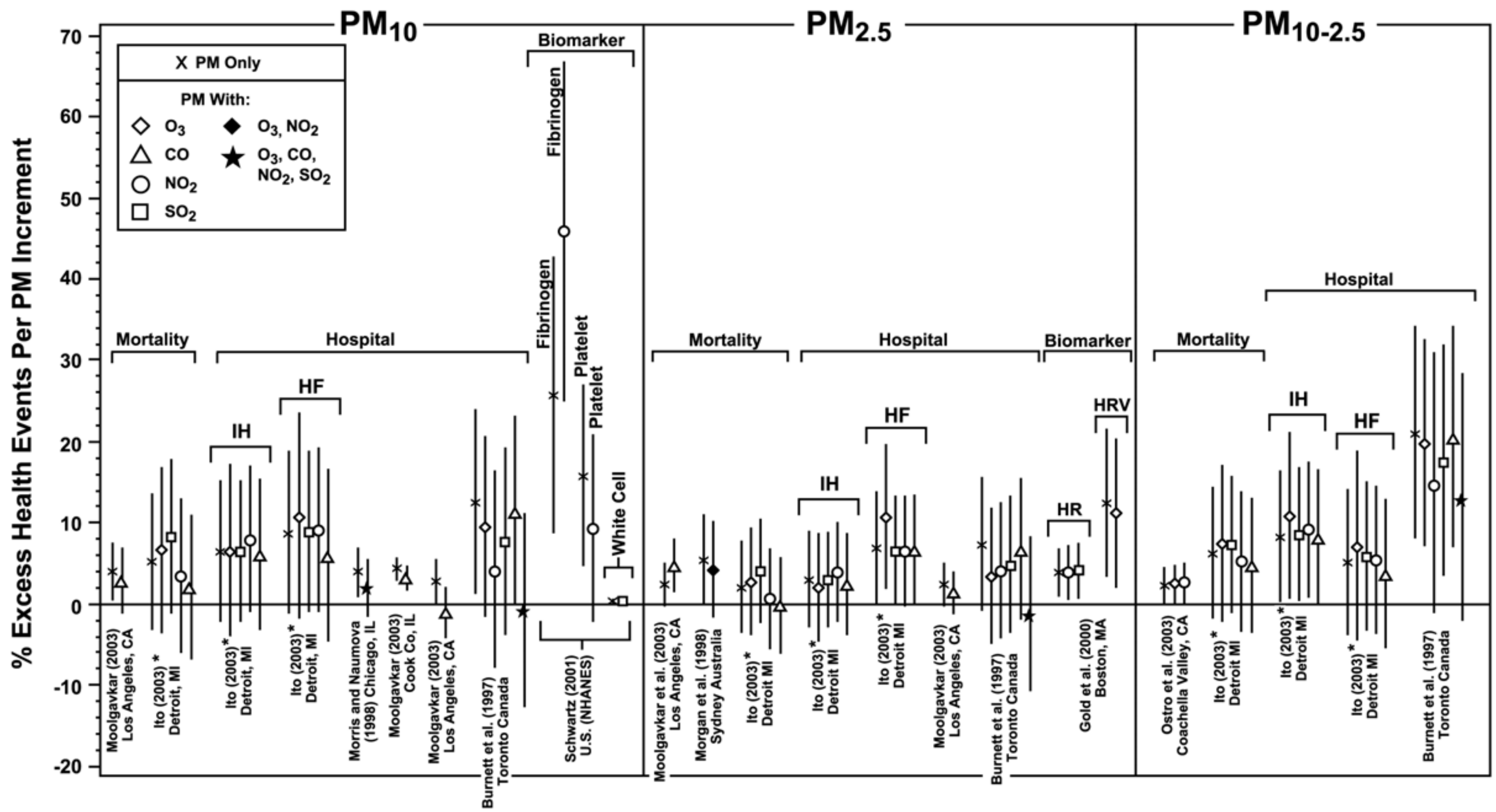

Figure 8-19. **Excess risk estimates for cardiovascular-related effects, including mortality, hospital admissions, and changes in biomarkers (e.g., increases in blood parameters or decreases in heart rate variability measures) in single-pollutant (PM only) and multi-pollutant models . PM increments: 50 μg/m^3 for PM_{10} and 25 μg/m^3 for $PM_{2.5}$ and $PM_{10\text{-}2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM. IH = ischemic heart disease; HF = heart failure; HR = heart rate; HRV = heart rate variability.**

*Estimates from multi-pollutant models in Ito (2003) obtained from the author via personal communication (November 25, 2003).

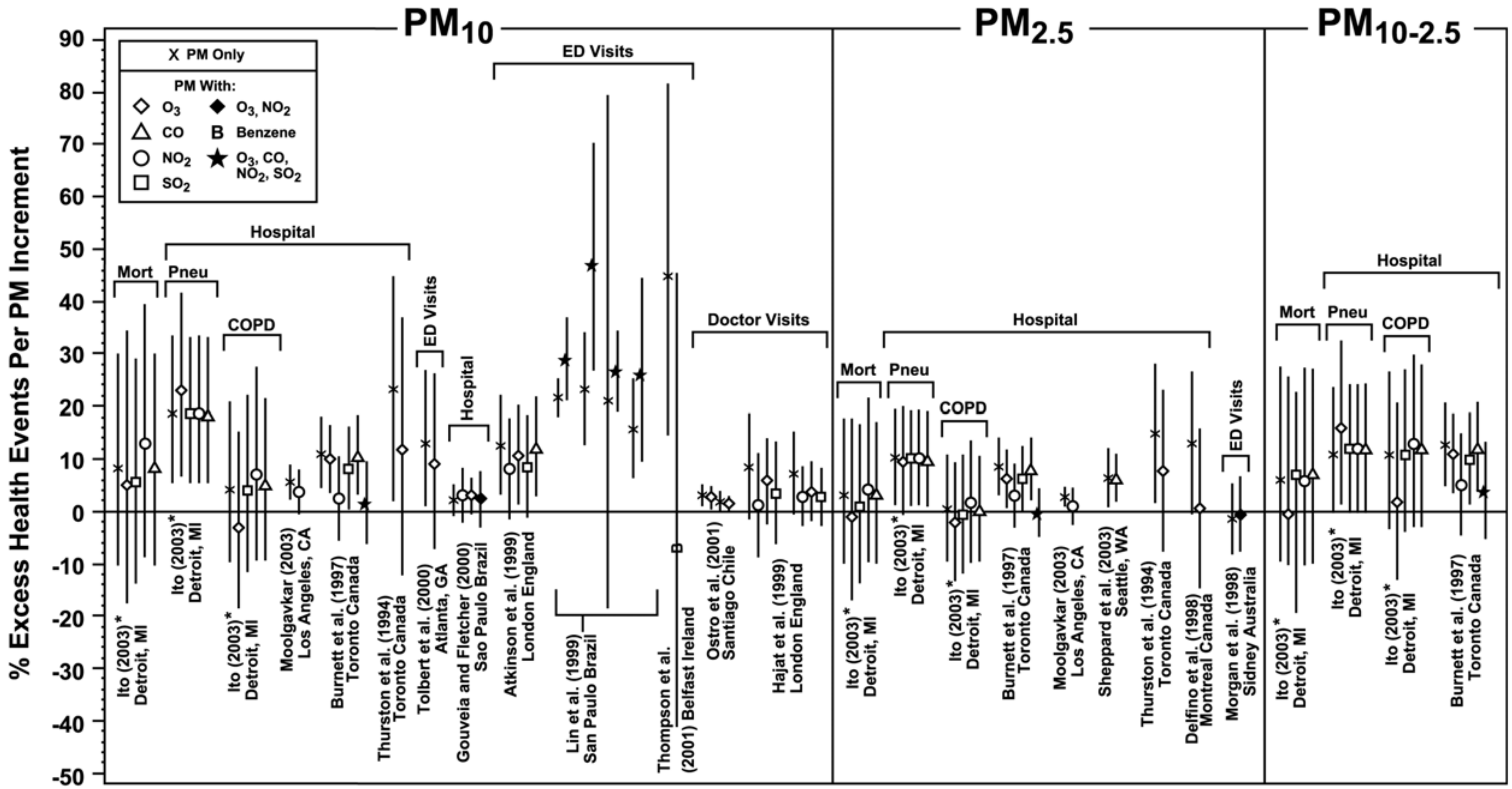

Figure 8-20. Excess risk estimates for respiratory-related effects, including mortality, hospital admissions and medical visits in single-pollutant (PM only) and multi-pollutant models. PM increments: 50 μg/m³ for PM_{10} and 25 μg/m³ for $PM_{2.5}$ and $PM_{10\text{-}2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM. Mort = mortality; Pneu = pneumonia; COPD = chronic obstructive pulmonary disease.

*Estimates from multi-pollutant models in Ito (2003) obtained from the author via personal communication (November 25, 2003).

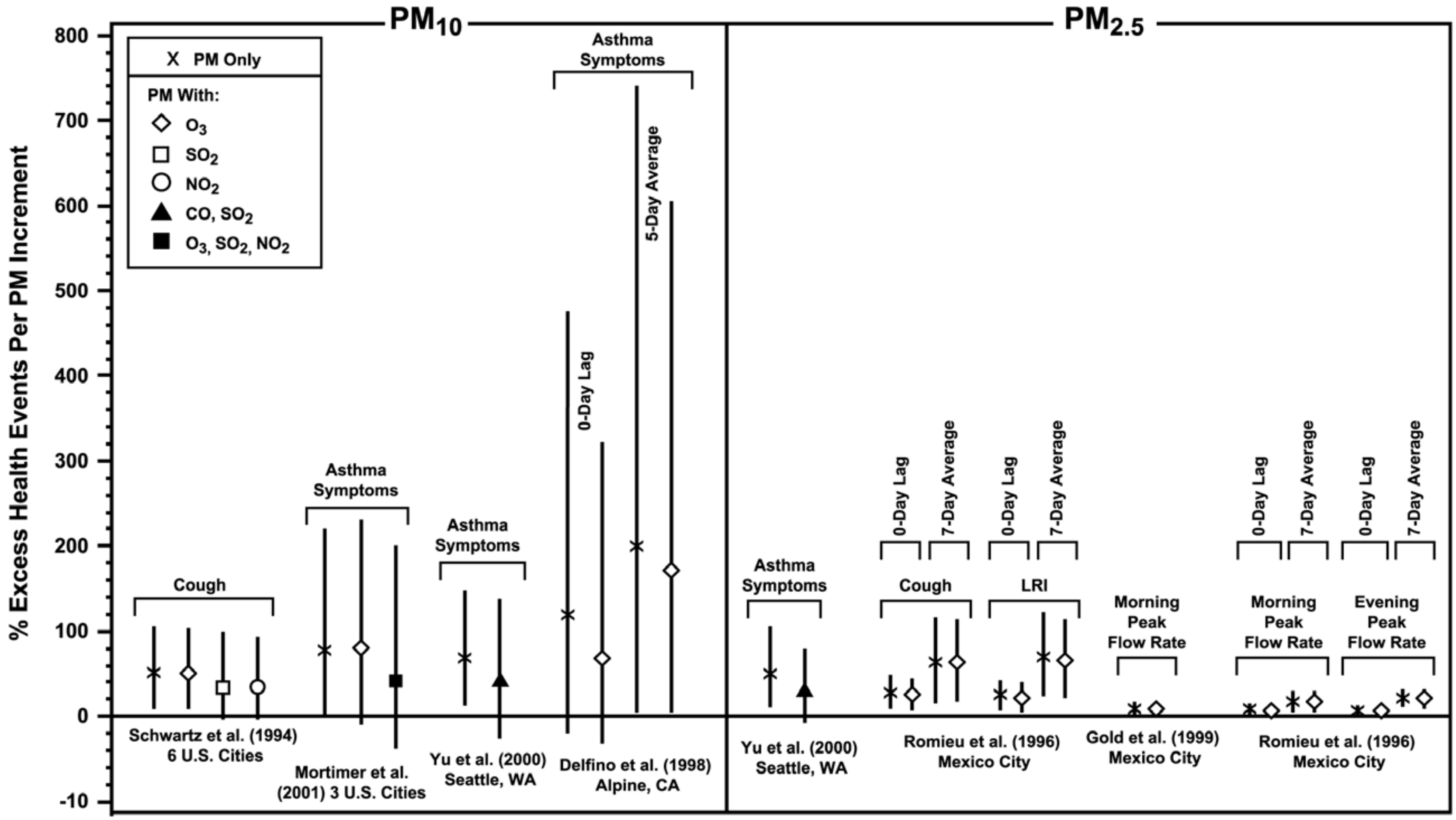

Figure 8-21. Excess risk estimates for increases in respiratory symptoms or decreases in lung function measures in single-pollutant (PM only) and multi-pollutant models. PM increments: 50 µg/m³ for PM_{10} and 25 µg/m³ for $PM_{2.5}$ and $PM_{10\text{-}2.5}$. Results presented from time-series studies that did not use GAM or were reanalyzed using GLM.

reduced with the inclusion of NO_2, but not CO; the inclusion of all four gaseous co-pollutants showed the most substantial reductions in the PM effect estimates for each indicator (Burnett et al., 1997). Ito (2003) presents results for cardiovascular mortality and hospital admissions in Detroit, and in most models, PM effect estimates are similar in models with and without co-pollutants; some variability is seen across these results, however, with the cardiovascular mortality effect estimates showing a decrease with the inclusion of either CO or NO_2, especially for PM_{10}. In Moolgavkar (2003), the inclusion of CO resulted in variable reductions in the PM_{10} effect estimates for cardiovascular mortality and hospital admissions, although the PM_{10} estimate for hospital admissions in Cook County remained significant. In the same study, for $PM_{2.5}$, the inclusion of CO increased the PM estimate for mortality, while somewhat reducing the estimate for hospital admissions.

As for cardiovascular-related effects, in many cases the PM effect estimates for respiratory-related mortality and morbidity effects do not show much change when various individual and combinations of co-pollutants were added to the models (Figure 8-20). However, for some endpoints PM effect estimates are changed substantially with specific co-pollutants, most notably with O_3 or NO_2. For example, in the Toronto study by Burnett et al. (1997), PM effect estimates for respiratory hospital admissions for all three PM indicators are appreciably reduced with the inclusion of NO_2, but not O_3; a larger reduction was seen with the inclusion of all four gaseous co-pollutants, as was seen in this study for cardiovascular hospital admissions. Other Canadian studies of respiratory hospital admissions or medical visits show appreciable reductions in PM_{10} and/or $PM_{2.5}$ effects estimates with the inclusion of O_3 (Thurston, 1994; Delfino, 1998). In Detroit (Ito, 2003), the COPD hospital admissions effect estimates for PM_{10} and $PM_{10-2.5}$ are reduced in models with O_3, as is the respiratory mortality effect estimate for $PM_{10-2.5}$; whereas the PM effect estimates for pneumonia hospital admissions are either unchanged or somewhat increased for all three indicators. In the results of studies on respiratory symptoms and lung function changes (Figure 8-21), PM effect estimates are generally robust to adjustment for ozone, though somewhat reduced in a study conducted in Alpine, CA (Delfino et al., 1998). Effect estimates for asthma symptoms were somewhat reduced in models that included both CO and SO_2 in Seattle (Yu et al., 2001) and in models that included O_3, SO_2, and NO_2 in a 3-city study by Mortimer et al. (2001).

In addition, a number of studies reported results of multi-pollutant models qualitatively, but did not provide quantitative results and thus are not included in Figures 8-18 through 8-21. From this group of studies, some report that PM effect estimates remained significant with adjustment for gaseous copollutants (e.g., Ostro et al., 2003; Cifuentes et al., 2000; Sunyer and Basagana, 2001; Lipsett et al., 1997; Desqueyroux et al., 2002), while others report more robust associations with gaseous pollutants (e.g., Lipfert et al., 2000; Stieb et al., 2000; Metzger et al., 2003; Peters et al., 2000). Beyond the quantitative results presented above, Moolgavkar (2003) also describes additional results of multi-pollutant models in the text in which PM effects may or may not be robust to the inclusion of gaseous co-pollutants, depending on the specific lag and co-pollutants used. For example, in Cook County, for a 0-day lag, the PM_{10} coefficient remained robust and statistically significant, while coefficients for each of the gases attenuated and became insignificant, while at a 1-day lag, PM_{10} coefficient attenuated and became insignificant, whereas coefficients for each of the gases were robust and remained statistically significant. In some studies there are reductions in PM effect estimates with adjustment for some gaseous pollutants for some, but not all, endpoints studied (e.g., Kwon et al., 2001; Prescott et al., 1998). Other authors report that it is difficult to distinguish among effects of closely correlated pollutants (e.g., Linn et al., 2000, for CO, NO_2 and PM_{10}; Atkinson et al., 1999b, for SO_2, NO_2 and PM_{10}; Pope et al., 1999, for CO and PM_{10}).

For many of the studies discussed above, PM and the gaseous co-pollutants are highly correlated, especially with CO, SO_2 and NO_2, and it is generally the case that where PM effect estimates were reduced in size with the inclusion of these co-pollutants, the pollutants were also highly correlated. Among the studies conducted in the U.S., O_3 was positively correlated with the PM indices in Detroit (Ito 2003), Atlanta (Tolbert et al., 2000b) and Cook County, IL (Moolgavkar, 2003), where in some cases PM effects were reduced with the inclusion of O_3. In other locations, such as Santa Clara County, CA (Fairley, 2003) and Boston (Peters et al., 2000),O_3 was not correlated with PM, and these studies did not report PM effect estimate changes in multi-pollutant models with O_3. In contrast with many areas of the U.S., CO and NO_2 were not highly correlated with PM indices in Coachella Valley, CA (Ostro et al., 2003), and the authors also report that the PM effects estimates were robust to inclusion of gaseous pollutants in the model. It also should be noted that in a number of studies where PM was highly correlated with the gaseous pollutants, the PM effect estimates were not affected by inclusion of the gaseous co-pollutants in the models.

Overall, a number of the recent studies have reported PM effect estimates that are robust to adjustment for gaseous co-pollutants; and in a number of studies, independent effects of the gaseous pollutants were also found. There are also a number of studies showing generally independent effects of PM, but for certain health outcomes and co-pollutants, the PM effect estimate is reduced. For example, in analyses of mortality and hospital admissions data in Detroit, the authors conclude "...the coefficients of PM mass indices often remain significant in two-pollutant models, but can be reduced, especially by O_3; and gaseous pollutants also are associated with mortality and morbidity outcomes, but cause specificity of associations has not been consistent."(Lippmann et al. 2000, p. 33; reanalyzed in Ito, 2003). Some authors have concluded, however, that PM effects were not robust to adjustment for gaseous co-pollutants. A notable example is the analyses of mortality and hospital admissions data in Cook and Los Angeles Counties, where the author concludes "...in Los Angeles (with the exception of COPD admissions with which NO_2 appeared to show the most robust association) it is clear that CO was the best single index of air pollution associations with health endpoints, far better than the mass concentration of either PM_{10} or $PM_{2.5}$. In Cook County the results were not so clear cut. However, any one of the gases was at least as good an index of air pollution effects on human health as PM_{10}." (Moolgavkar, 2003, p. 198)

In many of these studies, PM with and without added components of gases appears to be the putative agent. However, care must be exercised in interpreting such results, taking into account what is known about the toxicology and clinical studies of the gases. It is often clear that these gases, at concentrations present or given the nature of the effects, do not carry sufficient biologic plausibility to substantially affect the results seen. For example, SO_2 is mostly absorbed in upper airways under normal breathing conditions and, although it might affect airway neural reflexes to contribute to asthma exacerbation, at typical ambient levels in the U.S. it is not likely to exert sufficient effects on COPD or CVD to contribute to excess morbidity and mortality. Similarly, because of frequent lack of correlation, separating the effects of PM from O_3 seems justified on the basis of simply adjusting one for the other. The same may not be said for some of the other major gaseous pollutants. It is also the case that the most consistent findings from amidst the heterogeneity of studies done in different sites is that the PM signal comes through most often.

