Risk Assessment of Environmentally Influenced Airway Diseases Based on Time-Series Analysis

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Threshold values are of prime importance in providing a sound basis for public health decisions. A key issue is determining threshold or maximum exposure values for pollutants and assessing their potential health risks. Environmental epidemiology could be instrumental in assessing these levels, especially since the assessment of ambient exposures involves relatively low concentrations of pollutants. This paper presents a statistical method that allows the determination of threshold values as well as the assessment of the associated risk using a retrospective, longitudinal study design with a prospective follow-up. Morbidity data were analyzed using the Fourier method, a time-series analysis that is based on the assumption of a high temporal resolution of the data. This method eliminates time-dependent responses like temporal inhomogeneity and pseudocorrelation. The frequency of calls for respiratory distress conditions to the regional Mobile Medical Emergency Service (MMES) in the city of Leipzig were investigated. The entire population of Leipzig served as a pool for data collection. In addition to the collection of morbidity data, air pollution measurements were taken every 30 min for the entire study period using sulfur dioxide as the regional indicator variable. This approach allowed the calculation of a dose–response curve for respiratory diseases and air pollution indices in children and adults. Significantly higher morbidities were observed above a 24-hr mean value of 0.6 mg SO_2/m^3 air for children and 0.8 mg SO_2/m^3 for adults. Using the derived threshold value, the attributable risk for respiratory disease for children exposed to an increase, for example, from 0.6 to 1.2 mg SO_2/m^3 air (24-hr mean) (i.e., a doubling of the threshold level) was 30/10,000. For adults this risk was 2/10,000. *Key words*: airway diseases, epidemiology, risk assessment, threshold value, time-series analysis. *Environ Health Perspect* 103:852–856 (1995)

Much is known about the acute (*1*) and chronic respiratory health effects (*2*) associated with exposure to ambient air pollution. Studies are designed to address important issues associated with evaluating health effects of low-level exposure and actual exposure levels, while ensuring that independent effects of individual pollutants as well as their interactions in complex mixtures are detected (*3*).

The adverse effects of individual air pollutants such as total suspended particulates (TSP), total SO_4 (TSO_4), and total SO_2 (TSO_2) on lung function parameters have been investigated extensively (*4*). The results of these studies indicate that children are suffering from bronchial hyperreactivity, especially as a consequence of TSO_4. The harmful effects of PM_{10} (particulate matter < 10 μm in diameter) at levels below 150 $\mu g/m^3$ (24-hr standard mean) on the peak expiratory flow (PEF) have also been documented (*5*). The 5-day moving-average PM_{10} analysis indicated a strong association with adverse effects on PEF (*5*). These findings are supported by a reanalysis of the Steubenville, Ohio, study which evaluated the forced expiratory volume in 0.75 sec ($FEV_{0.75}$) and the forced vital capacity (FVC) (*6*).

Several studies report significant associations between air pollution and adverse health effects in susceptible individuals and groups, such as people suffering from chronic obstructive pulmonary disease (*7–10*). Many studies use hospital admissions or visits to the emergency unit with exacerbations of symptoms of respiratory illness as indicators of the health effects of pollution. Lag periods of one to several days depending on the pollution component have been observed between time of exposure and hospital admissions, visits to emergency units, or both.

All the studies cited above linked exposure [SO_2, TSO_4, SO_4, NO_x (nitrogen oxides), O_3] to adverse respiratory health effects without addressing possible threshold effects or the magnitude of change in the risk associated with concentrations of pollutants beyond this threshold value. The aim of the present investigation was to examine the quantification of risk using a dose-effect relationship assuming some of the same conditions as examined in those previouse studies (e.g., indicator component, measure of effect, lag time between exposure and effect, populations at risk).

Locality-dependent analysis of morbidity (incidence and prevalence of diseases) influenced by the environment may identify variations in the relationship between exposure and disease and may thus be relevant in assessing any increased risk. Ideally, the study group and the control group should be subject to the same environmental conditions, but should differ in the characteristic variable of the pollutant under investigation. However, in order to assess increased or decreased risk of disease due to a pollutant, the threshold limit beyond which the rate of disease increases above that occurring by chance (background frequency) must be known.

