Assessment of Deaths Attributable to Air Pollution: Should We Use Risk Estimates based on Time Series or on Cohort Studies?

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Epidemiologic studies are crucial to the estimation of numbers of deaths attributable to air pollution. In this paper, the authors present a framework for distinguishing estimates of attributable cases based on time-series studies from those based on cohort studies, the latter being 5–10 times larger. The authors distinguish four categories of death associated with air pollution: A) air pollution increases both the risk of underlying diseases leading to frailty and the short term risk of death among the frail; B) air pollution increases the risk of chronic diseases leading to frailty but is unrelated to timing of death; C) air pollution is unrelated to risk of chronic diseases but short term exposure increases mortality among persons who are frail; and D) neither underlying chronic disease nor the event of death is related to air pollution exposure. Time-series approaches capture deaths from categories A and C, whereas cohort studies assess cases from categories A, B, and C. In addition, years of life lost can only be derived from cohort studies, where time to death is the outcome, while in time-series studies, death is a once-only event (no dimension in time). The authors conclude that time-series analyses underestimate cases of death attributable to air pollution and that assessment of the impact of air pollution on mortality should be based on cohort studies. *Am J Epidemiol* 2001;153:1050–5.

air pollution; cohort studies; mortality; risk assessment; time factors

Epidemiologic studies published in the last 10–15 years have provided strong evidence that current levels of air pollution have a negative impact on public health (1, 2). It is therefore appropriate to ask scientists to quantify this impact. In fact, many impact assessment studies have been initiated by local, national, and international organizations and agencies (3–8). The involvement of epidemiologists is crucial to adequately addressing the questions related to impact assessment (9). Epidemiology contributes to air pollution impact assessment in a number of ways: 1) selection of health outcomes (e.g., respiratory symptoms, hospital admissions, etc.) associated with air pollution relies on epidemiologic studies; 2) the population frequency of these health outcomes is based on epidemiologic data; 3) the definition of "air pollution," i.e., selection of appropriate indicators of exposure, must acknowledge the availability of epidemiologic data; 4) the exposure-response function is usually derived from epidemiologic literature; and 5) the general concept of impact assessment is an application of calculation of the population attributable risk (10).

To date, there has been no commonly agreed upon method for impact assessment, and these projects usually follow the concepts outlined in the World Bank report by Ostro (3). A recent World Health Organization project supplied further methodological details (7, 11–13). Death is of particular interest for policy-makers, and in economic valuation, mortality-related costs are usually the dominant factor by far (7). Impact assessment studies follow at least three different strategies: the exposure-response function (slope) for mortality is based on either 1) time-series studies, 2) cohort studies, or 3) an average estimate of time-series and cohort study results. However, these estimates are rather different in size, and hence the attributable numbers of deaths differ strongly across projects, calling into question the scientific credibility of these assessments.

The purpose of this paper is to provide a framework that distinguishes between the types of attributable cases related to time-series and cohort studies. We extend the discussion of time-series studies raised by McMichael et al. (14) and place it into a broader context of study design. Thus, we also contribute to the clarification of an unsettled controversy (8, 12, 14–18). First, we will discuss the conceptual differences between definitions of "death" in time-series and cohort studies. Second, we will demonstrate how these differences translate into the derivation of deaths attributable to air pollution. This should help investigators to more reliably answer the final question of impact assessment: How many deaths can be attributed to air pollution every year? Other requirements, assumptions, and uncertainties, as well as the general method of impact assessment, are discussed elsewhere (3, 7, 11, 12).

MATERIALS AND METHODS

The concept of death in time-series and cohort studies

In the field of air pollution epidemiology, nonviolent death is the key measure of interest. The probability of death increases with increasing frailty or susceptibility. The "frailty" concept (19) is useful in acknowledging that, in most cases, the probability of death is influenced not by one single factor, e.g., air pollution, but rather by a function of a whole set of underlying conditions or risk factors. For example, preexisting diseases, genetic factors, age, socioeconomic status, nutrition, and other environmental stressors may contribute to a person's frailty level.