8.4.3.5 Bioaerosols as Possible Confounders or Effect Modifiers in PM Epidemiologic Studies

In addition to possible confounding or effect modification by gaseous co-pollutants, possible confounding or effect modification by bioaerosols needs to be considered in evaluating ambient PM epidemiologic findings.

A number of epidemiology studies have reported significant associations between asthma symptoms, hospital admissions, or medical visits for respiratory diseases and fungal spores (Neas et al., 1996; Delfino et al., 1996; Delfino et al., 1998; Delfino et al., 2002; Ostro et al., 2001; Stieb et al., 2000; Lewis et al., 2000), although not all studies have reported significant associations (e.g., Tolbert et al., 2000b). Significant associations between respiratory health outcomes and pollen count have also been reported (Moolgavkar et al., 2000; Stieb et al., 2000; Lewis et al., 2000), but a number of studies have not reported significant associations for pollen (Thurston et al., 1997; Delfino et al., 1998; Delfino et al., 2002; Ostro et al., 2001; Tolbert et al., 2000b; Anderson et al.,1998). Where the studies have included tests for interaction or potential confounding between aeroallergens and non-biological air pollutants for these health responses, all studies have indicated that the aeroallergen and air pollutant effects were independent, or the authors have concluded that effects were independent because the aeroallergens and pollutants were poorly correlated (Neas et al., 1996; Delfino et al., 1996; Delfino et al., 1997; Delfino et al., 1998; Delfino et al., 2002; Stieb et al., 2000; Moolgavkar et al., 2000; Anderson et al., 1998; Lewis et al., 2000).

8.4.4 Role of Particulate Matter Components

In the 1996 PM AQCD, extensive epidemiologic evidence substantiated very well positive associations between ambient PM_{10} concentrations and various health indicators, e.g., mortality, hospital admissions, respiratory symptoms, pulmonary function decrements, etc. Some studies were also then available which mortality and morbidity associations with various fine particle indicators (e.g., $PM_{2.5}$, sulfate, H^+, etc.). One mortality study, the Harvard Six Cities analysis by Schwartz et al. (1996a), evaluated relative contributions of the fine ($PM_{2.5}$) versus the coarse ($PM_{10-2.5}$) fraction of PM_{10}, and found, overall, that $PM_{2.5}$ appeared to be associated more strongly with mortality effects than $PM_{10-2.5}$. A few studies seemed to be indicative of possible coarse particle effects, e.g., increased asthma risks associated with quite high PM_{10} concentrations in a few locations where coarse particles strongly dominated the ambient PM_{10} mix.

8.4.4.1 Fine- and Coarse-Particle Effects on Mortality

A rapidly growing number of new studies published since the 1996 PM AQCD provide an expanded evidence base examining associations of ambient PM with increased human mortality and morbidity risks. As was indicated in Table 8-1, most newly reported analyses, with a few exceptions, continue to show statistically significant associations between short-term (24-h) PM concentrations and increases in daily mortality in many U.S. and Canadian cities (as well as elsewhere). Also, the reanalyses of Harvard Six City and ACS study data substantiate the original investigator's findings of long-term PM exposure associations with increased mortality as well.

8.4.4.1.1 Total Mortality Effects

The effects estimates from the newly reported studies are generally consistent with those derived from the earlier 1996 PM AQCD assessment, which reported risk estimates for excess total (nonaccidental) deaths associated with short-term PM exposures as generally falling within the range of ca. 1 to 8% per 50 $\mu g/m^3$ PM_{10} (24-h) increment and ca. 2 to 6% increase per 25 $\mu g/m^3$ $PM_{2.5}$ (24-h) increment.

Several new PM epidemiology studies which conducted time-series analyses in multiple cities were noted to be of particular interest, in that they provide evidence of effects across various geographic locations (using standardized methodologies) and more precise pooled effect size estimates with narrow confidence bounds, reflecting the typically much stronger power of such multi-city studies over individual-city analyses to estimate a mean effect. Based on pooled analyses across multiple cities, using GAM stringent convergence criteria, the percent total (non-accidental) excess deaths per 50 $\mu g/m^3$ PM_{10} (24-h) increment were estimated in different multi-city analyses to be: (a) 1.4% in the 90 largest U.S. cities; (b) 3.4% in 10 large U.S. cities; (c) 3.6% in the 8 largest Canadian cities; and (d) 3.0% in European cities.

Many new individual-city studies found positive associations (most statistically significant at $p < 0.05$) for the $PM_{2.5}$ fraction, with effect size estimates for U.S. and Canadian cities typically ranging from ca. 2.0 to ca. 8% per 25 μg/m^3 $PM_{2.5}$ (although one estimate for cardiovascular mortality ranged up to about 19%). Of the 10 or so new analyses that not only evaluated PM_{10} effects but also compared fine versus coarse fraction contributions to total mortality, only two are multi-city analyses yielding pooled effects estimates: (a) the Klemm and Mason (2000) and Klemm and Mason (2003) recomputation analyses for Harvard Six Cities data, confirming the original findings published by Schwartz et al. (1996a); and (b) the Burnett et al. (2000) and Burnett and Goldberg (2003) studies of the 8 largest Canadian cities. These studies found roughly comparable, statistically significant excess risk estimates for $PM_{2.5}$ (i.e., approximately 2% increased total mortality risk per 25 μg/m^3 $PM_{2.5}$ increment).

As for possible coarse particle short-term exposure effects on mortality, in those new studies which evaluated $PM_{10-2.5}$ effects as well as $PM_{2.5}$ effects, the coarse particle ($PM_{10-2.5}$) fraction was also consistently positively associated with increased total mortality, albeit the coarse fraction effect size estimates were generally less precise than those for $PM_{2.5}$ and statistically significant at $p < 0.05$ in only a few studies (as can be seen in Figure 8-6). Still, the overall picture tends to suggest that excess total mortality risks may well reflect actual coarse fraction particle effects, in at least some locations. This may be most consistently the case in arid areas, e.g., in the Phoenix area (as shown in Mar et al., 2000 and Mar et al., 2003) or in Mexico City and Santiago, Chile. On the other hand, elevations in coarse PM-related total mortality risks have also been detected for Steubenville, OH (an eastern U.S. urban area in the Harvard Six City Study), as shown by Schwartz et al. (1996a); Klemm et al. (2000), Klemm and Mason (2003). These results may reflect contamination of later-resuspended coarse PM by metals in fine PM emitted from smelters (Phoenix) or steel mills (Steubenville) that was earlier deposited on nearby soils. Excess total mortality risks associated with short-term (24-h) exposures to coarse fraction particles capable of depositing in the lower respiratory tract generally fall in the range of 0.2 to 6.0% per 25 μg/m^3 PM_{10-25} increment for U.S. and Canadian cities.

Three new papers provide particularly interesting new information on relationships between short-term coarse particle exposures and total elderly mortality (age 65 and older), using exposure TEOM data from the EPA ORD NERL monitoring site in Phoenix, AZ. Each used quite different models but each reported statistically significant relationships between mortality and coarse PM, specifically $PM_{10-2.5}$, an indicator for the thoracic fraction of coarse-mode PM.

Smith et al. (2000), using a three-day running average as the exposure metric, performed linear regression of the square root of daily mortality on the long-term trend, meteorological and PM-based variables. Two mortality variables were used, total (non-accidental) deaths for the city of Phoenix and the same for a larger, regional area. Using a linear analysis, effects based on coarse PM were statistically significant for both regions, whereas effects based on fine PM ($PM_{2.5}$) were not. However, when the possibility of a nonlinear response was taken into account, no evidence was found for a nonlinear effect for coarse PM; but fine PM was found to have a statistically significant effect for concentration thresholds of 20 and 25 µg/m^3. There was no evidence of confounding between fine and coarse PM, suggesting that fine and coarse PM are "essentially separate pollutants having distinct effects". Smith et al. (2000) also observed a seasonal effect for coarse PM, the effect being statistically significant only during spring and summer. Based on a principal component analysis of elemental concentrations, crustal elements are highest in spring and summer and anthropogenic elements lowest, but Smith et al. (2000) felt that the implication that crustal, rather than anthropogenic elements, were responsible for the PM mortality was counterintuitive.

Clyde et al. (2000) used a more conventional model, a Poisson regression of log deaths on linear PM variables; but they employed Bayesian model averaging to consider a wide variety of variations in the basic model. They considered three regions: the Phoenix metropolitan area; a small subset of zip code to give a region presumably with uniform $PM_{2.5}$; and a still smaller zip code region surrounding the monitoring site (thought to be uniform as to PM_{10} concentrations). The models considered lags of 0, 1, 2, or 3 days but only for single day PM variables (no running averages as used by Smith et al., 2000). A PM effect with a reasonable probability was found only in the uniform $PM_{2.5}$ region and only for coarse PM.

Mar et al. (2000, 2003) used conventional Poisson regression methods and limited their analyses to the smallest area (called "Uniform PM_{10}" by Clyde et al., 2000). They reported modeling data for lag days 0 to 4. Coarse fraction PM was marginally significant on lag day 0. No direct fine particle measures were statistically significant on day 0. A regional sulfate factor determined from source apportionment, however, was statistically significant. No correlations were reported for the source apportionment factors, but the correlation coefficient between sulfur

(S) in $PM_{2.5}$ (as measured by XRF) with coarse fraction PM was only 0.13, suggesting separate and distinct effects for regional sulfate and coarse fraction PM.

The above three studies of PM- total mortality relationships in Phoenix tend to suggest a statistical association of coarse fraction PM with total elderly mortality in addition to and different from any relationship with fine PM, fine PM components, or source factors for fine PM.

With regard to long-term PM exposure effects on total (non-accidental) mortality, the newly available evidence from the HEI Reanalyses of Harvard Six Cities and ACS data (and extensions, thereof), substantiate well associations attributable to chronic exposures to inhalable thoracic particles (indexed by PM_{15} or PM_{10}) and the fine fraction of such particles (indexed by $PM_{2.5}$ and/or sulfates). Statistically significant excess risk for total mortality was shown by the reanalyses to fall in the range of 4-18% per 20 $\mu g/m^3$ $PM_{15/10}$ increment and 14-28% per 10 $\mu g/m^3$ $PM_{2.5}$ increase.

Source-Oriented Analyses of Particle Component Contributions

Other new studies on the relation of mortality to particle composition and source (Laden et al., 2000; Mar et al., 2000; 1996; Tsai et al., 2000) suggest that particles from certain sources may have much higher potential for adverse health effects than others, as shown by source-oriented evaluations involving factor analyses. For example, Laden et al. (2000) conducted factor analyses of the elemental composition of $PM_{2.5}$ for Harvard Six Cities study data for 1979-1988. For all six cities combined, the excess risk for daily mortality was estimated to be 9.3% (95% CI; 4.0, 14.9) per 25 $\mu g/m^3$ $PM_{2.5}$ (average of 0 and 1 day lags) increment in a mobile source factor; 2.0% (95% CI; −0.3, 4.4) for a coal source factor, and −5.1% (95% CI; −13.9, 4.6) for a crustal factor. There was large variation among the cities and suggestion of an association (not statistically significant) with a fuel oil factor identified by V or Mn.

Mar et al. (2000) applied factor analysis to evaluate mortality in relation to 1995-1997 fine particle elemental components and gaseous pollutants (CO, NO_2, SO_2) in an area of Phoenix, AZ, close to the air pollution monitors. The $PM_{2.5}$ constituents included sulfur, Zn, Pb, soil-corrected potassium, organic and elemental carbon, and a soil component estimated from oxides of Al, Si, and Fe. Based on models fitted using one pollutant at a time, statistically significant associations were found between total mortality and PM_{10}, CO (lags 0 and 1), NO_2 (lags 0, 1, 3, 4), S (negative), and soil (negative). Statistically significant associations were also found between cardiovascular mortality and CO (lags 0 to 4), NO_2 (lags 1 and 4), SO_2 (lags 3 and 4), $PM_{2.5}$ (lags 1, 3, 4), PM_{10} (lag 0), $PM_{10-2.5}$ (lag 0), and elemental, organic, or total carbon. Cardiovascular mortality was significantly related to a vegetative burning factor (high loadings on organic carbon and soil-corrected potassium), motor vehicle exhaust/resuspended road dust factor (with high loadings on Mn, Fe, Zn, Pb, OC, EC, CO, and NO_2), and a regional sulfate factor (with a high loading on S). However, total mortality was negatively associated with a soil factor (high loadings on Al, Fe, Si) and a local SO_2 source factor, but was positively associated with the regional sulfate factor.

Tsai et al. (2000) analyzed daily time-series of total and cardiorespiratory deaths, using short periods of 1981-1983 data for Newark, Elizabeth, and Camden, NJ. In addition to inhalable particle mass (PM_{15}) and fine particle mass ($PM_{2.5}$), the study evaluated data for metals (Pb, Mn, Fe, Cd, V, Ni, Zn, Cu) and for three fractions of extractable organic matter. Factor analyses were carried out using the metals, CO, and sulfates. The most significant sources or factors identified as predictors of daily mortality were oil burning (targets V, Ni), Zn and Cd processing, and sulfates. Other factors (dust, motor vehicles targeted by Pb and CO, industrial Cu or Fe processing) were not significant predictors. In Newark, oil burning sources and sulfates were positive predictors, and Zn/Cd a negative predictor for total mortality. In Camden oil burning and motor vehicle emissions predicted total mortality, but copper showed a marginal negative association. Oil burning, motor vehicle emissions, and sulfates were predictors of cardiorespiratory mortality in Camden. In Elizabeth, resuspended dust indexed by Fe and Mn showed marginal negative associations with mortality, as did industrial sources traced by Cu.

The set of results from the above factor analyses studies do not yet allow one to identify with great certainty a clear set of specific high-risk chemical components of PM. Nevertheless, some commonalities across the studies seem to highlight the likely importance of mobile source and other fuel combustion emissions (and apparent lesser importance of crustal particles) as contributing to increased total or cardiorespiratory mortality.

8.4.4.1.2 Cause-Specific Mortality Effects

Cardiovascular- and Respiratory-Related Mortality

Numerous new studies have evaluated PM-related effects on cause-specific mortality. Most all report positive, often statistically significant (at $p < 0.05$), short-term (24-h) PM exposure associations with CVD- and respiratory-related deaths. Cause-specific effects estimates appear to mainly fall in the range of 3.0 to 7.0% per 25 μg/m^3 24-h $PM_{2.5}$ for cardiovascular or combined cardiorespiratory mortality and 2.0 to 7.0% per 25 μg/m^3 24-h $PM_{2.5}$ for respiratory mortality in U.S. cities. Effect size estimates for the coarse fraction ($PM_{10-2.5}$) for cause-specific mortality generally fall in the range of ca. 3.0 to 8.0% for cardiovascular and ca. 3.0 to 16.0% for respiratory causes per 25 μg/m^3 increase in $PM_{10-2.5}$.

Also of particular interest, the above noted study by Mar et al. examined the associations of a variety of PM indicators with cardiovascular mortality (for age ≥65), again in the zip code area near the Phoenix monitoring site. For this end point, coarse PM was statistically significant on lag day 0 but not on subsequent lag days. $PM_{2.5}$ and a number of fine PM indicators were statistically significant on lag day 1 but not on lag day 0. This suggests a distinct and separate relationship of $PM_{2.5}$ and $PM_{10-2.5}$. As in the case of total mortality, the only fine PM indicator found to be statistically significant on lag day 0 was regional sulfate. However, the low correlation coefficient between S in $PM_{2.5}$ and $PM_{10-2.5}$ ($r = 0.13$) suggests that the two relationships represent different sets of deaths. Thus, there is some evidence suggesting that the risk of cardiovascular mortality, as well as that of total mortality, may be statistically associated with $PM_{10-2.5}$ – possibly independent of any relationships with fine particle indicators.

Long-Term PM Exposure and Lung Cancer

Of particular interest with regard to PM-related cause-specific mortality is growing evidence linking long-term PM exposure with increased risk of lung cancer. Historical evidence includes studies of lung cancer trends, studies of occupational groups, comparisons of urban and rural populations, and case-control and cohort studies using diverse exposure metrics (Cohen and Pope, 1995). Numerous past ecological and case-control studies of PM and lung cancer have generally indicated a lung cancer RR greater than 1.0 to be associated with living in areas having higher PM exposures despite possible problems with respect to potential exposure and other risk factor measurement errors. Table 8-37 provides a partial listing of such studies.

TABLE 8-37. SUMMARY OF PAST ECOLOGIC AND CASE-CONTROL EPIDEMIOLOGIC STUDIES OF OUTDOOR AIR AND LUNG CANCER

Study Type	Authors	Locale	Exposure Classification	Rate Ratio (95% CI)
Ecologic	Henderson et al., 1975	Los Angeles, CA	High PAH Areas	1.3 @ 96-116 ug/m^3 TSP (CI: N/A)
	Buffler et al., 1988	Houston, TX	TSP by Census Tract	1.9 @ 16 ug/m^3 TSP (CI: N/A)
	Archer, 1990	Utah	TSP by county	1.6 @ 85 ug/m^3 TSP (CI: N/A)
Case-Control	Pike et al., 1979	Los Angeles	BAP Geo. Areas	1.3 @ 96-116 ug/m^3 TSP
	Vena, 1982	Buffalo, NY	TSP Geo. Areas	1.7 @ 80-200 ug/m^3 TSP (CI: 1.0-2.9)
	Jedrychowski, et al., 1990	Cracow, Poland	TSP and SO_2 Geo. Areas	1.1 @ TSP > 150 ug/m^3 (CI: N/A)
	Katsouyanni, et al., 1990	Athens, Greece	Soot Concentration Geo. Areas	1.1 @ soot up to 400 ug/m^3 (CI: N/A)
	Barbone et al., 1995	Trieste, Italy	High Particle Deposition Areas	1.4 @ > 0.3 g/m^2/day (CI: 1.1-1.8)
	Nyberg et al., 2000	Stockholm, Sweden	High NO_2 Areas	1.3 (CI: 0.9-1.9)

Source: Derived from Cohen (2000).

Prospective cohort studies offer a potentially more powerful approach to evaluation of apparent associations between PM exposures and development of lung cancer. The 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a) summarized three of these more elaborate studies that carefully evaluated PM air pollution exposure effects on lung cancer using the prospective cohort design. In the AHSMOG Study, Abbey et al. (1991) followed a cohort of Seventh Day Adventists, whose extremely low prevalence of smoking and uniform, relatively healthy dietary patterns reduce the potential for confounding by these factors. Excess lung cancer incidence was observed in females in relation to both particle (TSP) and O_3 exposure after 6 years follow-up time. Dockery et al. (1993) reported the results of a 14- to 16-year prospective follow-up of 8,111 adults living in six U.S. cities that evaluated associations between air pollution and mortality. After controlling for individual differences in age, sex, cigarette smoking, BMI, education, and occupational exposure, Dockery et al. (1993) found an elevated but non-significant risk for lung cancer (RR = 1.37; 95% CI = 0.81 to 2.31) for a difference in $PM_{2.5}$ pollution equal to that of the most polluted versus the least polluted city. Pope et al. (1995) similarly analyzed $PM_{2.5}$ and sulfate ($SO_4^{=}$) air pollution as predictors of mortality in a prospective study of 7-year survival data (1982 to 1989) for about 550,000 adult volunteers obtained by the American Cancer Society (ACS).

Both the ACS and Harvard studies have been subjected to much scrutiny, including an extensive independent audit and reanalysis of the original data (Krewski et al., 2000) that confirmed the originally published results. The ACS study controlled for individual differences in age, sex, race, cigarette smoking, pipe and cigar smoking, exposure to passive cigarette smoke, occupational exposure, education, BMI, and alcohol use. Lung cancer mortality was significantly associated with particulate air pollution when $SO_4^{=}$ was used as the index,, but not when $PM_{2.5}$ mass was used as the index for a smaller subset of the study population that resided in metropolitan areas where $PM_{2.5}$ data were available from the Inhalable Particle (IP) Network. Thus, while these prospective cohort studies have also indicated that long-term PM exposure is associated with an increased cancer risk, the effect estimates were generally not statistically significant, quite possibly due to inadequate statistical power by these studies at that time (e.g., due to inadequate population size and/or follow-up time for long-latency cancers).