There are two features of "death" as used as an outcome measure in epidemiology. In the first case, death is a once-only event. The occurrence of death has no dimension in time. The occurrence may be influenced by factors that act shortly before death. For example, an acute episode of pneumonia on top of underlying chronic bronchitis (an increased frailty level) may be considered the terminal cause or "exposure," leading, within a short period of time, to death. In this first case, we formally describe short term associations between exposure and death. There is evidence that the level of air pollution in the days shortly before death is associated with the probability of dying (20). In the same time domain, Schwartz has shown that not only exposure in the few days prior to death but also average concentrations across the last weeks before death are associated with the probability of the "event" (21).

In the second case, "death" is the endpoint of a person's lifetime. Instead of the event, we consider *time to death* or survival time as the outcome measure. There are a variety of well known "exposures," including morbidities, which have an impact on survival time—e.g., smoking, dietary habits, suffering due to chronic bronchitis, reduced forced vital capacity, occupational exposures, etc. In the time domain, several patterns of exposure may influence time to death, such as 1) a single exposure occurring once in the past over a short period of time (e.g., an accidental spill); 2) repeated exposures of short duration; 3) continuous exposure over a longer period of time; 4) a pattern of short term exposure just before death; or 5) a combination of all of the above. As we will show, it is useful to distinguish the first three categories of exposure, i.e., long periods of time between exposure(s) and outcome, from the fourth, in which exposure and outcome are closely related in time. The "time to death" concept may relate particularly though not exclusively to long term cumulative exposures.

Air pollution studies suggest that the greater the long term cumulative exposure to ambient air pollution, the more incidence (22) or prevalence (23) of chronic bronchitis increases and lung function deteriorates (24). Coherent with these effects on morbidity, long term air pollution levels are associated with shorter times to death (25–28).

Four categories of air pollution attributable deaths

Given these two dimensions of "death" and the two patterns of exposure (i.e., a rather short period before death, or short term exposure, versus cumulative or long term expo-

sure), four different categories of air pollution attributable deaths can be defined (table 1): A) air pollution increases both the risk of underlying diseases leading to frailty and the short term risk of death among the frail; B) air pollution increases the risk of chronic diseases leading to frailty but is unrelated to timing of death; C) air pollution is unrelated to risk of chronic diseases but short term exposure increases mortality among persons who are frail; and D) neither underlying chronic disease nor the event of death is related to exposure to air pollution.

For deaths in category A, air pollution may have played a role both in increasing the decedent's underlying susceptibility or frailty and in triggering the event. For example, patients with chronic bronchitis that has been enhanced by long term air pollution exposure may be hospitalized with an acute, air pollution-related exacerbation of their illness (29), leading to death shortly afterward.

For cases in category B, the underlying frailty is again related to (among other factors) long term air pollution, but the event or the occurrence of death itself is unrelated to the levels of air pollution shortly before death. For example, suffering from chronic bronchitis may be enhanced by long term ambient air pollution exposure (22) but the person may die of acute pneumonia acquired during a clean air period. Therefore, long term cumulative exposure to air pollution contributed to shortening of survival time, whereas air pollution during the final days of life had no further life-shortening effect.

Among deaths in category C, reduced health status or frailty is not related to air pollution, but ambient air pollution experienced before death may trigger the terminal event. For example, a person with diabetes mellitus may be susceptible to heart attacks due to long-standing coronary disease; in such a case, an air pollution episode may trigger the fatal infarction leading to hospital admission (30), arrhythmia (31), or death (21).

Finally, in category D, neither disease history nor the event of death may be related to air pollution. Thus, deaths in category D will be attributed not to air pollution but to other causes only.

Our framework makes it clear that the calculation of air pollution attributable deaths ought to include categories A, B, and C. Below we summarize the contribution of both time-series and cohort mortality studies to the derivation of air pollution attributable cases of death.

TABLE 1.   Air pollution attributable death: the four categories of cases

Category of cases	Impact of air pollution	
	Underlying frailty due to air pollution	Occurrence of death (event) triggered by air pollution
A	Yes	Yes
B	Yes	No
C	No	Yes
D	No	No

RESULTS

Air pollution attributable death in time-series studies

Time-series studies model the association between the probability of death and the level of air pollution shortly before the event. For general concepts and statistical approaches related to time-series studies, we refer the reader to the pertinent literature (32). The major characteristics of time-series studies that are relevant to this discussion are summarized in table 2. Time-series studies use counts as the outcome measure. This approach makes use of the *temporal* variability of air pollution; thus, it is in fact possible to estimate the effects of air pollution in a single city with one or more fixed-site monitors, as has been done in dozens of mortality studies (e.g., see Katsouyanni (20)). The model studies the short term relation between exposure and an event; that is, the time interval between the measure of exposure used in the statistical model and the event (death) is short. Although the vast majority of such studies have used only a few days as the time-to-event (or lag) structure, it may be feasible to consider several days or weeks as the amount of time to the event (33).