The AHSMOG investigators have re-examined the association between long-term PM exposure and increased risk of both lung cancer incidence and lung cancer mortality in nonsmokers using longer-term follow-up of this cohort and improved analytical approaches. Beeson et al. (1998) considered this cohort of some 6,338 nonsmoking, non-Hispanic, white Californian adults, ages 27-95, that was followed from 1977 to 1992 for newly diagnosed cancers. Incident lung cancer in males was positively and significantly associated with interquartile range (IQR) increases for mean concentrations of PM_{10} (RR = 5.21; 95% CI = 1.94-13.99). For females in the cohort, incident lung cancer was positively associated with IQR increases for SO_2 (RR = 2.14; CI, 1.36-3.37) and IQR increases for PM_{10} exceedance frequencies of 50 $\mu g/m^3$ (RR = 1.21; 95% CI = 0.55-2.66) and 60 ug/m^3 (RR = 1.25; 95% CI = 0.57-2.71). Thus, increased risks of incident lung cancer were deemed by the authors to be associated with elevated long-term ambient concentrations of PM_{10} and SO_2 in both genders. The higher PM_{10} risk effect estimate for cancer in males appeared to be partially due to gender differences in long-term air pollution exposures. Abbey et al. (1999) also related long-term ambient concentrations of PM_{10}, SO_4^{-2}, SO_2, O_3, and NO_2 to 1977-1992 mortality in the AHSMOG cohort. After adjusting for a wide array of potentially confounding factors, including occupational and indoor sources of air pollutants, PM_{10} showed a strong association with lung cancer deaths in males (PM_{10} IQR RR=2.38; 95% CI: 1.42 - 3.97). In this cohort, males spent more time outdoors than females, thus having higher estimated air pollution exposures than the cohort females. Ozone showed an even stronger association with lung cancer mortality for males, and SO_2 showed strong associations with lung cancer mortality for both sexes. The authors reported that other pollutants showed weak or no association with mortality. Therefore, increases in both lung cancer incidence and lung cancer mortality in the extended follow-up analysis of the AHSMOG study were found to be most consistently associated with elevated long-term ambient concentrations of PM_{10} and SO_2, especially among males.

A recent follow-up analysis of the major ACS study by Pope et al. (2002) responds to a number of criticisms previously noted for the earlier ACS analysis (Pope et al., 1995) in the 1996 PM AQCD (U.S. Environmental Protection Agency, 1996a). Most notably, the new study examined other pollutants, had better occupational indices and diet information, and also addressed possible spatial auto-correlations due to regional location. The recent extension of the ACS study included ~500,000 adult men and women drawn from ACS-CPS-II enrollment and follow-up during 1982-1998. This new analysis of the ACS cohort substantially expands the prior analysis, including: (1) more than doubling of the follow-up time to 16 years (and more than tripling of the number of deaths in the analysis); (2) substantially expanded exposure data, including gaseous co-pollutant data and new $PM_{2.5}$ data collected in 1999-2001; (3) improved control of occupational exposures; (4) incorporation of dietary variables that account for total fat consumption, as well as that of vegetables, citrus and high-fiber grains; and (5) utilization of recent advances in statistical modeling, including incorporation of random effects and non-parametric spatial smoothing components in the Cox proportional hazards model.

In the extended ACS analysis, long-term exposure to air pollution, and especially to $PM_{2.5}$, was found to be associated with increased annual risk of mortality. With the longer 15-year follow-up period and improved $PM_{2.5}$ exposure metrics, this study detected for the first time, a statistically significant association between living in a city with higher $PM_{2.5}$ and increased risk of dying of lung cancer. Each 10 ug/m^3 increment in annual average fine PM was associated with a 13 percent (95% CI=4%-23%) increase in lung cancer mortality. Coarse particles and gaseous pollutants were generally not significantly associated with excess lung cancer mortality. SO_4^{-2} was significantly associated with mortality and lung cancer deaths in this extended data set, yielding RR's consistent with (i.e., not significantly different from) the SO_4^{-2} RR's reported in the previously published 7-year follow-up (Pope et al, 1995). However, while $PM_{2.5}$ was specific to the causes most biologically plausible to be influenced by air pollution in this analysis (i.e., cardiopulmonary and cancer), SO_4^{-2} was significantly associated with every mortality category in this new analysis, including that for "all-other causes". This suggests that the $PM_{2.5}$ associations found are more biologically plausible than the less specific SO_4^{-2} associations found. The $PM_{2.5}$ cancer risk appears greatest for non-smokers and among those with lower socio-economic status (as indicated by lower educational attainment).

Overall, these new cohort studies confirm and strengthen the published older ecological and case-control evidence indicating that living in an area that has experienced higher PM exposures can cause a significant increase in the RR of lung cancer incidence and associated mortality. In particular, the new ACS cohort analysis more clearly indicates that living in a city with higher $PM_{2.5}$ levels is associated with an elevated risk of lung cancer amounting to an increase of some 10 to 15% above the lung cancer risk in a cleaner city.

With regard to specific ambient fine particle constituents that may significantly contribute to the observed ambient PM-related increases in lung cancer, PM components of diesel engine exhaust represent one class of likely important contributors. Diesel emission PM typically comprises a noticeable fraction of ambient fine particles in many urban areas, having been estimated to comprise from approximately 5 to 35% of ambient $PM_{2.5}$ in some U.S. urban areas (see Chapter 3). In addition, as discussed in a separate Health Effects Assessment of Diesel Engine Exhaust (U.S. Environmental Protection Agency, 2002), extensive epidemiologic and toxicologic evidence links diesel emissions (including fine PM components) to increased risk of lung cancer.

8.4.4.2 PM_{10}, $PM_{2.5}$ (Fine), and $PM_{10-2.5}$ (Coarse) Particulate Matter Effects on Morbidity

A body of new studies published since the 1996 PM AQCD provides further evidence examining ambient PM association with increased human morbidity. At the time of the 1996 PM AQCD, fine particle morbidity studies were mostly limited to Schwartz et al. (1994) , Neas et al. (1994, 1995); Koenig et al. (1993); Dockery et al. (1996); and Raizenne et al. (1996); and discussion of coarse particles morbidity effects was also limited to only a few studies (Gordian et al., 1996; Hefflin et al., 1994). Since the 1996 PM AQCD, several new studies have been published in which newly available size-fractionated PM data allowed investigation of the effects of both fine ($PM_{2.5}$) and coarse fraction ($PM_{10-2.5}$) particles. PM_{10}, fine (FP) and coarse fraction (CP) particle results are noted below for studies by morbidity outcome areas, as follows: cardiovascular disease (CVD) hospital admissions (HA's); respiratory medical visits and hospital admissions; and respiratory symptoms and pulmonary function changes.

As discussed in Section 8.3.1 (on cardiovascular effects associated with acute ambient PM exposure), a substantial body of new results has emerged since the 1996 PM AQCD that evaluates PM_{10} effects on cardiovascular-related hospital admissions and visits. Especially notable new evidence has been provided by multi-city studies (Samet et al., 2000a,b; Zanobetti and Schwartz, 2003b) that yield pooled estimates of PM-CVD effects across numerous U.S. cities and regions. This study found not only significant PM associations, but also associations with other gaseous pollutants as well, thus hinting at likely independent effects of certain gases (O_3, CO, NO_2, SO_2) and/or interactive effects with PM. These and other individual-city studies generally appear to confirm likely excess risk of CVD-related hospital admission for U.S. cities in the range of 2-9% per 50 $\mu g/m^3$ PM_{10}, especially among the elderly ($\geq$ 65 yr).

In addition to the PM_{10} studies, several new U.S. and Canadian studies evaluated fine-mode PM effects on cardiovascular outcomes. Lippmann et al. (2000) and Ito (2003) report a positive but not a significant association with $PM_{2.5}$; and Moolgavkar (2003) reported $PM_{2.5}$ to be significantly associated with CVD HA for lag 0 and 1 in Los Angeles. Burnett et al. (1997a) reported that fine particles were significantly associated with CVD HA in a single pollutant model, but not when gases were included in multipollutant models for the 8 largest Canadian city data. Stieb et al. (2000) reported both PM_{10} and $PM_{2.5}$ to be associated with CVD emergency department (ED) visits in single pollutant, but not multipollutant models. Similarly, Morgan et al. (1998) reported that $PM_{2.5}$ measured by nepholometry was associated with CVD HA for all ages and 65+ yr, but not in the multipollutant model. Tolbert et al. (2000a) reported that coarse particles were significantly associated with dysrhythmias, whereas $PM_{2.5}$ was not. Other studies (e.g., Liao et al., 1999; Creason et al., 2001; Pope et al., 1999b,c) reported associations between increases in $PM_{2.5}$ and several measures of decreased heart rate variability, but Gold et al. (2000) reported a negative association of $PM_{2.5}$ with heart rate and decreased variability in r-MSSD (one heart rate variability measure). A study by Peters and colleagues (2001a) reported significant temporal associations between acute (2-h or 24-h) measures of $PM_{2.5}$ and myocardial infarction. Overall, these new studies collectively appear to implicate fine particles, as well as possibly some gaseous co-pollutants, in cardiovascular morbidity; but the relative contributions of fine particles acting alone or in combination with gases such as O_3, CO, NO_2 or SO_2 remain to be more clearly delineated and quantified. Difficult issues also remain with regard to interpretation of (a) reduced PM effect size and /or statistical significance when co-pollutants derived from the same source(s) as PM are included in multipollutant models and (b) the medical significance of the overall pattern of reported ECG changes.

Section 8.3.1 also discussed U.S. and Canadian studies that present analyses of coarse fraction particles (CP) relationships to CVD outcomes. Lippmann et al. (2000) and Ito (2003) found significant positive associations of $PM_{10-2.5}$ with ischemic heart disease hospital admissions in Detroit (RR = 1.08, CI 1.04, 1.16). Tolbert et al. (2000a) reported significant positive associations of heart dysrhythmias with CP ($p = 0.04$) as well as for elemental carbon ($p = 0.004$), but these preliminary results must be interpreted with caution until more complete analyses are carried out and reported. Burnett et al. (1997b) noted that CP was the most robust of the particle metrics examined to inclusion of gaseous covariates for cardiovascular hospitalization, but concluded that particle mass and chemistry could not be identified as an independent risk factor for exacerbation of cardiorespiratory disease in this study. Based on another Canadian study, Burnett et al. (1999), reported statistically significant associations for CP in univariate models but not in multipollutant models; but the use of estimated rather than measured PM exposures indices limits the interpretation of the PM results reported.

The collective evidence reviewed above, in general, appears to suggest excess risks for CVD-related hospital admissions of approximately 1 to 10% per 25 $\mu g/m^3$ $PM_{2.5}$ or $PM_{10-2.5}$ increment.

Section 8.3.2 also discussed new studies of effects of short-term PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ exposure on the incidence of respiratory hospital admissions and medical visits. Several new U.S. and Canadian studies have yielded particularly interesting results that are also suggestive of roles of both fine and coarse particles in respiratory-related hospital admissions. In an analysis of Detroit data, Lippmann et al. (2000) and Ito (2003) found comparable effect size estimates for $PM_{2.5}$ and $PM_{10-2.5}$. That is, the excess risk for pneumonia hospital admissions (in no co-pollutant model) was 18.6% (CI 5.6, 33.1) per 50 μg/m^3 PM_{10}, 10% (CI 1.5, 19.5) per 25 μg/m^3 $PM_{2.5}$ and 11.2% (CI -0.02, 23.6) per 25 μg/m^3 $PM_{10-2.5}$. Because $PM_{2.5}$ and $PM_{10-2.5}$ were not highly correlated, the observed association between coarse particles and health outcomes were possibly not confounded by smaller particles. Despite the greater measurement error associated with $PM_{10-2.5}$ than with either $PM_{2.5}$ and PM_{10}, this indicator of the coarse particles within the thoracic fraction was associated with some of the outcome measures. The interesting result is that $PM_{10-2.5}$ appeared to be a separate factor from other PM metrics. Burnett et al. (1997b) also reported PM (PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$) associations with respiratory hospital admissions, even with O_3 in the model. Notably, the $PM_{10-2.5}$ association was significant (RR = 1.13 for 25 μg/m^3; CI = 1.05 - 1.20); and inclusion of ozone still yielded a significant coarse mass RR = 1.11 (CI = 1.04 – 1.19). Moolgavkar (2000a) and Moolgavkar (2003) reported that, in Los Angeles, both PM_{10} and $PM_{2.5}$ yielded both positive and negative associations at different lags for single pollutant models but not in two pollutant models. Delfino et al. (1997) reported that both $PM_{2.5}$ and PM_{10} are positively associated with ED visits for respiratory disease. Morgan et al. (1998) reported that $PM_{2.5}$ estimated from nephelometry yielded a $PM_{2.5}$ association with COPD hospital admissions for 1-hr max PM that was more positive than 24-h average $PM_{2.5}$.

A new study examines PM associations with asthma-related hospital admissions. Sheppard et al. (1999) and Sheppard (2003) studied relationships between PM metrics that included $PM_{10-2.5}$ and non-elderly adult hospital admissions for asthma in the greater Seattle area and reported significant relative risks for PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$ (lagged 1 day). For $PM_{10-2.5}$, the relative risk was 1.05 (95% CI 1.0, 1.14) and for PM2.5, the relative risk 1.07 (1.02, 1.11). For a 16% decrease in PM_{10} levels, Friedman et al. (2001) reported decreased hospital admissions for asthmatics during the Olympics in Atlanta.

Thus, although PM_{10} mass has most often been implicated as the PM pollution index affecting respiratory hospital admissions, the overall collection of new studies reviewed in Section 8.3.2 appear to suggest relative roles for PM_{10} and for both fine and coarse PM mass fractions, such as $PM_{2.5}$ and $PM_{10-2.5}$.

Section 8.3.3 assessed relationships between PM exposure on lung function and respiratory symptoms. While most data examine PM_{10} effects, several studies also examined fine and coarse fraction particle effects. Schwartz and Neas (2000) report that cough was the only response in which coarse fraction particles appeared to provide an independent contribution to explaining the increased incidence. The correlation between CP and $PM_{2.5}$ was moderate (0.41). Coarse fraction particles had little association with evening peak flow. Tiittanen et al. (1999) also reported a significant effect of $PM_{10-2.5}$ for cough. Thus, cough may be an appropriate outcome related to coarse fraction particle effects. However, the limited data base suggests that further study is appropriate. The report by Zhang, et al. (2000) of an association between coarse fraction particles and the indicator "runny nose" is noted also.

Published epidemiologic studies have collectively indicated that exposure to PM air pollution can be associated with adverse human health effects, and that asthmatics represent a population that can be especially affected by acute exposures to air pollution (e.g., see Koren and Utell, 1997). In particular, prospective epidemiologic studies of panels of individuals confirm the air pollution-asthma exacerbation association.

For respiratory symptoms and PFT changes, several new asthma studies report associations with ambient PM measures. The peak flow analyses results for asthmatics tend to show small decrements for both PM_{10} and $PM_{2.5}$. Several studies included $PM_{2.5}$ and PM_{10} independently in their analyses of peak flow. Of these, Pekkanen et al. (1997) and Romieu et al. (1996) found comparable results for $PM_{2.5}$ and PM_{10} and the study of Peters et al. (1997c) found slightly larger effects for $PM_{2.5}$. Of studies that included both PM_{10} and $PM_{2.5}$ in their analyses of respiratory symptoms, the studies of Peters et al. (1997c) and found similar effects for the two PM measures. Only the Romieu et al. (1996) study found slightly larger effects for $PM_{2.5}$. While the PM associations with adverse health effects among asthmatics and others are well documented, the type/source(s) of those particles most associated with adverse health effects among asthmatics are not known at this time. Indeed, the makeup of PM varies greatly from place to place and over time, depending upon factors such as the sources that contribute to the pollution and the prevailing atmospheric conditions, affecting particle formation, coagulation, transformation, and transport. One suspected causal PM agent is the fine particle component of diesel combustion exhaust.

Two studies (Delfino et al., 1998; Ostro et al., 2001) examined PM effects on asthmatics using one hour maximum exposure measures by TEOM, and both studies indicate a relationship with measures of respiratory symptoms. Further research is needed at these shorter exposure times for different PM size fractions.

For non-asthmatics, several studies evaluated $PM_{2.5}$ effects. Naeher et al. (1999) reported similar AM PEF decrements for both $PM_{2.5}$ and PM_{10}. Neas et al. (1996) reported a nonsignificant negative association for PEF and $PM_{2.1}$, and Neas et al. (1999) also reported negative but nonsignificant PEF results. Schwartz and Neas (2000) reported a significantly PM PEF association with $PM_{2.5}$, and Tiittanen et al. (1999) also reported negative but nonsignificant association for PEF and $PM_{2.5}$. Gold et al. (1999) reported significantly PEF results. Schwartz and Neas (2000) reported significant $PM_{2.5}$ effects relative to lower respiratory symptoms. Tiittanen et al. (1999) showed significant effects for cough and $PM_{2.5}$ for a 4-day average.

The best evidence for chronic effects are found in the newer studies that combine the features of cross-sectional and cohort studies. These studies include Peters et al. (1999b,c), Gauderman et al. (2000), and Gauderman et al. (2002). The Gauderman studies found significant decreases in lung function growth related to PM_{10} levels. However, Peters et al. (1999) found no relationship between symptoms and PM_{10} levels. The cross-sectional studies by Dockery et al. (1996) and Raizenne et al. (1996), reported in the previous 1996 PM AQCD, found differences in peak flow and bronchitis rates associated with fine particle acidity.

The above new studies offer much more information than was available in 1996. Effects were noted for several morbidity endpoints: cardiovascular hospital admissions, respiratory hospital admissions and cough. Still insufficient data exists from these relatively limited studies to allow strong conclusions at this time as to which size-related ambient PM components may be most strongly related to one or another morbidity endpoints. Very preliminarily, however, fine particles appear to be more strongly implicated in cardiovascular outcomes than are coarse fraction particles, whereas both seem to impact respiratory endpoints.

8.4.5 The Question of Lags

The effect of selecting lags on the resulting model for PM health effects is an important issue in model selection. Using simulated data with parameters similar to a Seattle $PM_{10-2.5}$ data series, Lumley and Sheppard (2000) showed that the bias resulting from the selection is shown to be similar in size to the relative risk estimates from the measured data. More precisely, the log relative risk from the measured Seattle data is about twice the mean bias in the simulated control data, and the published estimate of relative risk is only at the 90^{th} percentile of the bias distribution in these control analysis. The selection rule used was to choose the lag (between 0 and 6 day) with the largest estimated relative risk. In comparisons to real data from Seattle for other years and from Portland, OR (with similar weather patterns to Seattle), similar bias issues became evident.

In most of the past air pollution health effects time-series studies, after the basic model (the best model with weather and seasonal cycles as covariates) was developed, several pollution lags (usually 0 to 3 or 4 days) were individually introduced and the most significant lag(s) chosen for the RR calculation. Due to likely individual variability in response to air pollution, the apparent lags of effects observed for aggregated population counts are expected to be "distributed" (i.e., symmetric or skewed bell-shape). The "most significant lag" in such distributed lags is also expected to fluctuate statistically. The "vote-counting" of the most significant lags reported in the past PM-mortality studies shows that 0 and 1 day lags are, in that order, the most frequently reported "optimal" lags, but such estimates may be biased because these lags are also likely the most frequently examined ones. Thus, a more systematic approach across different data sets was needed to investigate this issue.

The Samet et al. (2000b) analysis, and the reanalysis by Dominici et al. (2002), of the 90 largest U.S. cities provides particularly useful information on this matter. Figure 8-22 depicts the Dominici et al. (2002) overall pooled results, showing the posterior distribution of PM_{10} effects for the 90 cities for lag 0, 1, and 2 days. It can be seen that the effect size estimate for lag 1day is about twice that for lag 0 or lag 2 days, although their distributions overlap. The pattern of lagged effects pooled for each of the seven regions (see Figure 8-3) in the 90 cities study also shows that the lag with the largest effect was at 1 day, with the exception of Upper Midwest where the estimated PM_{10} effect was about the same for lag 0 and 1 days. However, the studies that examined PM-mortality associations in individual cities sometimes show the "most significant lags" at other lags. For example, in Moolgavkar's analysis of Los Angeles data (2000 and reanalysis 2003), both total non-accidental mortality and cardiovascular mortality showed the strongest associations with PM_{10} at lag 2 days.