A further feature relates to the length of the relevant exposure period: In the time-series approach, "exposure duration" is "short," e.g., the mean of a day or several days or the maximum of a few weeks (21). Schwartz modeled exposure windows of up to 60 days, the results of which he called "longer term" effects (21). In our framework, these effects still fall into the category of "short term." "Exposure" cannot be years or a lifetime, as temporal variability is a key requirement in the time-series approach; the long term exposure history does not change from day to day. For example, within one city, 20-year exposure up to day t will not be different from 20-year exposure up to day $t + 1$; thus, it will not be possible to detect any association between 20-year exposure and death counts on day t as compared with death counts on day $t + 1$. Therefore, time-series studies are usually said to assess "short term" effects. However, these deaths may not be exclusively due to the effects of exposure to air pollution *shortly before death*. Some of the "air pollution victims" may have already been suffering from a disease enhanced by past cumulative exposure to air pollution, whereas among other "victims," the underlying susceptibility may not have been a consequence of air pollution. In other words, cases in both category A and category C are well captured in a time-series mortality study; thus, these cases may be considered examples of a mixture of long term and short term exposure effects (16). The lack of a distinction between categories A and C and the fussiness involved in use of the terminology "short term" and "long term" leads to much confusion and controversy (14, 16–18).

Although time-series studies cannot directly model the contribution of (short term and long term) air pollution to underlying conditions or frailty, stratification or restriction of time-series data or the application of the case-crossover design to the analysis of time-series data (34) leads to the conclusion that different underlying conditions—whatever their causes may be—influence susceptibility to short term "acute" effects of air pollution (35–38).

An important piece of information required in public health impact assessment of air pollution is years of life lost (7). In fact, the public view of environmental problems and priority-setting in policy-making may well depend on whether "pollution victims" lose years of life or only a few days or weeks of an otherwise limited lifetime. The time-series approach has inherent limitations for addressing these different outcomes. If it were true that death was advanced by only a few days among *all* "victims," lifetime lost could be indirectly addressed from time-series data through assessment of the average time between the mortality peak and the subsequent rebound ("harvesting"). However, it has been demonstrated recently that, although harvesting does exist (i.e., some air pollution-related deaths are due to harvesting among the most frail), it is neither the only explanation nor the most important explanation for the short term effects seen in time-series studies (19, 21). Harvesting may partly explain the findings, particularly for respiratory causes of death (21). On the other hand, in these same studies, increased mortality from heart attacks is not followed by a decreased probability of heart attack mortality in the immediate or distant (months) future. Thus, as Schwartz suggested, these patients might not have suffered a heart attack for quite a long time had it not been triggered by air

TABLE 2. Major design features of time-series studies and cohort studies in air pollution epidemiology

Study design issue	Time-series studies	Cohort studies
Outcome	Counts	Person-time
Exposure variance	Temporal	Spatial
Time from exposure to outcome	Short (days or weeks)	Cumulative (years, lifetime)
Duration of exposure considered	Short term	Can be long term, in the past, etc.
Frailty assessment (underlying condition)	Indirect, by restriction, stratification, case-crossover design	May be investigated as the outcome
Morbidity history of "pollution victims"	Unknown	Known
Years of life lost	Assessable only for the (short) time explained by "harvesting" (or "mortality displacement")	Measured (person-time)

pollution. The distinction between risk groups experiencing short term displacement of mortality and groups in which air pollution may trigger death much earlier than would otherwise be expected should be further addressed (39). However, years of life lost among the pool of "victims" whose deaths are not explained by short term displacement (harvesting) cannot be quantified in time-series studies.

Air pollution attributable death in cohort studies

Cohort studies model the association between an exposure and time to death (40). Thus, in cohort studies, time is the outcome measure of interest.

Regarding exposure variability, it is long term cumulative air pollution that must be heterogeneous across study participants. Thus, the cohort study design requires a setting with *spatial* variability of long term exposure. Given that ambient air pollution exposures are similar across large areas and are often measured at one or a few fixed-site monitors, multicenter approaches are required. In strong contrast to time-series studies, the impact of air pollution on time to death (survival time) cannot be assessed in one single study area.