A review of current studies on the short-term adverse health effects of air pollution indicates that there are essentially three different approaches to deal with temporal structure: (1) assume all sites have the same lag (e.g., 1 day, for a given effect); (2) use the lag or moving average giving the largest or most significant effect and for each pollutant and endpoint; and (3) use a flexible distributed lag model, with parameters adjusted to each site. The NMMAPS

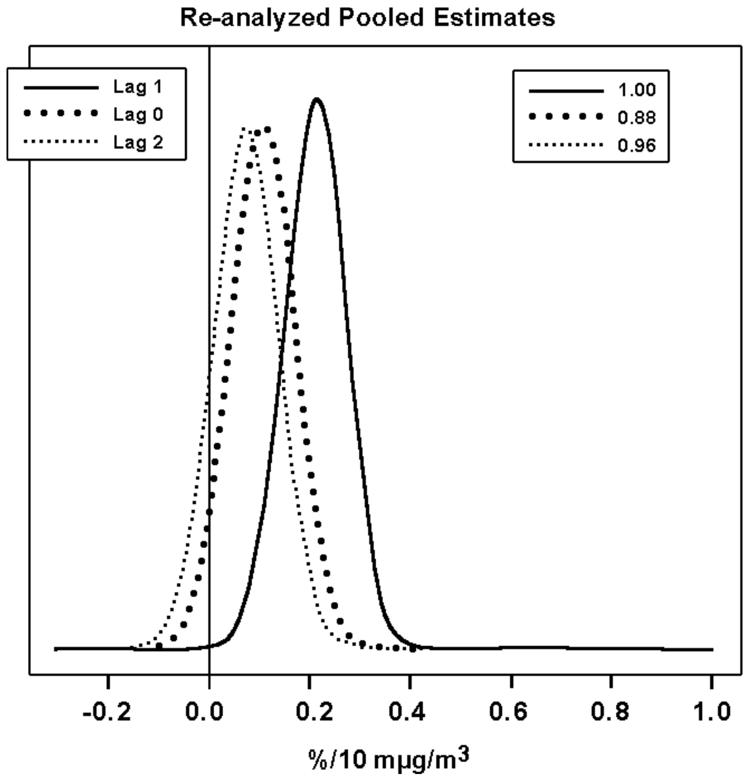

Figure 8-22. Marginal posterior distribution for effects of PM_{10} on all cause mortality at lag 0, 1, and 2 for the 90 cities. From Dominici et al. (2002a). The numbers in the upper right legend are posterior probabilities that overall effects are greater than 0.

Source: Dominici et al. (2002).

mortality analyses used the first approach. This approach introduces a consistent response model across all locations. However, since the cardiovascular, respiratory, or other causes of acute mortality usually associated with PM are not at all specific, there is little *a priori* reason to believe that they must have the same relation to current or previous PM exposures at different sites. The obvious advantage of the first approach in dealing with multi-city data is its consistency in summarizing the point estimate. The major factor that makes it difficult to conduct a meta-analysis of existing PM health effects studies is the lack of consistency in the way lag structures were modeled across the studies.

The approach used in most of PM time-series studies is to use the model that maximizes some global model goodness-of-fit criterion. This leads to selection of different models at different sites, as might be expected. However, the best-fitting model (for lags, for example) is often the model with the largest or most significant PM_{10} coefficient (i.e., the approach [2] above). All models for the pollutant(s) of interest are usually compared among themselves only after a preliminary baseline model has been fitted. The baseline model takes into account most of the other variables with which PM_{10} could be plausibly associated, so that the remaining variation in morbidity or mortality that can be explained by including PM_{10} indicators with different temporal structures is nearly "orthogonal" or independent of the baseline model. The restriction to the same lag day at all sites certainly increases the precision of that estimate, but possibly at the cost of obscuring different relationships between time of exposure and health effect at other sites.

An additional complication in assessing the shape of a distributed lag is that the apparent spread of the distributed lag may depend on the pattern of persistence of air pollution (i.e., episodes may persist for a few days), which may vary from city to city and from pollutant to pollutant. If this is the case, fixing the lag across cities or across pollutants may not be ideal, and may tend to obscure important nuances of lag structures that may provide important clues to possible different lags between PM exposures and different cause-specific effects.

It should also be noted that if one chooses the most significant single lag day only, and if more than one lag day shows positive (significant or otherwise) associations with mortality, then reporting a RR for only one lag would also underestimate the pollution effects. Schwartz (2000b; reanalysis 2003b) investigated this issue, using the 10 U.S. cities data where daily PM_{10} values were available for 1986-1993. Daily total (non-accidental) deaths of persons 65 years of age and older were analyzed. For each city, a GAM Poisson model (with stringent convergence criteria) and penalized splines adjusting for temperature, dewpoint, barometric pressure, day-of-week, season, and time were fitted. Effects of distributed lag were examined using two models: second-degree distributed lag model using lags 0 through 5 days; and unconstrained distributed lag model using lags 0 through 5 days. The inverse variance weighted averages of the ten cities' estimates were used to combine results. The results indicated that the effect size estimates for the quadratic distributed model and unconstrained distributed lag model using GAM were similar: 6.3% (95% CI: 4.9-7.8) per 50 $\mu g/m^3$ increase for the quadratic distributed lag model, and 5.8% (95% CI: 4.4-7.3). These risk estimates are about twice as large as the two-day average (lag 0 and 1 day) estimate (3.4%; 95% CI: 2.6-4.1) obtained in the reanalysis of the original 10 cities study (Schwartz, 2003b). There are indications that such distributed lag estimates are even larger when more specific cause of deaths are examined (see US 10 cities study description in section 8.2.2.3).

Mis-specification of the lag structure may cause important modeling biases. Most of the published literature for the U.S. evaluates only single-day models, a choice dictated by the every-sixth-day sampling schedule used for PM_{10} in many U.S. cities. When this occurs, it is not possible to evaluate multi-day models with greater biological plausibility, such as moving average models and distributed lag models. It should also be noted that, with the every-sixth-day PM data, a different set of days of mortality series were evaluated at each lag. An every-other-day sampling schedule was used in the Harvard Six City Study, for which the PM data on a given day has been used as though it were a two-day moving, alternately concurrent with mortality on half the days and lagging mortality by one day on the other days. While the most commonly used lags in PM time-series models are zero or one day, some studies have found PM effects with longer lags (e.g., Wichmann et al. (2000) and reanalysis by Stölzel et al. (2003); Lippmann et al. (2000) and reanalysis by Ito (2003). It is plausible that mortality or hospital admissions from PM may arise from different responses or PM-associated diseases with different characteristic lags, for example, that cardiovascular responses may arise almost immediately after exposure, within zero or one days or even within two hours (Peter et al., 2001a, for myocardial infarction). One would then expect to see different best-fitting lags for different cause-specific mortality or hospital admissions.

In summary, the largest time-series study to date (90 cities study) indicated that, of the 0, 1, and 2 day PM_{10} lags examined, lag 1 day showed the strongest mortality associations. However, other lags are reported for various mortality and morbidity outcomes from studies that examined individual cities' data. Examinations of lag structures are often limited by the prevailing every-6^{th}-day sampling schedule for PM in the U.S., but a limited number of studies that examined daily PM data using distributed lag model suggest that multi-day effects are larger than the single-day effects. Thus, it is possible that current PM risk estimates, most frequently computed for a single day or for two-day averages, may be underestimating these multi-day effects.

8.4.6 Concentration-Response Relationships for Ambient PM

In the 1996 PM AQCD, the limitations of identifying 'threshold' in the concentration-response relationships in observational studies were discussed including the low data density in the lower PM concentration range, the small number of quantile indicators often used, and the possible influence of measurement error. Also, a threshold for a population, as opposed to a threshold for an individual, has some conceptual issues that need to be noted. For example, Schwartz (1999) discussed that, since individual thresholds would vary from person to person due to individual differences in genetic level susceptibility and pre-existing disease conditions, it would be almost mathematically impossible for a threshold to exist in the population. This argument holds only if the most sensitive members of a population are sensitive to very low concentrations, which may not be the case. The person-to-person difference in the relationship between personal exposure and the concentration observed at a monitor would also add to the variability. Because one cannot directly measure but can only compute or estimate a population threshold, it would be difficult to interpret an observed threshold, if any, biologically. Despite these issues, several studies have attempted to address the question of threshold by analyzing large databases, or by conducting simulations.

Daniels et al. (2000; reanalysis by Dominici et al., 2003) examined the presence of threshold using the largest 20 U.S. cities for 1987-1994. In the original analysis, the authors compared three log-linear GAM regression models: (1) using a linear PM_{10} term; (2) using a natural cubic spline of PM_{10} with knots at 30 and 60 $\mu g/m^3$ (corresponding approximately to 25 and 75 percentile of the distribution); and, (3) using a threshold model with a grid search in the range between 5 and 200 $\mu g/m^3$ with 5 $\mu g/m^3$ increment. The covariates included in these models are similar to those used by the same research group previously (Kelsall et al., 1997; Samet et al., 2000a,b), including the smoothing function of time, temperature and dewpoint, and day-of-week indicators. In the reanalysis, the covariate adjustments were made using natural splines in GLM models. Total, cardiorespiratory, and other mortality series were analyzed. These models were fit for each city separately, and for model (1) and (2) the combined estimates across cities were obtained by using inverse variance weighting if there was no heterogeneity across cities, or by using a two-level hierarchical model if there was heterogeneity. The best fit among the models, within each city and over all cities, were also determined using the Akaike's Information Criterion (AIC). The results using the natural spline model showed that, for total and cardiorespiratory mortality, the spline curves were roughly linear, consistent with the lack of a threshold (see Figure 8-23). For mortality from other causes, however, the curve did not increase until PM_{10} concentrations exceeded 50 µg/m^3. The hypothesis of linearity was examined by comparing the AIC values across models. The results suggested that the linear model was preferred over the spline and the threshold models. Thus, these results suggest that linear models without a threshold may well be appropriate for estimating the effects of PM_{10} on the types of mortality of main interest.

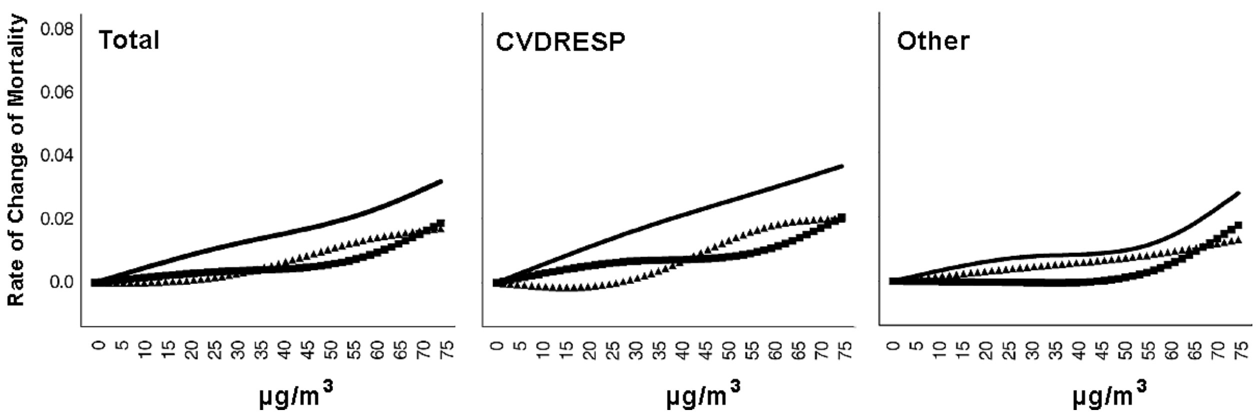

Figure 8-23. Particulate matter < 10 µm in aerodynamic diameter (PM_{10})-total mortality concentration-response curves for total (TOTAL) mortality, cardiovascular and respiratory (CVDRESP) mortality, and other causes (OTHERS) mortality, 20 largest US cities, 1987-1994. The concentration-response curves for the mean lag, current day, and previous day PM_{10} are denoted by solid lines, squared points, and triangle points, respectively.

Source: Dominici et al. (2003).

Cakmak et al. (1999) investigated methods to detect and estimate threshold levels in time-series studies. Based on the realistic range of error observed from actual Toronto pollution data (average site-to-site correlation: 0.90 for O_3; 0.76 for CoH; 0.69 for TSP; 0.59 for SO_2; 0.58 for NO_2; and 0.44 for CO), pollution levels were generated with multiplicative error for six levels of exposure error (1.0, 0.9, 0.8, 0.72, 0.6, 0.4, site-to-site correlation). Mortality series were generated with three PM_{10} threshold levels (12.8 µg/m^3, 24.6 µg/m^3, and 34.4 µg/m^3). LOESS with a 60% span was used to observe the exposure-response curves for these 18 combinations of exposure-response relationships with error. A parameter threshold model was also fit using non-linear least squares. Both mortality and PM_{10} data were pre-filtered for the influence of seasonal cycles using LOESS smooth function. The threshold regression models were then fit to the pre-filtered data. Graphical presentations indicate that LOESS adequately detects threshold under no error, but the thresholds were "smoothed out" under the extreme error scenario. Use of a parametric threshold model was adequate to give "nearly unbiased" estimates of threshold concentrations even under the conditions of extreme measurement error, but the uncertainty in the threshold estimates increased with the degree of error. They concluded, "if threshold exists, it is highly likely that standard statistical analysis can detect it."

The Smith et al. (2000) study of associations between daily total mortality and $PM_{2.5}$ and $PM_{10-2.5}$ in Phoenix, AZ (during 1995-1997) also investigated the possibility of a threshold. In the linear model, the authors found that mortality was significantly associated with $PM_{10-2.5}$, but not with $PM_{2.5}$. In modeling possible thresholds, they applied: (1) a piecewise linear model in which several possible thresholds were specified; and (2) a B-spline (spline with cubic polynomials) model with 4 knots. Using the piecewise model, there was no indication that there was a threshold for $PM_{10-2.5}$ However, for $PM_{2.5}$, the piecewise model resulted in suggestive evidence for a threshold, around 20 to 25 $\mu g/m^3$. The B-spline results also showed no evidence of threshold for $PM_{10-2.5}$, but for $PM_{2.5}$, a non-linear curve showed a change in the slope around 20 $\mu g/m^3$. A further Bayesian analysis for threshold selection suggested a clear peak in the posterior density of $PM_{2.5}$ effects around 22 $\mu g/m^3$. These results, if they in fact reflect reality, make it difficult to evaluate the relative roles of different PM components (in this case, $PM_{2.5}$ versus $PM_{10-2.5}$). However, the concentration-response curve for $PM_{2.5}$ presented in this publication suggests more of a U- or V-shaped relationship than the usual "hockey stick" relationship. Such a relationship is, unlike the temperature-mortality relationship, difficult to interpret biologically. Because the sample size of this data (3 years) is relatively small, further investigation of this issue using similar methods but a larger data set is warranted. Other studies evaluate non-linear relationships using a multi-city meta-smoothing approach based on non- or semi-parametric smoothers rather than on linear parametric models.

Smith et al. (1999) analyzed PM_{10}-mortality association in Birmingham, AL and Cook County, IL. Temperature was modeled using piece-wise linear term with a change point. PM_{10}

were modeled at lag 0 through 3 and 3-day averages at these lags. In addition to the linear model, they also investigated the existence of a threshold using B-splines and a parametric threshold model with the profile log likelihood evaluated at changing threshold points. B-splines results suggest that an increasing effect above 80μg/m^3 for Birmingham, and above 100 μg/m^3 for Chicago. The threshold model through examination of log likelihood across the range of threshold levels also suggested similar change points, but not to the extent that could achieve statistical distinctions.

In summary, the results from large multi-city studies suggest that there is no strong evidence for a threshold mortality effect of PM. Some single city studies suggest a hint of a threshold, but not in a statistically clear manner. More data may need to be examined with alternative approaches (e.g., Smith et al.'s parametric model), but meanwhile, the use of linear PM effect model appears to be appropriate.

8.4.7 Heterogeneity of Particulate Matter Effects Estimates

Approximately 35 then-available acute PM exposure community epidemiologic studies were assessed in the 1996 PM AQCD as collectively demonstrating increased risks of mortality being associated with short-term (24-h) PM exposures indexed by various ambient PM measurement indices (e.g., PM_{10}, $PM_{2.5}$, BS, CoH, sulfates, etc.) in many different cities in the United States and internationally. Much homogeneity appeared to exist across various geographic locations, with many studies suggesting, for example, increased relative risk (RR) estimates for total nonaccidental mortality on the order of 1.025 to 1.05 (or 2.5 to 5.0% excess deaths) per 50 μg/m^3 increase in 24-h PM_{10}, with statistically significant results extending more broadly in the range of 1.5 to 8.0%. The elderly $\geq$ 65 yrs. old and those with preexisting cardiopulmonary conditions had somewhat higher excess risks. One study, the Harvard Six City Study, also provided estimates of increased RR for total mortality falling in the range of 1.02 to 1.056 (2.0 to 5.6% excess deaths) per 25 μg/m^3 24-h $PM_{2.5}$ increment.

Now, more than 80 new time-series PM-mortality studies assessed earlier in this chapter provide extensive additional evidence which, qualitatively, largely substantiates significant ambient PM-mortality relationships, again based on 24-h exposures indexed by a wide variety of PM metrics in many different cities of the United States, in Canada, in Mexico, and elsewhere (in South America, Europe, Asia, etc.). The newly available effect size estimates from such studies are reasonably consistent with the ranges derived from the earlier studies reviewed in the 1996 PM AQCD. For example, newly estimated PM_{10} effects generally fall in the range of 1.0 to 8.0% excess deaths per 50 μg/m^3 PM_{10} increment in 24-h concentration; and new $PM_{2.5}$ excess estimates for short-term exposures generally fall in the range of 2 to 8% per 25 μg/m^3 increment in 24-h $PM_{2.5}$ concentration.

However, somewhat greater spatial heterogeneity appears to exist across newly reported study results, both with regard to PM-mortality and morbidity effects. The newly apparent heterogeneity of findings across locations is perhaps most notable in relation to reports based on multiple-city studies in which investigators used the same analytical strategies and models adjusted for the same or similar co-pollutants and meteorological conditions, raising the possibility of different findings reflecting real location-specific differences in exposure-response relationships rather than potential differences in models used, pollutants measured and included in the models, etc. Some examples of newly reported and well-conducted multiple-city studies include: the NMMAPS analyses of mortality and morbidity in 20 and 90 U.S. cities (Samet et al., 2000a,b; Dominici et al., 2000a); the Schwartz (2000b,c) analyses of 10 U.S. cities; the study of eight largest Canadian cities (Burnett et al., 2000); the study of hospital admissions in eight U.S. counties (Schwartz, 1999); and the APHEA studies of mortality and morbidity in several European cities (Katsouyanni et al., 1997; Zmirou et al., 1998). The recently completed large NMMAPS studies of morbidity and mortality in U.S. cities add especially useful and important information about potential U.S. within- and between-region heterogeneity.

HEI (2003a) concluded that after examining the NMMAPS GAM reanalyses by Dominici et al. (2002) that while formal tests of PM effects across cities did not indicate evidence of heterogeneity because of the individual-city effects standard error being generally large that the power to assess the presence of heterogeneity was low and, as such, the possibility of heterogeneity still exists.

8.4.7.1 Evaluation of Heterogeneity of Particulate Matter Mortality Effect Estimates

In all of the U.S. multi-city analyses, the heterogeneity in the PM estimates across cities was not explained by city-specific characteristics in the 2nd stage model. The heterogeneity of effects estimates across cities in the multi-city analyses may be due to chance alone, to mis-specification of covariate effects in small cities, or to real differences from location to location in effects of different location-specific ambient PM mixes, for which no mechanistic explanations are yet known. Or, the apparent heterogeneity may simply reflect imprecise PM effect estimates derived from smaller-sized analyses of less extensive available air pollution data or numbers of deaths in some cities mixed in with more precise (and possibly larger) effects estimates from larger-size analyses for other locations.

Some of these possibilities can be evaluated by using data from the NMMAPS study (Samet et al., 2000b). Data for excess risk and 95% confidence intervals were plotted by EPA against the total number of effective observations, measured by the number of days of PM_{10} data times the mean number of daily deaths in the community. This provides a useful measure of the weight that might be assigned to the results, since the uncertainty of the RR estimate based on a Poisson mean is roughly inversely proportional to this product. That is, the expected pattern typically shows less spread of estimated excess risk with increasing death-days of data. A more refined weight index would also include the spread in the distribution of PM concentrations. The results for NMMAPS, including the GAM reanalyses results, confirm the expected pattern. That is, the more the mortality-days observations, the narrower the 95% confidence intervals and the more precise the effects estimates.

However, the results for relationships between effect size estimates and precision estimates for different regions vary considerably. In the Northeast, for example, there is considerable homogeneity (not heterogeneity) of effect size for larger study-size cities, even with moderately wide confidence intervals for those with log mortality-days > 8 to 9, and all clearly exceed the overall nationwide grand mean. On the other hand, the smaller study-size Northeast cities (with much wider confidence intervals at log < 8) show much greater heterogeneity of effects estimates and less precision. Also, most of the estimates for larger study-size (log > 9) cities in the industrial midwest are positive and several statistically significant, so that an overall significant regional risk is plausible there as well. There may even be some tendency for relatively large risk estimates for some cities with small study sizes and wide confidence intervals in the industrial midwest, and further investigation of that would be of interest. As for the estimates derived for cities in other regions, there is much less consistency between magnitude of effect size and precision of the estimates, suggesting other factors may account for differences in direction and/or size of the risk estimates.

In fact, closer reexamination of results for each of the regions may reveal interesting new insights into what factors may account for any apparent disparities among the cities within a given region or across regions. Several possibilities readily come to mind. First, cursory inspection of the mean PM_{10} levels shown for each city in Appendix A of Samet et al., 2000b suggests that many of the cities showing low effects estimates and wide confidence intervals tend to be among those having the lowest mean PM_{10} levels and, therefore, likely the smallest range of PM_{10} values across which to distinguish any PM-related effect, if present. It may also be possible that those areas with higher $PM_{2.5}$ proportions of PM_{10} mass (i.e., larger percentages of fine particles) may show higher effects estimates (e.g., in Northeastern cities) than those with higher coarse-mode fractions (e.g., as would be more typical of Southwestern cities). Also, more industrialized cities with greater fine-particle emissions from coal combustion (e.g., in the industrial Midwest) and/or those with high fine-particle emissions from heavy motor vehicle emissions (e.g., typical of Southern California cities) may show larger PM_{10} effects estimates than other cities. Lastly, the extent of air-conditioning use may also account for some of the differences, with greater use in many Southeastern and Southwestern cities perhaps decreasing actual human exposure to ambient particles present versus higher personal exposure to ambient PM (including indoors) in those areas where less air-conditioning is used (e.g., the Northeast and industrial Midwest).

8.4.7.2 Comparison of Spatial Relationships in the NMMAPS and Cohort Reanalyses Studies

Both the NMMAPS and HEI Cohort Reanalyses studies had a sufficiently large number of U.S. cities to allow considerable resolution of regional PM effects within the "lower 48" states, but an attempt was made to take this approach to a much more detailed level in the Cohort Reanalysis studies than in NMMAPS. There were: 88 cities with PM_{10} effect size estimates in NMMAPS; 50 cities with $PM_{2.5}$ and 151 cities with sulfates in the original Pope et al. (1995) ACS analyses and in the HEI reanalyses using the original data; and 63 cities with $PM_{2..5}$ data and 144 cities with sulfate data in the additional analyses done by the HEI Cohort Reanalysis team. The relatively large number of data points utilized in the HEL reanalyses effort and additional analyses allowed estimation of surfaces for elevated long-term concentrations of $PM_{2.5}$, sulfates, and SO_2 with resolution on a scale of a few tens to hundreds of kilometers.

The patterns for $PM_{2.5}$ and sulfates are similar, but not identical. In particular, the modeled $PM_{2.5}$ surface (Krewski et al., 2000; Figure 18) had peak levels around Chicago - Gary, in the eastern Kentucky - Cleveland region, and around Birmingham AL, with elevated but lower $PM_{2.5}$ almost everywhere east of the Mississippi, as well as southern California. This is similar to the modeled sulfate surface (Krewski et al., 2000; Figure 16), with the absence of a peak in Birmingham and an emerging sulfate peak in Atlanta. The only area with markedly elevated SO_2 concentrations was the Cleveland - Pittsburgh region. Secondary sulfates in particles derived from local SO_2 appeared more likely to be important in the industrial midwest, south from the Chicago - Gary region into Ohio, northeastern Kentucky, West Virginia, and southwest Pennsylvania, possibly related to combustion of high-sulfur fuels.

The overlay of mortality with air pollution patterns is also of much interest. The spatial overlay of long-term $PM_{2.5}$ and mortality (Krewski et al., 2000; Figure 21) was highest from southern Ohio to northeastern Kentucky/West Virginia, but also included a significant association over most of the industrial midwest. This was reflected, in diminished form, by the sulfates and SO_2 maps (Krewski et al., 2000; Figures 19 and 20), where there appeared to be a somewhat tighter focus of elevated risk in the upper Ohio River Valley area. This suggests that, while SO_2 was an important precursor of sulfates in this region, there may also be some other (non-sulfur) contributors to associations between $PM_{2.5}$ and long-term mortality, encompassing a wide area of the North Central Midwest and non-coastal Mid-Atlantic region.

The apparent differences in PM_{10} and/or $PM_{2.5}$ effect sizes across different regions should not be attributed merely to possible variations in measurement error or other statistical artifact(s). Some of these differences may reflect: real regional differences in particle composition or co-pollutant mix; differences in relative human exposures to ambient particles or other gaseous pollutants; sociodemographic differences (e.g., percent of infants or elderly in regional population); or other important, as of yet unidentified PM effect modifiers.

In their reanalyses of daily mortality in eight Canadian cities, Burnett and Goldberg (2003) report positive estimates of heterogeneity of particulate effects across cities using LOESS, whereas negative estimates of heterogeneity were obtained using natural splines. They stated that this finding was due to the reduction in effect estimate using natural splines that resulted in smaller observed variation in effect estimates across cities in addition to the increased within-city estimate error compared to models using LOESS for time and weather. However, Burnett and Goldberg (2003) ultimately concluded that evidence from their study is insufficient to conclude that the PM association with mortality varies across Canadian cities.

8.4.8 Age-Related Differences in PM Effect Estimates

Numerous epidemiological studies have reported health responses to PM and other pollutants for one or another specific age group. For example, in the U.S., data on hospital admissions for older people (aged 65 years and olde) are available through a national data system maintained by the Health Care Financing Administration; and, thus, many U.S. hospital admissions studies have focused on health responses in this age group. Other studies, such as panel studies for asthma symptoms, have evaluated groups of schoolchildren. In general, such studies have indicated that both the elderly and children and are likely susceptible subpopulations for PM-related effects (see Sections 8.3.1.4 and 8.3.2.5).

Though less commonly done, possible age-related differences in ambient PM health effects have been evaluated in certain recently published epidemiological studies that assessed health responses to air pollution by means of stratified analyses for different age groups within the population studied. For example, a number of studies have assessed relationships between PM and total mortality across all ages, then evaluated possible differences in risk for the subset of older adults (50+ or 65+ years); and some of these have reported slightly larger effect estimates for the older age group (e.g., Schwartz et al., 1996; Styer et al., 1995; Borja-Aburto et al., 1998), whereas others have found associations that are similar in magnitude or even slightly smaller for the older age group (e.g., Ostro et al., 1999, 1995; Castillejos et al., 2000). Also, Chock et al. (2000) reported associations between PM and total mortality that were not substantially different for age groups of 0-74 and 75+ years.

In other studies of hospital admissions or medical visits for asthma or respiratory disease, some studies have reported larger effect estimates for children than for adults (e.g., Anderson et al., 1999; Medina et al., 1997), whereas others have reported effect estimates of generally similar size across young and adult age groups (e.g., Atkinson et al., 1999; Hajat et al., 1999; Wong et al., 1999) and some studies of respiratory hospital admissions have shown larger effect sizes for adults (e.g., Prescott et al., 1998). For hospital admissions or medical visits for cardiovascular diseases, most studies (but not all -- e.g., Atkinson et al., 1999), have reported somewhat larger effect estimate sizes for older adults (65+ years) than adults in younger age categories (e.g., Le Tertre et al., 2003; Wong et al., 1999; Prescott et al., 1998; Morgan et al., 1998).

The above rather small group of studies does not show striking differences in effect estimates from analyses across age group strata, but they do tend to support previous findings that, depending on the specific type of effect under study, older adults and children may be more susceptible to certain PM- related effects. More specifically, older adults (aged 65+ yrs) appear to be most clearly at somewhat higher risk for PM exacerbation of cardiovascular-related disease effects and , perhaps, tend to experience higher PM-related total (non-accidental) mortality risk, as well . On the other hand, more limited evidence points toward children possibly being at somewhat higher risk for respiratory-related (especially asthma) PM effects than adults.

8.4.9 New Assessments of Measurement Error Consequences

8.4.9.1 Theoretical Framework for Assessment of Measurement Error

Since the 1996 PM AQCD, advances have been made in conceptual framework development to investigate effects of measurement error on PM health effects estimated in time-series studies. Several new studies evaluate the extent of bias caused by measurement errors under scenarios with varying extent of error variance and covariance structure between co-pollutants.

Zidek et al. (1996) investigated, through simulation, the joint effects of multi-collinearity and measurement error in Poisson regression model, with two covariates with varying extent of relative errors and correlation. Their error model was of classical error form ($W = X + U$, where W and X are surrogate and true measurements, respectively, and the error U is normally distributed). The results illustrated the transfer of effects from the "causal" variable to the confounder. However, for the confounder to have larger coefficients than the true predictor, the correlation between the two covariates had to be large ($r = 0.9$), with moderate error ($\sigma > 0.5$) for the true predictor, and no error for the confounder in their scenarios. The transfer-of-causality effect was mitigated when the confounder also became subject to error. Another interesting finding that Zidek et al. reported is the behavior of the standard errors of these coefficients: when the correlation between the covariates was high ($r = 0.9$) and both covariates had no error, the standard errors for both coefficients were inflated by factor of 2; however, this phenomenon disappeared when the confounder had error. Thus, multi-collinearity influences the significance of the coefficient of the causal variable only when the confounder is accurately measured.

Marcus and Chapman (1998) also conducted a mathematical analysis of PM mortality effects in ordinary least square model (OLS) with the classical error model, under varying extent of error variance and correlation between two predictor variables. The error described here was analytical error (e.g., discrepancy between the co-located monitors). In general, they found that positive regression coefficients are only attenuated; and null predictors (zero coefficient) or weak predictors are only able to appear stronger than true positive predictors under unusual conditions: (1) true predictors must have very large positive or negative correlation (i.e., $|r| > 0.9$); (2) measurement error must be substantial (i.e., error variance ≈ signal variance); and (3) measurement errors must have a large negative correlation. They concluded that estimated FP health effects are likely underestimated, although the magnitude of bias due to the analytical measurement error is not very large.

Zeger et al. (2000) illustrated the implication of the classical error model and the Berkson error model (i.e., $X = W + U$) in the context of time-series study design. Their simulation of the classical error model with two predictors, with various combinations of error variance and correlation between the predictors/error terms, showed results similar to those reported by Zidek et al. (1996). Most notably, for the transfer of the effects of one variable to the other (i.e., error-induced confounding) to be large, the two predictors or their errors must to be substantially correlated. Also, for the spurious association of a null predictor to be more significant than the true predictor, their measurement errors have to be extremely negatively correlated—a condition not yet seen in actual air pollution data sets.

Zeger et al. (2000) also laid out a comprehensive framework for evaluating effects of exposure measurement error on estimates of air pollution mortality relative risks in time-series studies. The error, i.e., the difference between personal exposure and a central station’s measurement of ambient pollutant concentration, was decomposed into three components: (1) the error due to having aggregate rather than individual exposure; (2) the difference between the average personal exposure and the true ambient concentration level; and, (3) the difference between the true and measured ambient concentration level. By aggregating individual risks to obtain expected number of deaths, they showed that the first component of error (the aggregate rather than individual) is a Berkson error, and, therefore is not a significant contributor to bias in the estimated risk. The second error component is a classical error and can introduce bias if there are short-term associations between indoor source contributions and ambient concentration levels. Recent analysis, however, both using experimental data (Mage et al., 1999; Wilson et al., 2000) and theoretical interpretations and models (Ott et al., 2000) indicate that there is no relationship between the ambient concentration and the nonambient components of personal exposure to PM. Still, a bias could arise due to the difference between the personal exposure to ambient PM (indoors plus outdoors) and the ambient concentration. The third error component is the difference between the true and the measured ambient concentration. According to Zeger et al. the final term is largely of the Berkson type if the average of the available monitors is an unbiased estimate of the true spatially averaged ambient level.

Using this framework, Zeger et al. (2000) then used PTEAM Riverside, CA data to estimate the second error component and its influence on estimated risks. The correlation coefficient between the error (the average population PM_{10} total exposure minus the ambient PM_{10} concentration) and the ambient PM_{10} concentration was estimated to be −0.63. Since this correlation is negative, the $\hat{\beta}_z$ (the estimated value of the pollution-mortality relative risk in the regression of mortality on z_t, the daily ambient concentration) will tend to underestimate the coefficient $\hat{\beta}_x$ that would be obtained in the regression of mortality on $\bar{x}_t$, the daily average total personal exposure, in a single-pollutant analysis. Zeger et al. (2000) then proceeded to assess the size of the bias that will result from this exposure misclassification, using daily ambient concentration, z_t. As shown in Equation 9, the daily average total personal exposure, $\bar{x}_t$, can be separated into a variable component, $\theta_1 z_t$, dependent on the daily ambient concentration, z_t, and a constant component, θ_o, independent of the ambient concentration:

$$\bar{x}_t = \theta_0 + \theta_1 Z_t + \varepsilon_t \qquad (8\text{-}5)$$

where ϵ_t is an error term.

If the nonambient component of the total personal exposure is independent of the ambient concentration, as appears to be the case, Equation 9 from Zeger et al. (2000) becomes the regression analysis equation familiar to exposure analysts (Dockery and Spengler, 1981; Ott et al., 2000; Wilson et al., 2000). In this case, θ_0 gives the average nonambient component of the total personal exposure and θ_1 gives the ratio of the ambient component of personal exposure to the ambient concentration. (The ambient component of personal exposure includes exposure to ambient PM while outdoors and, while indoors, exposure to ambient PM that has infiltrated indoors.) In this well-known approach to adjust for exposure measurement error, called regression calibration (Carroll et al., 1995), the estimate of β_x has the simple form $\hat{\beta}_x = \hat{\beta}_z / \hat{\theta}_1$. Thus, for the regression calibration, the value of β_x (based on the total personal exposure) does not depend on the total personal exposure but is given by β_z, based on the ambient concentration, times θ_1, the ratio of the ambient component of personal exposure to the ambient concentration. A regression analysis of the PTEAM data gave an estimate $\theta_1 = 0.60$.

Zeger et al. (2000) used Equation 9, with $\hat{\theta}_o = 59.95$ and $\theta_1 = 0.60$, estimated from the PTEAM data, to simulate values of daily average personal exposure, x^*_t, from the ambient concentrations, z_t, for PM_{10} in Riverside, CA, 1987-1994. They then compared the mean of the simulated $\hat{\beta}_x$ s, obtained by the series of log-linear regressions of mortality on the simulated x^*_t, with the normal approximation of the likelihood function for the coefficient $\hat{\beta}_z$ from the log-linear regression of mortality directly on z_t. The resulting $\hat{\beta}_z / \hat{\beta}_x = 0.59$ is very close to θ1 = 0.60. Dominici et al. (2000b) provide a more complete analysis of the bias in $\hat{\beta}_z$ as an estimate of β_x using the PTEAM Study and four other data sets and a more complete statistical model. Their findings were qualitatively similar in that was close to $/\theta_1$. Thus, it appears that the bias is very close to θ_1, which depends not on the total personal exposure but only on the ratio of the ambient component of personal exposure to the ambient concentration.

Zeger et al. (2000), in the analyses described above, also suggested that the error due to the difference between the average personal exposure and the ambient level (the second error type described above) is likely the largest source of bias in estimated relative risk. This suggestion at least partly comes from the comparison of PTEAM data and site-to-site correlation (the third type of error described above) for PM_{10} and O_3 in 8 US cities. While PM_{10} and O_3 both showed relatively high site-to-site correlation (≈ 0.6-0.9), a similar extent of site-to-site correlation for other pollutants is not necessarily expected. Ito et al. (2000) estimated site-to-site correlations (after adjusting for seasonal cycles) for PM_{10}, O_3, SO_2, NO_2, CO, temperature, dewpoint temperature, and relative humidity, using multiple stations' data from seven central and eastern states (IL, IN, MI, OH, PA, WV, WI), and found that, in a geographic scale of less 100 miles, these variables could be categorized into three groups in terms of the extent of correlation:

weather variables (r > 0.9); O_3, PM_{10}, NO_2 (r: 0.6-0.8); CO and SO_2 (r < 0.5). These results suggest that the contribution from the third component of error, as described in Zeger et al. (2000), would vary among pollution and weather variables. Furthermore, the contribution from the second component of error would also vary among pollutants; i.e., the ratio of ambient exposure to ambient concentration, called the attenuation coefficient, is expected to be different for each pollutant. Some of the ongoing studies are expected to shed some light on this issue. However, more information is needed on attenuation coefficients for a variety of pollutants.

With regard to the PM exposure, longitudinal studies (Wallace, 2000; Mage et al., 1999), show reasonably good correlation (r = 0.6 to 0.9) between ambient PM concentrations and average population PM exposure, lending support for the use of ambient data as a surrogate for personal exposure to ambient PM in time-series mortality or morbidity studies. Furthermore, fine particles are expected to show even better site-to-site correlation than PM_{10}. Wilson and Suh (1997) examined site-to-site correlation of PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$ in Philadelphia and St. Louis, and found that site-to-site correlations were high ($r \approx 0.9$) for $PM_{2.5}$ but low for $PM_{10-2.5}$ ($r \approx 0.4$), indicating that fine particles have smaller errors in representing community-wide exposures. This finding supports Lipfert and Wyzga's (1997) speculation that the stronger mortality associations for fine particles than coarse particles found in the Schwartz et al. (1996a) study may be due in part to larger measurement error for coarse particles.

However, as Lipfert and Wyzga (1997) suggested, the issue is not whether the fine particle association with mortality is a "false positive", but rather, whether the weaker mortality association with coarse particles is a "false negative." Carrothers and Evans (2000) also investigated the joint effects of correlation and relative error, but they specifically addressed the issue of fine (FP) versus coarse particle (CP) effect, by assuming three levels of relative toxicity of fine versus coarse particles (β_{FP} / β_{CP} = 1, 3, and 10) and, then, evaluating the bias, (B = $\{E[\beta_{F'}]/ E[\beta_{C'}]\} / \{\beta_F / \beta_C\}$, as a function of FP-CP correlation and relative error associated with FP and CP. Their results indicate: (1) if the FP and CP have the same toxicity, there is no bias (i.e., B=1) as long as FP and CP are measured with equal precision, but, if, for example, FP is measured more precisely than CP, then FP will appear to be more toxic than CP (i.e., B > 1); (2) when FP is more toxic than CP (i.e., β_{FP}/β_{CP} = 3 and 10), however, the equal precision of FP and CP results in downward bias of FP (B < 1), implying a relative overestimation of the less toxic CP. That is, to achieve non-bias, FP must be measured more precisely than CP, even more so as the correlation between FP and CP increases. They also applied this model to real data from the Harvard Six Cities Study, in particular, the data from Boston and Knoxville. Estimation of spatial variability for Boston was based on external data and a range of spatial variability for Knoxville (since there was no spatial data available for this city). For Boston, where the estimated FP-CP correlation was low (r = 0.28), estimated error was smaller for FP than for CP (0.85 versus 0.65, as correlation between true versus error-added series), and the observed FP to CP coefficient ratio was high (11), the calculated FP to CP coefficient ratio was even larger (26)-thus providing evidence against the hypothesis that FP is absorbing some of the coefficient of CP. For Knoxville, where FP-CP correlation was moderate (0.54), the error for FP was smaller than for CP (0.9 versus 0.75), and the observed FP to CP coefficient ratio was 1.4, the calculated true FP to CP coefficient ratio was smaller (0.9) than the observed value, indicating that the coefficient was overestimated for the better-measured FP, while the coefficient was underestimated for the worse-measured CP. Since the amount (and the direction) of bias depended on several variables (i.e., correlation between FP and CP; the relative error for FP and CP; and, the underlying true ratio of the FP toxicity to CP toxicity), the authors concluded "...for instance, it is inadequate to state that differences in measurement error among fine and coarse particles will lead to false negative findings for coarse particles".