The currently available cohort studies of air pollution (25–27) modeled the statistical association between measures of long term cumulative exposure and time to death. In comparison with time-series studies, assessment of the short term association between exposure and death in a cohort study is inefficient because of lack of statistical power. However, this design allows investigation of the associations between various kinds of repeated exposure or cumulative long term exposure and time to death. Furthermore, morbidity history and its association with air pollution can be explicitly addressed in the cohort design. For example, the effect of air pollution on the occurrence of underlying "frailty" conditions such as chronic bronchitis may be estimated in cohort studies (22). A difficulty with the cohort design relates to the potential for confounding and misclassification of retrospective exposure, which may limit the validity of results from such studies.

Given that person-time is the default outcome measure, the association between exposure and years of life lost can be derived. However, the cohort-based effect estimates capture the full amount of time lost across all three types of air pollution attributable cases (categories A, B, and C), and time lost due to short term "acute" advancement of death (categories A and C in table 1; also see figure 1) cannot be disentangled from time lost due to air pollution-enhanced chronic morbidity (category B).

Attributable number of deaths

Technically, exposure-response functions from either time-series studies or cohort studies may be applied to calculate the number of attributable cases. According to the inherent features of the two approaches, the results must be interpreted differently. First, in time-series studies, only two (A and C) of the three categories of air pollution-related cases are captured. The time-series-based attributable cases reflect those "victims" whose occurrence of death has been
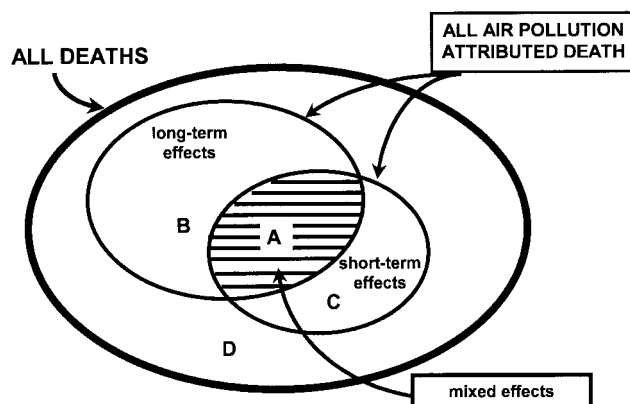

FIGURE 1. Graphic illustration of deaths due to ambient air pollution in a population, including cases related to both long term and short term air pollution. Exposure may affect the occurrence (event) of death ("short term effects") and/or increase the underlying frailty in the population ("long term effects"), leading to a shortening of lifetime. The four different types of cases, A, B, C, and D, correspond to the category definitions given in table 1. Circle sizes do not reflect relative effects. (Adapted from a report of the UK Department of Health (8)).

triggered by air pollution shortly before death. Second, among the cases in categories A and C, the degree of anticipation of death (i.e., time lost) is incompletely addressed by time-series studies, since they may only indirectly estimate *time*, namely among the fraction of cases explained by "harvesting" or short term displacement of death. Third, the time-series-based number of attributable deaths, summed across 1 year, indicates the number of subjects whose deaths have been advanced by air pollution shortly before death (8). However, it may not be correct to interpret these deaths as additional cases of death *per year*. Whether these subjects would have died during the same year or later, had air pollution levels been lower, requires knowledge about the average amount of lifetime lost across the air pollution attributable victims. As we explained above, time-series studies cannot fully address the amount of time lost. Fourth, total years of life lost, an important aspect of the public health relevance of the problem, is captured only by cohort studies, including the contribution of all three categories of air pollution attributable cases (A, B, and C). Figure 1 depicts these portions of air pollution-related cases. Fifth, cohort data have very limited power to separately assess short term effects (categories A and C). For this specific purpose, time-series analyses remain the first choice. Sixth, in contrast to time-series results, the attributable number of cases derived from person-time data (cohort estimates) can in fact be interpreted as the additional number of deaths per year (table 2). Seventh, confounding and misclassification of long term exposure may limit validity and thus may require particular attention in retrospective cohort studies.