Fung and Krewski (1999) conducted a simulation study of measurement error adjustment methods for Poisson models, using scenarios similar to those used in the simulation studies that investigated implication of joint effects of correlated covariates with measurement error. The measurement error adjustment methods employed were the Regression Calibration (RCAL) method (Carroll et al., 1995) and the Simulation Extrapolation (SIMEX) method (Cook and Stefanski, 1994). Briefly, RCAL algorithm consists of: (1) estimation of the regression of X on W (observed version of X, with error) and Z (covariate without error); (2) replacement of X by its estimate from (1), and conducting the standard analysis (i.e., regression); and (3) adjustment of the resulting standard error of coefficient to account for the calibration modeling. SIMEX algorithm consists of: (1) addition of successively larger amount of error to the original data; (2) obtaining naive regression coefficients for each of the error added data sets; and, (3) back extrapolation of the obtained coefficients to the error-free case using a quadratic or other function. Fung and Krewski examined the cases for: (1) $\beta_X = 0.25$; $\beta_Z = 0.25$; (2) $\beta_X = 0.0$; $\beta_Z = 0.25$; (3) $\beta_X = 0.25$; $\beta_Z = 0.0$., all with varying level of correlation (-0.8 to 0.8) with and without classical additive error, and also considering Berkson type error. The behaviors of naive estimates were essentially similar to other simulation studies. In most cases with the classical error, RCAL performed better than SIMEX (which performed comparably when X-Z correlation was small), recovering underlying coefficients. In the presence of Berkson type error, however, even RCAL did not recover the underlying coefficients when X-Z correlation was large (> 0.5). This is the first study to examine the performance of available error adjustment methods that can be applied to time-series Poisson regression. The authors recommend RCAL over SIMEX. Possible reasons why RCAL performed better than SIMEX in these scenarios were not discussed, nor are they clear from the information given in the publication. There has not been a study to apply these error adjustment methods in real time-series health effects studies. These methodologies require either replicate measurements or some knowledge on the nature of error (i.e., distributional properties, correlation, etc.). Since the information regarding the nature of error is still being collected at this time, it may take some time before applications of these methods become practical.

Another issue that measurement error may affect is the detection of threshold in time-series studies. Lipfert and Wyzga (1996) suggested that measurement error may obscure the true shape of the exposure-response curve, and that such error could make the exposure-response curve to appear linear even when a threshold may exist. However, based on a simulation with realistic range of exposure error (due to site-to-site correlation), Cakmak et al. (1999) illustrated that the modern smoothing approach, LOESS, can adequately detect threshold levels (12.8 μg/m^3, 24.6 μg/m^3, and 34.4 μg/m^3) even with the presence of exposure error.

Other issues related to exposure error that have not been investigated include potential differential error among subpopulations. If the exposure errors are different between susceptible population groups (e.g., people with COPD) and the rest of the population, the estimation of bias may need to take such differences into account. Also, the exposure errors may vary from season to season, due to seasonal differences in the use of indoor emission sources and air exchange rates due to air conditioning and heating. This may possibly explain reported season-specific effects of PM and other pollutants. Such season-specific contributions of errors from indoor and outdoor sources are also expected to be different from pollutant to pollutant.

In summary, the studies that examined joint effects of correlation and error suggest that PM effects are likely underestimated, and that spurious PM effects (i.e., qualitative bias such as change in the sign of coefficient) due to transferring of effects from other covariates require extreme conditions and are, therefore, unlikely. Also, one simulation study suggests that, under the likely range of error for PM, it is unlikely that a threshold is ignored by common smoothing methods. More data are needed to examine the exposure errors for other pollutants, since their relative error contributions will influence their relative significance in relative risk estimates.

8.4.9.2 Spatial Measurement Error Issues That May Affect the Interpretation of Multi-Pollutant Models with Gaseous Co-Pollutants

The measurement error framework put forth in Dominici et al. (2000) and Zeger et al. (2000) explicitly assumes that one of the error components has a Berkson error structure. As summarized in (Zeger et al., 2000, p. 421): "This Berkson model is appropriate when z represents a measurable factor [e.g., measured PM or another pollutant] that is shared by a group of participants whose individual [true] exposures x might vary because of time-activity patterns. For example, z might be the spatially averaged ambient level of a pollutant without major indoor sources and x might be the personal exposures that, when averaged across people, match the ambient level." This assumption is likely accurate for sulfates, less so for fine particles and for PM_{10}, and almost certainly incorrect for gases such as CO and NO_2 that may vary substantially on an intra-urban spatial scale with widely distributed local sources.

The usual characterization of longitudinal or temporal pollutant correlation may not adequately characterize the spatial variation that is the more important aspect of association in evaluating possible Berkson errors. Temporal correlation coefficients, even across large distances (e.g., Ito et al., 2001) may be a consequence of large-scale weather patterns affecting the concentrations of many pollutants. Local concentrations for some pollutants with strong local sources and low regional dispersion (especially for CO and NO_2, and $PM_{10-2.5}$ to a lesser extent) may have somewhat smaller temporal correlations and much greater relative spatial variations than PM. Thus, individuals in a large metropolitan area may have roughly similar levels of PM exposure x on any given day for which the ambient average PM concentration z is an adequate surrogate, whatever their space-time activity patterns, residence, or non-residential micro-environments, while the same individuals may be exposed to systematically higher or lower concentrations of a co-pollutant than the spatial average of the co-pollutant. This violates the basic assumption of the Berkson error model that within each stratum of the measured (spatially averaged) level z, the average value of the true concentration x is equal to z, i.e.,

$$E\left\{ x \,\middle|\, z \right\} = z, \tag{8-6}$$

where E{.} is the average or expected value over the population.

There are empirical reasons to believe that if the strata are chosen to be locations within a metropolitan area, some individuals far from local sources have consistently less exposure than the average ambient concentration (denoted p) for co-pollutants with local sources such as CO and NO_2, and $PM_{2.5}$, whose true exposure (denoted q) depends on the location of the person's residence or other micro-environment where most exposure occurs. For this group,

$$E\left\{ q \,\middle|\, p \right\} < p, \tag{8-7}$$

while others in locations near the local source (such as a busy highway) have systematically higher exposure, so that

$$E\left\{ q \,\middle|\, p \right\} > p. \tag{8-8}$$

There is a substantial and growing body of evidence that adverse health effects are associated with proximity to a major road or highway (Wjst et al., 1993; Monn et al., 2001; Roemer and Van Wijnen, 2001). As shown below, there is good reason to believe that intra-city variation (even in $PM_{2.5}$) is substantial within some U.S. cities. If we assume for the sake of argument that concentrations of PM_{10} or $PM_{2.5}$ are relatively uniformly distributed, then associations of adverse health effects with proximity to a source cannot be readily attributed to a pollutant such as PM with a uniform spatial distribution. NO_2 is a pollutant often used to illustrate the spatial non-uniformity of the gaseous co-pollutants. Figure 8-24 from Monn et al. (1997) compares the concentrations of NO_2 and PM_{10} as a function of curbside distance in a moderately busy urban street in Zurich. The PM_{10} levels decrease only slightly with increasing distance, the decrease more likely being due to decreasing coarse particle than decreasing fine particle concentrations. The NO_2 concentrations show a much stronger seasonal dependence, decreasing rapidly with increasing distance in the summer and showing little decrease with

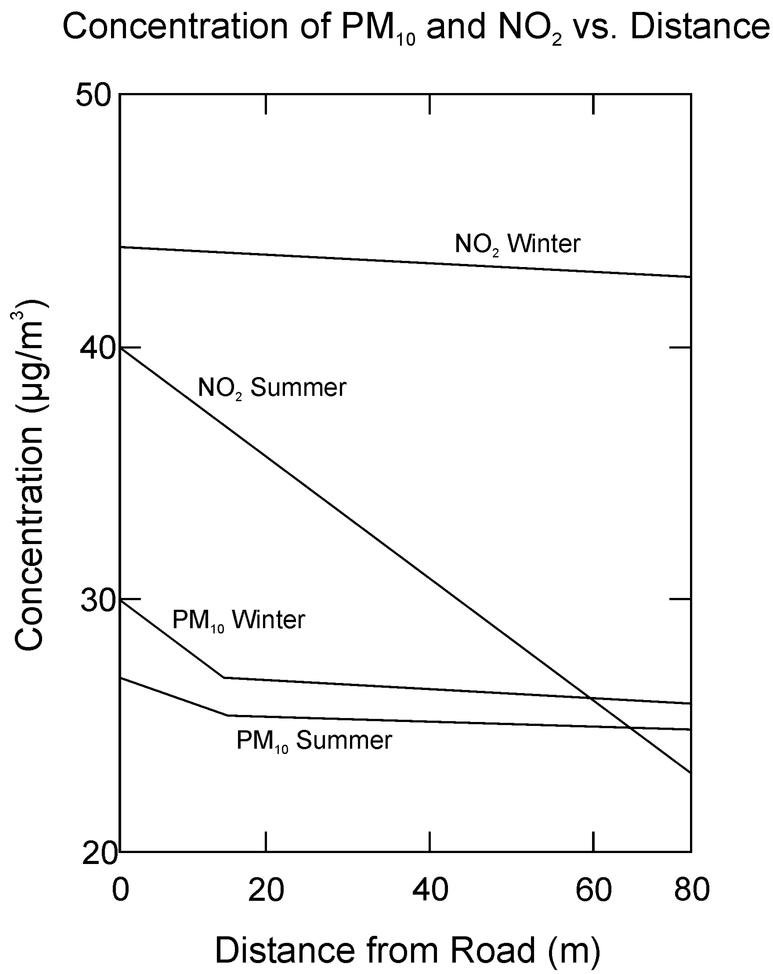

Figure 8-24. Concentration of PM_{10} and NO_2 versus distance.

Source: Monn et al. (2000).

distance in the winter. However, the belief that $PM_{2.5}$ is spatially uniform should also not be accepted uncritically, as recent analyses for 27 U.S. cities shown in Chapter 3 and Appendix 3A of this document demonstrate.

The 90th Percentile differences (P_{90}) between a pair of sites may provide a useful guide to the differences between monitor pairs (and by implication, personal exposure to fine particles) that might be reasonably expected within a metropolitan area. Shown below in Table 8-38 are the maximum, median, and minimum differences between monitor pairs, the monitor pairs at which the largest 90th percentile difference occurs (by reference to tables in Appendix 3A).

TABLE 8-38. MAXIMUM, MEAN, AND MINIMUM 90th PERCENTILE OF ABSOLUTE VALUES OF DIFFERENCES BETWEEN FINE PARTICLE CONCENTRATIONS AT PAIRS OF MONITORING SITES IN 27 METROPOLITAN AREAS IN ORDER OF DECREASING MAXIMUM DIFFERENCE

City	N Sites	Maximum (Pair)	Mean	Minimum
Pittsburgh, PA	11	21.0 (CJ)	8.4	4.2
Los Angeles, CA	6	18.2 (CF)	13.1	6.2
Seattle, WA	5	17.9 (AE)	9.8	3.6
	4 (w/o A) *	8.5 (CE)	6.8	3.6
Riverside-San Bernardino, CA	5	17.8 (BC)	12.3	6.6
Birmingham, AL	5	15.2 (AE)	10.6	6.7
St. Louis, MO	11	15.2 (AH)	6.7	2.8
Cleveland, OH	8	14.3 (BG)	8.6	3.3
Detroit, MI	10	13.8 (DI)	8.1	5
Atlanta, GA	7	13.2 (EG)	9.4	5.3
	6 (w/o G) *	10.8 (CF)	8.1	5.3
Salt Lake City, UT	6	11.4 (CF)	7.5	4.4
Gary, IN	4	11.3 (BC)	7.8	4.2
Chicago, IL	11	11.3 (EJ)	6.8	3.5
San Diego, CA	4	11.0 (CD)	9.1	6.3
Steubenville, OH	5	10.0 (BE)	7.9	6.2
Washington, DC	6	9.1 (DF)	6.6	3.5
	5 (w/o F)	7.7 (AE)	5.8	3.5
Boise, ID	4	8.8 (BD)	5.3	3.8
Philadelphia, PA	7	7.5 (BC)	6.7	3.3
Kansas City, MO	6	6.5 (CF)	4.2	1.9
Portland, OR	4	6.5 (AB)	4.8	4.1
Grand Rapids, MI	4	6.1 (BC)	4.8	3.1
Louisville, KY	4	6.0 (AC)	5.2	3.8
Dallas, TX	7	5.5 (EG)	3.4	1.9
Milwaukee, WI	8	5.0 (FH)	3.7	2.8
Tampa, FL	4	5.0 (BD)	4.1	3.1
Norfolk, VA	5	5.0 (AC)	3.6	2.6
Columbia, SC	3	3.3 (AB)	3.1	2.8
Baton Rouge, LA	3	2.9 (AC)	2.7	2.5

* Without one site > 100 km from the others.

Source: Based on Chapter 3 and Appendix 3A analyses.

TABLE 8-39. SUMMARY OF WITHIN-CITY HETEROGENEITY BY REGION

Relative Heterogeneity Among Pairs of Monitors			
Relatively Heterogenous		**Relatively Homogeneous**	
East	West	East	West
Atlanta, GA	Los Angeles, CA	Baton Rouge, LA	Boise, ID
Birmingham, AL	Riverside, CA	Columbia, SC	Portland, OR
Chicago, IL	Salt Lake City, UT	Dallas, TX	
Cleveland, OH	San Diego, CA	Grand Rapids, MI	
Detroit, MI		Kansas City, KS-MO	
Gary, IN		Milwaukee, WI	
Pittsburgh, PA		Norfolk, VA	
St. Louis, MO		Louisville, KY	
Steubenville, OH		Philadelphia, PA	
		Tampa, FL	
		Washington, DC	
	Seattle, WA (with A)		Seattle, WA (w/o A)

Based on these differences, Table 8-39 shows cities to be "relatively homogeneous" (with P90 < 10 μg/m^3) and "relatively heterogeneous" (if P90 $\geq$ 10 μg/m^3). The results in Appendix 3A and Table 8-38 show a variety of spatial patterns of association of $PM_{2.5}$ within a Metroplitan Statistical Area (MSA). There may be some discernable regional differences; but, because many major population centers are not represented in Appendix 3A, further investigation is likely warranted.

The results shown here provide clear evidence that fine particle concentrations may be less homogenous in at least some MSAs than has been previously assumed. This provides support for earlier studies using TSP and PM_{10} cited below. As noted in Chapter 3, these differences may not be strictly related to the distance between monitors, especially where topography and sources of primary PM play a role. In many eastern sites, however, particle distribution may be more substantially governed by regional rather than by local sources.

Several recent studies have examined the role of spatial siting of monitors on the estimation of PM effects. Ito et al. (1995) examined the ability of single-site versus multi-site averages to best estimate total mortality versus PM_{10} in Cook County (Chicago), IL and Los Angeles County, CA. In order to have a sufficiently large sample size to detect effects, Ito et al. used six PM_{10} sites in Cook County (Chicago), IL and four sites in Los Angeles County, CA. A sinusoidal model was used to account for temporal components, although spline or LOESS methods would now be used. Only one Cook County site had every-day PM samples, and the others as well as the Los Angeles sites had a one-in-six-day sampling schedule. The monitor sites were located in urban and suburban settings, according to the State's objectives. Three of the Los Angeles sites were located in residential areas and one was located in an area zoned for commercial use. One of the Cook County sites was classified as residential, two as commercial, and three as industrial. One of the Chicago sites was intended to monitor population exposure, three to monitor maximum concentrations, and two to monitor both maximum concentrations and personal exposure. There was considerable variation among the distribution of PM_{10} in Cook County (Chicago), IL sites, and among Los Angeles County, CA sites, especially at the upper end of the distribution. The sites were temporally correlated, 0.83 to 0.63 in Cook County, 0.9 to 0.7 in Los Angeles (except for one site pair), across distances of 4 to 26 miles. The Cook County mortality estimates were better estimated by some single-site estimates (Site 2 with everyday data, N = 1251) than by an average using all available data with missing values estimated from non-missing data (N = 1357). The every-six-day subsamples from Site 1 (N = 281) and Site 2 (lag 0, N = 246) were better predictors, and from Site 4 (N = 243) and Site 6 (N = 292) about as good predictors of mortality as the corresponding every-six-day averages (N = 351). In Los Angeles, only Site 4 (N = 349) was about as predictive as the spatial averages (N = 405).

Lipfert et al. (2000a) examined the relationship between the area in which mortality occurred among residents and the locations of monitoring sites or averages over monitoring sites for several particle size components and particle metrics. The mortality data were located for Philadelphia, PA, for three additional suburban Philadelphia counties, for Camden, NJ and other New Jersey counties in the Philadelphia – Camden MSA. A single site was used for fine and coarse particles from the Harvard School of Public Health monitors. Additional PA and NJ thoracic particle data were available for 2 to 4 stations and results averaged for at least two stations reporting data. The authors conclude that mortality in any part of the region may be associated with air pollution concentrations or average concentrations in any other part of the region, whether particles or gases. The authors suggest two interpretations: (a) the associations of mortality with pollution were random (from carrying out multiple significance tests) and not causal, or (b) both particles and gaseous pollutants have a broad regional distribution. The authors note that interpretation (b) may lead to large uncertainties in identifying which pollutant exposures for the population are primarily responsible for the observed effects. These data could be studied further to evaluate smaller-scale spatial relationships among health effects and gases.

Lippmann et al. (2000) evaluated the effects of monitor siting choice using 14 TSP monitoring stations in Detroit, MI, and nearby Windsor, ON, Canada. The stations operated from 1981-1987 with almost complete data. When a standard log-linear link Poisson regression model for mortality was fitted to TSP data for each of the 14 sites, the relative risk estimates were similar for within-site increments of 5^{th} to 95^{th} percentiles, generally highest and positive at lag day 1, but not statistically significant except for site “w” (site 12, south of the urban center of Wayne County) and nearly significant at sites “f” (west of the city of Detroit), “g” (south of the city) and “v” (suburban site in northwestern Wayne County, MI, generally “upwind” of the urban center). However, as the authors note, all of the reported relative risks are for site-specific increments, which vary by a factor of about 2.5 over the Wayne County - Windsor area. When converted to a common increment of 100 $\mu g/m^3$ TSP, the largest excess risks are found when the monitor used in the model is “f” (4.5%), “v” (4.2%), or “w” (3.8%), which also show the most significant effects among the 14 monitors. As the authors note, “. . . the distributional increments [used] to calculate relative risk tend to standardize the scale of relative risks. This actually makes sense in that if there is a concentration gradient of TSP within a city, and if the various TSP concentrations fluctuate together, then using a site with a low mean TSP for time-series analysis would result in a larger coefficient. This result does warn against extrapolating the effects from one city to an other using a raw regression coefficient [excess relative risk]”

Other recent studies also point out other aspects of intra-urban spatial variation in PM concentrations. Kinney et al. (2000) note that, in a study of personal and ambient $PM_{2.5}$ and diesel exhaust particle (DEP) exposure in a dense urban area of New York City, $PM_{2.5}$ concentrations showed only a moderate site-to-site variation (37 to 47 $\mu g/m^3$), probably due to broader regional sources of $PM_{2.5}$, whereas elemental carbon concentrations (EC) showed a four-fold range of site-to-site variations, reflecting the greater local variation in EC from DEP.

Several PM health studies for Seattle (King County), WA (e.g., Levy et al., 2001a, for out-of-hospital primary cardiac arrests) found few statistically significant relationships, attributed by the authors in part to the fact that Seattle has topographically diverse terrain with local "hot spots" of residential wood burning, especially in winter. Sheppard et al. (2001) explored reasons for these findings, particularly focusing on adjustments for location by use of a "topographic index" that includes "downstream" normal flow of wood smoke from higher elevations and trapping of wood smoke in topographic bowls or basins even at higher elevations. They also adjusted for weather using a "stagnation index" (the average number of hours per day with wind speed less than the 25th percentile of wind speeds) and temperature, as well as interaction terms for stagnation on hilltop sites and temperature at suburban wood-smoke-exposed valley sites.

The adjustments for exposure measurement error based on methods developed in Sheppard and Damian (2000) and Sheppard et al. (2001) had little effect on effect size estimates for the case-crossover study (Levy et al., 2001a), but may be useful in other studies where localized effects are believed to be important, particularly for the gaseous co-pollutants. Bateson and Schwartz (2001) note that investigators should be careful when making assumptions about the reference exposure distribution, in that the issue of comparability of the case and reference groups is a general one for case-cross over analyses.

Daniels et al. (2001) evaluated relative sources of variability or heterogeneity in PM_{10} monitoring in Pittsburgh, PA in 1996. The area is data-rich, having 25 monitors in a ~40 by 80 km rectangle. The authors found no isotropic spatial dependence after accounting for other sources of variability, but an indication of heterogeneity in the variability of the small-scale processes over time and space and heterogeneity in the mean values and covariate effects across sites. Important covariates included temperature, precipitation, wind speed and direction. The authors concluded that significant unmeasured processes might be in operation. These methods should also be useful in evaluating spatial and temporal variations in gaseous co-pollutants, where small-scale processes are important.

8.4.9.3 Measurement Error and the Assessment of Confounding by Co-Pollutants in Multi-Pollutant Models

The Zeger et al. (2000) discussion may be interpreted as addressing the extent to which the apparent lack of a $PM_{10-2.5}$ effect in models with both fine and coarse particles demonstrates a "false negative" due to larger measurement error of coarse particle concentrations. However, a more important question may involve the relative attenuation of estimated effects of $PM_{2.5}$ and gaseous co-pollutants, especially those such as CO that are known to be highly correlated with $PM_{2.5}$. Tables 1 and 2 in (Zeger et al., 2000) may be particularly relevant here. The evidence discussed in this chapter supports the hypothesis that PM has adverse health effects, but leaves open the question as to whether the co-pollutants have effects as well when their exposure is measured much less accurately than that of the PM metric. If both the PM metric and the co-pollutant have effects, Table 1 of Zeger et al. (2000) shows that the co-pollutant effect size estimate may be greatly attenuated and the PM effect size estimate much less so, depending on the magnitude of correlation between the true PM and gaseous pollutant exposures and the correlation between their measurement errors. One would expect that $PM_{2.5}$, CO, and NO_2 would often have a high positive correlation and their "exposure measurement errors" would also be positively correlated if PM and the gaseous pollutants were positively correlated due to common activity patterns, weather, and source emissions. Thus, the line with $corr(x_1,x_2) = 0.5$, $var(\delta_1) = 0.5$, $var(\delta_2) = 2$, $corr(\delta_1, \delta_2) = 0.7$ seems appropriate. This implies that the estimated effect of the more accurately measured pollutant is 64% of the true value, and that of the less accurately measured pollutant is 14% of the true value. In view of the substantially greater spatial heterogeneity of traffic-generated ambient pollutants such as CO and NO_2, and the relative (though not absolute) regional spatial uniformity of ambient $PM_{2.5}$ in some cities, but not in others, it is likely that effect size estimates in multi-pollutant models are attenuated downward to a much greater extent for the gaseous co-pollutants than for the PM metric in some cities, but not in others. This may explain part of the heterogeneity of findings for multi-pollutant models in different cities. Low effect size estimates for the gaseous co-pollutants in a multi-pollutant model should be interpreted cautiously. The representativeness of the monitoring sites for population exposure of both the particle metrics and gaseous pollutants should be evaluated as part of the interpretation of the analysis. Indices such as the maximum 90^{th} percentile of the absolute difference in concentrations between pairs of sites as well as the median cross-correlation across sites may be useful for characterizing for spatially heterogeneity of gaseous co-pollutants as well as for fine particles.

8.4.9.4 Air Pollution Exposure Proxies in Long-Term Mortality Studies

The AHSMOG Study of mortality (Abbey et al., 1999; McDonnell et al., 2000), the Harvard 6-Cities Study of mortality (Dockery et al, 1993), the ACS Study (Pope et al., 1995), and the VA/Washington Univ. Study (Lipfert et al., 2000b) together provided a major step forward in the assessment of the long-term effects of air pollution. These cohort studies responded to many of the major criticisms of the prior cross-sectional mortality studies, while largely confirming the results of those prior studies. In particular, unlike the ecological cross-sectional studies, these new cohort studies had individual-level information about the members of the study cohort, allowing the analysis to more properly control for other major factors in mortality, such as smoking and socio-economic factors.

While several of these studies made use of newly available fine particle ($PM_{2.5}$) mass data to derive useful estimates of health effects of $PM_{2.5}$ well before it was routinely measured, these studies utilized air pollution exposure information in a manner similar to past studies, i.e., the studies used central site metropolitan area (MA) spatial and time averages of air pollution exposures, rather than exposure information at the individual level. For this reason, the AHSMOG, Harvard Six-Cities, ACS, and VA/Washington Univ. studies have been term "semi-individual" cohort studies of air pollution.

The AHSMOG Study

Although this study covers a large number of years (1977-1992 in Abbey et al., 1999), it is much more limited in the availability of actually-observed versus estimated particle metrics. Prior to 1987, PM_{10} could only be estimated from TSP, not observed. Also, for more recent years, McDonnell et al. (2000) used participants who lived near an airport, so that $PM_{2.5}$, and $PM_{10-2.5}$ as the difference of PM_{10} and $PM_{2.5}$, could be estimated from airport visibility data using methods described earlier (Abbey et al., 1995b). All this adds potential measurement error to the exposure estimates.

The Veterans' Administration/Washington University Study

The air pollution concentrations for participants' counties of residence at time of enrollment were used in analyses, rather than concentrations at the 32 VA hospitals in the final study. County-wide pollution variables for five particle metrics and three gaseous pollutants were used in the study, although TSP was most often the particle metric observed for the earlier years of the study (before 1975 up to1988), which are important in assessing pollution effects for many years of exposure. However, IPMN data for fine particles and sulfates were available for ca. 1979-1983, as in the ACS study. Effects on average mortality for the intervals 1976-1981, 1982-1988, and 1989-1996 were related to multi-year particle exposures for four long intervals: < 1975, 1975-1981, 1982-1988, and 1989-1996. TSP was used in the first three exposure intervals; PM_{10} in the most recent. This study examined “concurrent” exposures (same interval as average mortality), “causal” prior exposures (exposure interval precedes mortality interval), and “non-causal” PM versus mortality associations. The mortality associations were also examined for $PM_{2.5}$, PM_{15}, and $PM_{15-2.5}$ for 1979-1981 and 1982-1984. This study uses essentially the same air pollution data as the ACS study, which should be adequate for characterizing fixed-site air pollution concentrations in the place of residence at the time of enrollment. However, if any participants moved away from the county where air pollution is measured, but were retained in the study because they continued in follow-ups at the same clinic, then use of initial residence location may not be an adequate proxy for actual exposure after initial enrollment.

Harvard Six-Cities Air Pollution Exposure Data

In the Harvard Six Cities Study, ambient concentrations of fine particles ($PM_{2.5}$), total suspended particles (TSP), sulfur dioxide (SO_2), ozone (O_3), nitrogen dioxide (NO_2), and sulfate ($SO_4^{=}$) were measured at a centrally located air monitoring station within each of six communities. Long-term mean concentrations for each pollutant were calculated for periods that were consistent among the six cities, but not across pollutants. The original epidemiologic analysis characterized ambient air quality as long-term mean concentrations of total particles (TSP) (1977-1985), inhalable and fine particles (1979-1985), sulfate particles (1979-1984), aerosol acidity (H^+) (1985–1988), sulfur dioxide (1977-1985), nitrogen dioxide (1977-1985), and ozone (1977-1985), as follows:

Particles: Mean PM concentrations were reported for four classifications of particles in each of the six cities: TSP (particles with aerodynamic diameters up to 50 μm), inhalable particles, fine particles, and sulfate particles. Values of mass for TSP and sulfate particles were determined from 24-h high-volume samplers. Inhalable particle mass was calculated from coarse and fine particle mass, which had been determined from 24-h sample pairs collected by dichotomous samplers. In these, the fine particle channel collected particles smaller than about 2.5 μm and the measurement was recorded directly as fine particle (FP) mass. The coarse particle channel collected particles 2.5 μm to 10 or 15 μm in aerodynamic diameter (the upper bound measurement depended on the inlet size used at the time).

Acidity: Aerosol acidity (H^+) was measured for about one year in each city. However, measurements were conducted in only two cities at a time. Thus, it was not possible to compare acidity for a common time period. Furthermore, the acidity data were not linked with particle data in the same city. Thus, intercity and inter-pollutant comparisons of H^+ in this study were confounded by inter-annual variability.

Gases: The gases (SO_2, NO_2, and O_3) were measured (in parts per billion) hourly by conventional continuous monitors.

ACS Study Air Pollution Exposure Data

In the ACS Study (Pope et al., 1995), two measures of particulate air pollution, fine particles, and sulfate, but no gaseous pollutants were considered. The mean concentration of sulfate air pollution by metropolitan area (MA) during 1980 was estimated using data from the EPA Aerometric Information Retrieval System (AIRS) database. These means were calculated as the averages of annual arithmetic mean 24-h sulfate values for all monitoring sites in the 151 MA's considered. The median concentration of fine particles between 1979 and 1983 was estimated from the EPA's dichotomous sampler network. These estimates of fine particle levels had been used previously in a population-based cross-sectional mortality study of 50 MA's. Gaseous co-pollutants were not considered in Pope et al's original ACS analysis.

Six-City Study and ACS Exposure Data Strengths and Weaknesses

In each of these studies, there was a single mean pollution concentration assigned for each city for each pollutant for the entire follow-up period considered. Concentrations were not broken into each year or sub-groups of years (e.g., 5 year averages), largely because data were not available in this form. This may represent a potential weakness, as a single number could not accurately account for the different exposures in different years of follow-up. It is possible, however, that the simultaneous or immediately preceding years alone might not as well represent the effects of long-term pollution exposure.

The ACS analysis also uses metropolitan area (MA) pollutant concentrations for air pollution exposure estimates, rather than individual level measurements. Thus, spatial variability in air pollution levels and potential effects of different housing infiltration rates were not addressed as potential factors in exposure variability. However, individual exposure data would be economically impractical for such large cohorts, and the use of more localized measurements (e.g., by county) might well lead to more error, due to day-to day mobility between counties by individuals (e.g., to work and back) and changes of specific residence within an MA over time. Thus, the MA average may actually be the best metric that can be developed in the absence of individual level exposure data.

Another notable weakness of the original ACS Study was that only two PM air pollution metrics were considered. Thus, this study did not consider the potentially confounding influences of gaseous air pollutants or other particle indicators.

These two studies' analyses assign the subjects' residence MA on the basis of where they were enrolled, which can lead to exposure errors if the subjects moved to another MA during the follow-up period. However, a recent reanalysis of the Six Cities Study cohort (Krewski et al., 2000) indicates that mobility in these older populations is limited, with only 18.5% leaving the original city of enrollment over subsequent decades.

The HEI Reanalysis of the ACS Study

The HEI Reanalysis of these two cohort studies (Krewski et al, 2000) confirmed the databases used in these two studies, but also developed new exposure data for the ACS Study cohort. In particular, data for the gaseous pollutants (for the year 1980) were added to the analysis. Table 8-38 displays summary data for the most recent data available for the analysis of the ACS cohort (Pope et al., 2002). The variables noted with the data source "HEI" were added to the analysis during the HEI reanalysis. These HEI results largely confirmed the original ACS analysis results for PM, but also indicated that SO_2 was also correlated with U.S. mortality.

TABLE 8-40. SUMMARY OF ACS POLLUTION INDICES: UNITS, PRIMARY SOURCES, NUMBER OF CITIES AND SUBJECTS AVAILABLE FOR ANALYSIS, AND THE MEAN LEVELS (standard deviations)

Pollutant (years of data)	Units	Sources of Data*	No. of Metro Areas	No. of Sub. (1000s)	Mean (SD)
$PM_{2.5}$ (79-83)	μg/m³	IPMN (HEI)	61	359	21.1 (4.6)
$PM_{2.5}$ (99-00)	μg/m³	AIRS (NYU)	116	500	14.0 (3.0)
$PM_{2.5}$ (ave)	μg/m³	Average of two above	51	319	17.7 (3.7)
PM_{10} (82-98)	μg/m³	AIRS (NYU)	102	415	28.8 (5.9)
PM_{15} (79-83)	μg/m³	IPMN (HEI)	63	359	40.3 (7.7)
$PM_{15-2.5}$ (79-83)	μg/m³	IPMN (HEI)	63	359	19.2 (6.1)
TSP (80-81)	μg/m³	NAD (HEI.)	156	590	68.0 (16.7)
TSP (79-83)	μg/m³	IPMN (HEI)	58	351	73.7 (14.3)
TSP (82-98)	μg/m³	AIRS (NYU)	150	573	56.7 (13.1)
SO_4 (80-81)	μg/m³	IPMN and NAD, artifact adjusted (HEI)	149	572	6.5 (2.8)
SO_4 (90)	μg/m³	NYU compilation and analysis of PM_{10} filters	53	269	6.2 (2.0)
SO_2 (80)	ppb	AIRS (HEI)	118	520	9.7 (4.9)
SO_2 (82-98)	ppb	AIRS (NYU)	126	539	6.7 (3.0)
NO_2 (80)	ppb	AIRS (HEI)	78	409	27.9 (9.2)
NO_2 (82-98)	ppb	AIRS (NYU)	101	493	21.4 (7.1)
CO (80)	ppm	AIRS (HEI)	113	519	1.7 (0.7)
CO (82-98)	ppm	AIRS (NYU)	122	536	1.1 (0.4)
O_3 (80)	ppb	AIRS (HEI)	134	569	47.9 (11.0)
O_3 (82-98)	ppb	AIRS (NYU)	119	525	45.5 (7.3)
O_3 (82-98 3rd Q.)	ppb	AIRS (NYU)	134	557	59.7 (12.8)

Source: Pope et al. (2002).

The 16-Year Follow-Up of the ACS Cohort

Table 8-40 also includes summaries of the pollutant data developed to provide exposure estimates for the latest 16-year follow-up analysis of the ACS cohort (Pope et al, 2002). These new data are similarly city-wide averages of all monitoring stations in the MA's considered, but for the entire period of follow-up (1982-1998), when possible. In addition, this new analysis has incorporated the new $PM_{2.5}$ air monitoring data collected routinely from 1999 onward. As a result, this new analysis has increased the analysis power both by extending the length of follow-p, and by adding significant new multiple and multi-year air pollution exposure data to the analysis.

8.4.10 Implications of Airborne Particle Mortality Effects

The public health burden of mortality associated with exposure to ambient PM depends not only on the increased risk of death, but also on the amount of life shortening that is attributable to those deaths. The 1996 PM AQCD concluded that confident quantitive determination of years of life lost to ambient PM exposure was not yet possible and life shortening may range from days to years (U.S. Environmental Protection Agency, 1996a). Now, some newly available analyses provide further interesting insights with regard to potential life-shortening associated with ambient PM exposures.

8.4.10.1 Short-Term Exposure and Mortality Displacement

A few studies have investigated the question of “harvesting,” a phenomenon in which a deficit in mortality occurs following days with (pollution-caused) elevated mortality, due to depletion of the susceptible population pool. This issue is very important in interpreting the public health implication of the reported short-term PM mortality effects. The 1996 PM AQCD discussed suggestive evidence observed by Spix et al. (1993) during a period when air pollution levels were relatively high. Recent studies, however, generally used data from areas with lower, non-episodic pollution levels.

Schwartz (2000c; reanalysis 2003) separated time-series air pollution, weather, and mortality data from Boston, MA, into three components: (1) seasonal and longer fluctuations; (2) “intermediate” fluctuations; (3) “short-term” fluctuations. By varying the cut-off between the intermediate and short term, evidence of harvesting was sought. The idea is, for example, if the extent of harvesting were a matter of a few days, associations between weekly average values of mortality and air pollution (controlling for seasonal cycles) would not be seen. Schwartz’s reanalysis using natural splines reported reductions in COPD mortality $PM_{2.5}$ risk estimates for longer time scale, suggesting that most of the COPD mortality was only displaced by a few weeks. However, for pneumonia, ischemic heart disease, and all cause mortality, the effect size increased, as longer time scales were included. For example, the percent increase in non-accidental deaths associated with a 25 μg/m^3 increase in $PM_{2.5}$ increased from 5.8% (95% CI: 4.5, 7.3) for the15-day window to 9.7% (95% CI: 8.2, 11.2) for the 60-day window. Note, however, that the 60-day time scale window is in the range of influenza epidemics. Some caution is therefore needed in interpreting risk estimates in this range.

Zanobetti et al. (2000b) used what they termed "generalized additive distributed lag models" (penalized splines using algorithm that did not require back-fitting were used for all the smoothing terms) to help quantify mortality displacement in Milan, Italy, 1980-1989. Non-accidental total deaths were regressed on smooth functions of TSP distributed over the same day and the previous 45 days using penalized splines for the smooth terms and seasonal cycles, temperature, humidity, day-of-week, holidays, and influenza epidemics. The mortality displacement was modeled as the initial positive increase, negative rebound (due to depletion), followed by another positive coefficients period, and the sum of the three phases were considered as the total cumulative effect. TSP was positively associated with mortality up to 13 days, followed by nearly zero coefficients between 14 and 20 days, and then followed by smaller but positive coefficients up to the 45 th day (maximum examined). The sum of these coefficients was over three times larger than that for the single-day estimate.

Zanobetti et al. (2001; reanalysis by Zanobetti and Schwartz, 2003) also applied the same concept described above (up to 41 lag days) to 10 cities from APHEA2 to estimate distributed lag PM_{10} mortality risks. They applied the covariate adjustment in a GAM model used in APHEA2 (Katsouyanni et al., 2001); and in reanalysis (Zanobetti and Schwartz, 2003), they also used penalized splines in addition to the GAM model with stringent convergence criteria. The resulting city specific coefficients were pooled in the second-stage model taking into account heterogeneity across cities. The estimated shape of the distributed lag pooled across 10 cities showed a similar pattern to that from Milan data described above, with the second "hump" of smaller but positive coefficients between approximately 20 to 35 days. The results indicated that, compared to PM_{10} risk estimates obtained for the average of lag 0 and 1 days, the distributed lag estimates up to 40 days were about twice larger in both GAM and penalized splines models. For example, the combined distributed lag estimates for the 10 cities using penalized splines was 5.6% (95% CI: 1.5, 9.8), as compared to 2.9% (95% CI: 1.4, 4.4). It should be noted, however, that the results for individual cities varied. For example, the estimates for average of lag 0 and 1 days and the distributed lag model were comparable in Tel

Aviv, whereas it was nearly seven times bigger for distributed lag model in Lodz. Thus, while these results do support the lack of mortality displacement up to 40-45 day period, the pattern of lagged associations may vary from city to city.