DISCUSSION

In this paper, we have illustrated that time-series and cohort studies address different aspects of the association between air pollution and death. In terms of number of air pollution

attributable deaths, time-series-based estimates capture only two types of cases, whereas cohort-based estimates include the total number of cases. If the underlying epidemiologic studies were unbiased, we would expect time-series estimates to be smaller than cohort-based effects. In fact, this assumption corresponds to the current literature. Only under the unsupported assumption of no independent effect of cumulative long term exposure to air pollution will the slope of the two designs (and thus the attributable cases) be the same. First, "long term" effect studies suggest such effects (22–26, 41). Second, "short term" time-series studies show that increases in daily levels of air pollution may trigger heart attacks (35). If we assume that not all of these attacks are fatal, we must acknowledge that increases in daily levels of air pollution have an impact on life expectancy, since persons who have suffered heart attacks have shorter survival times.

In this paper, we have conceptually shown that time-series-based numbers of attributable cases must underestimate the total effect. However, we do not argue about the "true size" of the cohort-based effect estimates and years of life lost. We are well aware that the currently available cohort studies have limitations that must be addressed in further research. In addition, the studies do not yet provide years of life lost, only mortality rates. Thus, the derivation of years of life lost still requires assumptions and indirect estimations. This adds uncertainty to those portions of the impact assessment that rely on lifetime estimates rather than on numbers of deaths.

For example, Brunekreef applied US long term effect estimates to the Dutch life table, assuming a 10-$\mu g/m^3$ increment in exposure to particulate matter ≤ 2.5 μm in diameter (42), and he concluded that life expectancy among Dutch men might decrease by 1.11 years as a result of such exposure. In our impact assessment (7), we assumed that cases' deaths were due to cardiorespiratory disease and that these air pollution-related deaths had the same age distribution as all persons who died from cardiorespiratory diseases. Thus, the amount of time lost, per statistical victim, turned out to be 9.8 years, which corresponds to a change in life expectancy of approximately 0.6 years in the total population. The uncertainties in these estimates relate to the different approaches, underlying slopes, and populations.

The available evidence from cohort studies is based on only three studies (25–27), all of which were conducted in the United States. It is not yet clear to what extent the observed effect is influenced by differential changes in long term exposure profiles across the participating areas, erroneous retrospective exposure assignment, uncontrolled between-area confounding, interaction, and constituents of historical air pollution that may not currently be present.

To improve impact assessment and reduce interpretative uncertainties, future cohort studies could fill several gaps. New (preferably prospectively planned) cohort studies or reanalyses of published data directly assessing the impact of air pollution on time to death, including the distribution of ages at death, are to be encouraged. Such studies may even include measures of quality of life. The measurement of quality-adjusted years of life lost might yield highly valuable information for impact assessment and priority-setting in policy-making. Furthermore, cohort data may allow researchers to better address the open question of the time windows and patterns of air pollution exposure that are relevant to health. In fact, assuming the availability of long term air pollutant monitoring data, exposure may be defined for different periods of life (43) and for a variety of patterns (e.g., number of peaks, seasonal averages, cumulative exposure, etc.).

Cohort studies on morbidity and mortality due to air pollution are particularly needed in Europe, where studies have indicated that air pollution exposure is qualitatively different from that in the United States. For instance, an independent effect of particulate matter from sulfur dioxide on mortality has been shown in the United States (44) but not in Europe, where the impact of sulfur dioxide is not modified by particulate matter levels (20). Furthermore, errors in exposure assignment may be different in Europe, where air conditioning is much less prevalent. Established research populations, such as the SAPALDIA population (23, 24), participants in the European Community Respiratory Health Survey (45), and 20-year survivors of the French PAARC mortality cohort study (28), should be followed up for assessment of the environmental impact of air pollution on time to death.

Regarding short term exposure effects, future studies should address the issue of risk groups and should better describe the individual characteristics of deaths related to air pollution (46).

In summary, both types of air pollution mortality studies—the time-series approach and the cohort approach—are of value in air pollution epidemiology. However, they measure two different aspects of mortality that are not interchangeable. Whereas time-series approaches capture only cases in which death has been triggered by air pollution exposure incurred shortly before death, cohort studies capture all air pollution-related categories of death, including deaths of persons whose underlying health condition leads to premature death without being related to the level of pollution shortly before death. For these conceptual reasons, we propose that epidemiologists base attributable risk mortality calculations on cohort study estimates. However, further cohort studies, preferably prospective studies, are needed to corroborate the effect size of long term air pollution exposure on life expectancy.

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