Smith et al. (1999), as part of their analysis of PM_{10}-mortality association in Birmingham, AL and Cook County, IL, also examined the existence of mortality displacement. Their model attempted to estimate the size of the frail population and the number of migrants into the frail population. PM_{10} was modeled to affect both the entry into the frail population and death. The latent variable structure was fitted through Bayesian techniques using Monte Carlo sampling. The resulting posterior mean for the frail population in Chicago was 765 (posterior s.d. = 189). The mean numbers of days lost as a result of 10 $\mu g/m^3$ increase in PM_{10} was estimated to be 0.079 day (posterior s.d. = 0.032). These results indicate that the frail population is small and therefore has short lifetime (less than 10 days) in that state. Consequently, the impact of PM (life shortening) had to be small. These results are not consistent with those suggested by Zanobetti or Schwartz studies described above.

Murray and Nelson (2000) used Kalman filtering to estimate hazard function of TSP in a state space model in the Philadelphia mortality data during 1973-1990. The model framework, which assumes harvesting effect, allows estimation of at-risk population and the effect of changes in air quality on the life expectancy of the at-risk population. The model was first verified by simulation. Combinations of TSP, linear temperature, squared temperature, and interaction of TSP and temperature were considered in six models. The size of at-risk (or frail) population estimated was about 500 people, with its life expectancy between 11.8 to 14.3 days, suggesting that the hazard causing agent making the difference of 2.5 days in the at-risk population. These results are, taking into account the difference in population size between Philadelphia and Cook County, comparable with those obtained by Smith et al. described above. In both cases, the size of the frail population is small with short lifetime such that life-shortening by PM or any external stress for the frail population could not be long (more than a few days). These results are, again, in contrast to the results from the Zanobetti or Schwartz studies above or a frequency domain approach described below.

Zeger et al. (1999) first illustrated, through simulation, the implication of harvesting for PM regression coefficients (i.e., mortality relative risk) as observed in frequency domain. Three levels of harvesting (3 days, 30 days, and 300 days) were simulated. As expected, the shorter the harvesting, the larger the PM coefficient in the higher frequency range. However, in the analysis (and reanalysis by Dominici et al., 2003) of real data from Philadelphia, regression coefficients increased toward the lower frequency range, suggesting that the extent of harvesting, if it exists, is not in the short-term range. Zeger suggested that "harvesting-resistant" regression coefficients could be obtained by excluding coefficients in the very high frequency range (to eliminate short-term harvesting) and in the very low frequency range (to eliminate seasonal confounding). Since the observed frequency domain coefficients in the very high frequency range were smaller than those in the mid frequency range, eliminating the "short-term harvesting" effects would only increase the average of those coefficients in the rest of the frequency range.

Frequency domain analyses are rarely performed in air pollution health effects studies, except perhaps the spectral analysis (variance decomposition by frequency) to identify seasonal cycles. Examinations of the correlation by frequency (*coherence*) and the regression coefficients by frequency (*gain*) may be useful in evaluating the potentially frequency-dependent relationships among multiple time series. A few past examples in air pollution health effects studies include: (1) Shumway et al.'s (1983) analysis of London mortality analysis, in which they observed that significant coherence occurred beyond two week periodicity (they interpreted this as "pollution has to persist to affect mortality"); (2) Shumway et al.'s (1988) analysis of Los Angeles mortality data, in which they also found larger coherence in the lower frequency; (3) Ito's (1990) analysis of London mortality data in which he observed relatively constant gain (regression coefficient) for pollutants across the frequency range, except the annual cycle. These results also suggest that associations and effect size, at least, are not concentrated in the very high frequency range.

Schwartz (2000c), Zanobetti et al. (2000b), Zanobetti et al., (2001); reanalysis by Zanobetti and Schwartz, (2003) and Zeger et al.'s analysis (1999); reanalysis by Dominici et al., (2003) all suggest that the extent of harvesting, if any, is not a matter of only a few days. Other past studies that used frequency domain analyses are also at least qualitatively in agreement with the evidence against the short-term only harvesting. Since long wave cycles (> 6 months) need to be controlled in time-series analyses to avoid seasonal confounding, the extent of harvesting beyond 6 months periodicity is not possible in time-series study design. Also, influenza epidemics can possibly confound the PM-mortality associations in the 1 to 3 month periodicity ranges. Therefore, interpreting PM risk estimates in these "intermediate" time scale also requires cautions. In contrast to Zanobetti, Schwartz and Zeger et al. studies, Smith et al. and Murray and Nelson studies suggest that the frail population is very small and its lifetime short, such that PM or any external stress cannot have more than a few days of life-shortening impacts. This may be an inherent limitation of the model itself. Thus, there appears to be consistency in results within the similar models but not across different types of models. Clearly, more research is needed in this area both in terms of development of conceptual framework that can be tested with real data, and applications of these models to more data sets. However, at least in the models that extend the common time-series modeling, there appears to be no strong evidence to suggest that PM is shortening life by only a few days.

8.4.10.2 Life-Shortening Estimates Based on Semi-Individual Cohort Study Results

Brunekreef (1997) reviewed the available evidence of the mortality effects of long-term exposure to PM air pollution and, using life table methods, derived an estimate of the reduction in life expectancy implied by those effect estimates. Based on the results of Pope et al. (1995) and Dockery et al. (1993), a relative risk of 1.1 per 10 $\mu g/m^3$ exposure over 15 years was assumed for the effect of PM air pollution on men 25-75 years of age. A 1992 life table for men in the Netherlands was developed for 10 successive five-year categories that make up the 25-75 year old age range. Life expectancy of a 25 year old was then calculated for this base case and compared with the calculated life expectancy for the PM-exposed case, in which the death rates were increased in each age group by a factor of 1.1. A difference of 1.11 years was found between the “exposed” and “clean air” cohorts’ overall life expectancy at age 25. Looked at another way, this implies that the expectation of the lifespan for persons who actually died from air pollution was reduced by more than 10 years, because they represent a small percentage of the entire cohort population. A similar calculation by the authors for the 1969-71 life table for U.S. white males yielded an even larger reduction of 1.31 years for the entire population’s life expectancy at age 25. Thus, these calculations imply that relatively small differences in long-term exposure to ambient PM can have substantial effects on life expectancy.

8.4.10.3 Potential Effects of Infant Mortality on Life-Shortening Estimates

Deaths among children can logically have the greatest influence on a population’s overall life expectancy, but the Brunekreef (1997) life table calculations did not consider any possible long-term air pollution exposure effects on the population aged < 25 years. As discussed above, some older cross-sectional studies and some of the more recent studies (Bobak and Leon, 1992; Woodruff et al., 1997; Loomis et al., 1999), but not all (Lipfert et al., 2000c), suggest that infants may be among the sub-populations notably affected by long-term PM exposure. Thus, although it is difficult to quantify, any premature mortality that may occur among children due to long-term PM exposure (as suggested by some new studies) would logically be likely to significantly increase the overall population life shortening over and above that estimated by Brunekreef (1997) for long-term PM exposure of adults aged 25 years and older.

8.5 SUMMARY OF KEY FINDINGS AND CONCLUSIONS DERIVED FROM PARTICULATE MATTER EPIDEMIOLOGY STUDIES

The most important types of additions to the database beyond that assessed in the 1996 PM AQCD, as evaluated above in this chapter, are:

(1) New multi-city studies on a variety of endpoints which provide more precise estimates of the average PM effect sizes than most smaller-scale individual city studies;

(2) More studies of various health endpoints using ambient PM_{10} and/or closely related mass concentration indices (e.g., PM_{13} and PM_7), which substantially lessen the need to rely on non-gravimetric indices (e.g., BS or CoH);

(3) New studies evaluating relationships of a variety of health endpoints to the ambient PM coarse fraction ($PM_{10-2.5}$), the ambient fine-particle fraction ($PM_{2.5}$), and even ambient ultrafine particles measures ($PM_{0.1}$ and smaller), using direct mass measurements and/or estimated from site-specific calibrations;

(4) A few new studies that evaluated the relationship of some health endpoints to ambient particle number concentrations;

(5) Many new studies which evaluated the sensitivity of estimated PM effects to the inclusion of gaseous co-pollutants in the model;

(6) Preliminary attempts to evaluate the effects of air pollutant combinations or mixtures including PM components, based on empirical combinations (e.g., factor analysis or source profiles);

(7) Numerous new studies of cardiovascular endpoints, with particular emphasis on assessment of cardiovascular risk factors as well as symptoms;

(8) Additional new studies on asthma and other respiratory conditions potentially exacerbated by PM exposure;

(9) New analyses of lung cancer associations with long-term exposures to ambient PM;

(10) New studies of infants and children as a potentially susceptible population.

It is not possible to assign any absolute measure of certainty to conclusions based on the findings of the epidemiology studies discussed in this chapter. However, these observational study findings would be further enhanced by supportive findings of causal studies from other scientific disciplines (dosimetry, toxicology, etc.), in which other factors could be eliminated or controlled, as discussed in Chapters 6 and 7. The epidemiology studies discussed in this chapter demonstrate biologically-plausible responses in humans exposed at ambient concentrations. The most salient conclusions derived from the PM epidemiology studies include:

(1) A large and reasonably convincing body of epidemiology evidence confirms earlier associations between short- and long-term ambient PM_{10} exposures (inferred from stationary air monitor measures) and mortality/morbidity effects and suggest that PM_{10} (or one or more PM_{10} components) is a probable contributing cause of adverse human health effects.

(2) There appears to be some spatial heterogeneity in city-specific excess risk estimates for the relationships between short-term ambient PM_{10} concentrations and acute health effects. The reasons for such variation in effects estimates are not well understood, but do not negate ambient PM's likely causative contribution to observed PM-mortality and/or morbidity associations in many locations. Possible factors contributing to the apparent heterogeneity include geographic differences in air pollution mixtures, composition of PM components, and personal and sociodemographic factors affecting PM exposure (such as use of air conditioners, education, and so on).

(3) A growing body of epidemiology studies confirm associations between short- and long-term ambient $PM_{2.5}$ exposures (inferred from stationary air monitor measures) and adverse health effects and suggest that $PM_{2.5}$ (or one or more $PM_{2.5}$ components) is a probable contributing cause of observed PM-associated health effects. Some new

epidemiology findings also suggest that health effects are associated with mass or number concentrations of ultrafine (nuclei-mode) particles, but not necessarily more so than for other ambient fine PM components.

15 (4) A smaller body of evidence appears to support an association between short-term ambient thoracic coarse fraction ($PM_{10-2.5}$) exposures (inferred from stationary air monitor measures) and short-term health effects in epidemiology studies. This suggests that $PM_{10-2.5}$, or some constituent component(s) of $PM_{10-2.5}$, may be a contributory cause of adverse health effects in some locations. Reasons for differences among findings on coarse-particle health effects reported for different cities are still poorly understood, but several of the locations where significant $PM_{10-2.5}$ effects have been observed (e.g., Phoenix, Mexico City, Santiago) tend to be in drier climates and may have contributions to observed effects due to higher levels of organic particles from biogenic processes (endotoxins, molds, etc.) during warm months. Other studies suggest that particles of crustal origin are generally unlikely to exert notable health effects under most ambient exposure conditions, (however, see Item 14, below). Also, in some western U.S. cities where $PM_{10-2.5}$ is a large part of PM_{10}, the relationship between hospital admissions and PM_{10} may be an indicator of response to coarse thoracic particles from wood burning.

16 (5) Long-term PM exposure durations, on the order of months to years, as well as on the order of a few days, are statistically associated with serious human health effects (indexed by mortality, hospital admissions/medical visits, etc.). More chronic PM exposures, on the order of years or decades, appear to be associated with life shortening well beyond that accounted for by the simple accumulation of the more acute effects of short-term PM exposures (on the order of a few days). Some uncertainties remain regarding the magnitude of and mechanisms underlying chronic health effects of long-term PM exposures and the relationship between chronic exposure and acute responses to short-term exposure.

17 (6) Recent investigations of the public health implications of such chronic PM exposure-mortality effect estimates were also reviewed. Life table calculations by Brunekreef (1997) found that relatively small differences in long-term exposure to airborne PM of

ambient origin can have substantial effects on life expectancy. For example, a calculation for the 1969-71 life table for U.S. white males indicated that a chronic exposure increase of 10 μg/m^3 PM was associated with a reduction of 1.31 years for the entire population's life expectancy at age 25. Also, new evidence of associations of PM exposure with infant mortality (Bobak and Leon, 1992, 1999; Woodruff et al., 1997; Loomis et al., 1999) and/or intrauterine growth retardation (Dejmek et al., 1999) and consequent increase risk for many serious health conditions associated with low birth weight, if further substantiated, would imply that life shortening in the entire population from long-term PM exposure could well be significantly larger than that estimated by Brunekreef (1997).

18 (7) Considerable coherence exists among effect size estimates for ambient PM health effects. For example, results derived from several multi-city studies, based on pooled analyses of data combined across multiple cities (thought to yield the most precise estimates of mean effect size), show the percent excess total (non-accidental) deaths estimated per 50 μg/m^3 increase in 24-h PM_{10} to be: 1.4% in the 90 largest U.S. cities with the estimate for the Northeast being the largest (approximately twice the nationwide estimate); 3.4% in 10 large U.S. cities; 3.6% in the 8 largest Canadian cities; and 3.0% in western European cities (using PM_{10} = TSP*0.55). These combined estimates are consistent with the range of PM_{10} estimates previously reported in the 1996 PM AQCD. These and excess risk estimates from many other individual-city studies, generally falling in the range of ca. 1.5 to 8.0% per 50 μg/m^3 24-h PM_{10} increment, also comport well with numerous new studies confirming increased cause-specific cardiovascular- and respiratory-related mortality. They are also coherent with larger effect sizes reported for cardiovascular and respiratory hospital admissions and visits, as would be expected for these morbidity endpoints versus those for PM_{10}-related mortality.

19 (8) Several independent panel studies (but not all) that evaluated temporal associations between PM exposures and measures of heart beat rhythm in elderly subjects provide generally consistent indications of decreased heart rate variability (HRV) being associated with ambient PM exposure (decreased HRV being an indicator of increased risk for serious cardiovascular outcomes, e.g., heart attacks). Other studies point

toward changes in blood characteristics (e.g., C-reactive protein levels) related to increased risk of ischemic heart disease also being associated with ambient PM exposures. However, these heart rhythm and blood characteristics findings should currently be viewed as providing only limited or preliminary support for PM-related cardiovascular effects.

20 (9) Notable new evidence now exists which substantiates positive associations between ambient PM concentrations and increased respiratory-related hospital admissions, emergency department, and other medical visits, particularly in relation to PM_{10} levels. Of much interest are new findings tending to implicate not only fine particle components but also coarse thoracic (e.g., $PM_{10-2.5}$) particles as likely contributing to exacerbation of asthma conditions. Also of much interest are emerging new findings indicative of likely increased occurrence of chronic bronchitis in association with (especially chronic) PM exposure. Also of particular interest are reanalyses or extensions of earlier prospective cohort studies of long-term ambient PM exposure effects which demonstrate substantial evidence for association of increased lung cancer risk with such PM exposures, especially exposure to fine PM or its subcomponents.

21 (10) One major methodological issue affecting epidemiology studies of both short-term and long-term PM exposure effects is that ambient PM of varying size ranges is typically found in association with other air pollutants, including gaseous criteria pollutants (e.g, O_3, NO_2, SO_2, CO), air toxics, and/or bioaerosols. Available statistical methods for assessing potential confounding arising from these associations may not yet be fully adequate. The inclusion of multiple pollutants often produces statistically unstable estimates. Omission of other pollutants may incorrectly attribute their independent effects to PM. Second-stage regression methods may have certain pitfalls that have not yet been fully evaluated. Much progress in sorting out relative contributions of ambient PM components versus other co-pollutants is nevertheless being made and, overall, tends to substantiate that observed PM effects are at least partly due to ambient PM acting alone or in the presence of other covarying gaseous pollutants. However, the statistical association of health effects with PM acting alone or with other pollutants should not be taken as an indicator of a lack of effect of the other pollutants. Indeed,

the effects of the other pollutants may at times be greater or less than the effects attributed to PM and may vary from place to place or from time to time.

22 (11) It is possible that differences in observed health effects will be found to depend on site-specific differences in chemical and physical composition characteristics of ambient particles and on factors affecting exposure (such as air conditioning) as well as on differences in PM mass concentration. For example, the Utah Valley study (Dockery et al., 1999; Pope et al., 1991, 1999b) showed that PM_{10} particles, known to be richer in metals during exposure periods while the steel mill was operating, were more highly associated with adverse health effects than was PM_{10} during the PM exposure reduction while the steel mill was closed. In contrast, PM_{10} or $PM_{2.5}$ was relatively higher in crustal particles during windblown dust episodes in Spokane and in three central Utah sites than at other times, but was not associated with higher total mortality. These differences require more research that may become more feasible as the $PM_{2.5}$ sampling network produces air quality data related to speciated samples.

23 (12) The above reasons suggest it is inadvisable to pool epidemiology studies at different locations, different time periods, with different population sub-groups, or different health endpoints, without assessing potential causes and the consequences of these differences. Published multi-city analyses using common data bases, measurement devices, analytical strategies, and extensive independent external review, as carried out in the APHEA and NMMAPS studies are likely to be useful. Pooled analyses of more diverse collections of independent studies of different cities, using varying methodology and/or data quality or representativeness, are likely less credible and should not, in general, be used without careful assessment of their underlying scientific comparability.

24 (13) It may be possible that different PM size components or particles with different composition or sources produce effects by different mechanisms manifested at different lags, or that different preexisting conditions may lead to different delays between exposure and effect. Thus, although maximum effect sizes for PM effects have often been reported for 0-1 day lags, evidence is also beginning to suggest that more consideration should be given to lags of several days. Also, if it is considered that all

health effects occurring at different lag days are all real effects, so that the risks for each lag day should be additive, then higher overall risks may exist that are higher than implied by maximum estimates for any particular single or two-day lags. In that case, multi-day averages or distributed lag models should be used.

25 (14) Certain classes of ambient particles may be distinctly less toxic than others and may not exert human health effects at typical ambient exposure concentrations or only under special circumstances. Coarse thoracic particles of crustal origin, for example, may be relatively non-toxic under most circumstances compared to those of combustion origin such as wood burning. However, crustal particles may be sufficiently toxic to cause human health effects under some conditions; resuspended crustal particles, for example, may carry toxic trace elements and other components from previously deposited fine PM, e.g., metals from smelters (Phoenix) or steel mills (Steubenville, Utah Valley), PAH's from automobile exhaust, or pesticides from administration to agricultural lands. Likewise, fine particles from different sources have different effect sizes. More research is needed to identify conditions under which one or another class of particles may cause little or no adverse health effects, as well as conditions under which partices may cause notable effects.

26 (15) Certain epidemiology evidence suggests that reducing ambient PM_{10} concentrations may reduce a variety of health effects on a time scale from a few days to a few months. This has been found in epidemiology studies of "natural experiments" such as in the Utah Valley, and by supporting toxicology studies using the particles from ambient community sampling filters from the Utah Valley. Recent studies in Germany and in the Czech Republic also tend to support a hypothesis that reductions in air pollution are associated with reductions in the incidence of adverse health effects.

27 (16) Studies that combine the features of cross-sectional and cohort studies provide some of the best evidence for chronic effects of PM exposure. Gauderman et al. (2000, 2002) have found significant decreases in lung function growth related to PM_{10} levels using these techniques. Other, so-called "intervention studies" or "found experimentals" also provide compelling evidence for decreases in mortality and/or morbidity being associated with marked declines in PM (and/or gases such as SO_2) as the result of interventions aimed at reducing air pollution.

1 (17) Adverse health effects in children are emerging as a more important area of concern than in the 1996 PM AQCD. Unfortunately, relatively little is known about the relationship of PM to the most serious health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions and mortality in older children).

2 (18) Little is yet known about involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life. This is an important health issue because childhood illness or death may cost a very large number of productive life-years.

3 (19) Lastly, new epidemiologic studies of ambient PM associations with increased non-hospital medical visits (physician visits) and asthma effects suggest likely much larger health impacts and costs to society due to ambient PM than just those indexed by mortality and/or hospital admissions/visits.

4

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