An increased risk of adverse health effects above this threshold level, measured by the frequency of visits to emergency units or hospital admissions, is assessed by comparing above-threshold days with data obtained on days when pollution levels are below the threshold. This type of analysis would not necessitate, as do classical case–control studies, an investigation of two or more population groups in which the control group is not exposed to the pollution variable under investigation. A quantitative difference in the exposure burden alone would be sufficient.

Methods

The study was conducted in Leipzig, a city of approximately 500,000 people, located in the most highly industrialized area of east Germany. The frequency of calls to the Mobile Medical Emergency Service (MMES) was investigated retrospectively for the 6-year time period of 1981–1987, with prospective follow-ups in 1988 and 1990.

Records of daily calls to the MMES for respiratory distress conditions were the basis for data collection and analysis. All reported respiratory distress conditions occurring within Leipzig were covered by the study because during the study period, the MMES was the only such service responding to medical emergency events in the city. However, the study focused only on respiratory illnesses among children and young adults. These illnesses included bronchitis, asthma, and croup.

Data from adults are presented for comparison only when appropriate. Overall, 358,000 calls to the MMES were registered and analyzed during 1981–1987. Of those,

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90,800 calls were for acute respiratory distress. On average, this amounts to 40–60 calls daily (*11*).

Relevant ambient air pollution measurements were conducted routinely during the same time span. Five monitoring stations distributed within the city limits measured SO_2 levels. SO_2 was (and still is) the indicator variable for air pollution in this region. During the winter months, domestic coal-burning heating units contributed approximately 65% of the total emissions measured within Leipzig. At times of extreme peak events (smog episodes), this could increase to 90%. Thus, these pollutants are not generated in other regions and transported but are emitted locally.

One monitoring station collected, in addition to SO_2, suspended particulates (PM_{10}) and carbon monoxide (CO). A previous investigation indicated that data collected at this particular monitoring station were representative for the yearly average conditions within Leipzig (*12*). All other monitoring stations were located in such a way to ensure that the data were representative and allow generalizations of the results for the entire city.

Measurements were taken continuously at each monitoring station. A central register collected the data automatically; each station produced 30-min mean values, for a total of 48 measurements per day. These were combined to obtain one 24-hr mean. These 24-hr mean values were then compared with the number of calls to the MMES. Figure 1 shows the SO_2 concentrations (24-hr means) for 1 year. In addition, using data from all stations, a 24-hr mean was calculated for the entire city. This value was calculated because the precise origin of the MMES calls could not be identified for each call. Therefore, an average citywide mean value was more representative for the analysis. During extreme pollution episodes (smog), the exposure measures collected at each station were virtually identical.

Time-Series Analysis

To analyze the data, the Fourier method, a time-series analysis, was applied. In using this method, two general problems have to be addressed: 1) stray data, which tend to lead to an inhomogenous data distribution and 2) pseudocorrelations, which tend to occur whenever deviations from the otherwise normal distributions of both the independent and the dependent variable temporally coincide, but actually depend on other parameters (e.g., temporality of association).

Clusters of data (temporal inhomogeneities) tend to occur whenever an increase in frequency is recorded that cannot be attributed to those external influences already under investigation, yet they coincide temporally. For example, it was noticed that the number of calls to the MMES increased on weekends or holidays, a time when the family physician was not available. For this reason and other minor incongruities, data collected on holidays were completely omitted from the analysis; Saturdays and Sundays were individually averaged according to the weekly average number of calls, Monday through Friday.

Many investigations relate the actual relevant air pollution event (smog) to the average duration of the entire event, which is actually comprised of a pre-event, actual event, and post-event time interval. First, this practice results in loss of information about the independent (air pollution) as well as the dependent variable (change in morbidity rate). Averaging any data contributes to loss of information as extreme values disappear, i.e., they are "averaged out." This will influence the outcome, especially when extreme events contribute to the effect. Second, this practice results in arbitrarily defining the length of the time intervals. Third, this practice results in effects being dependent on the length of each time interval, which may result in a shift of association between the three time intervals depending on the arbitrarily chosen duration of the total time period (i.e., the sum of the three time intervals).

This last point often makes comparison of studies impossible, as the length of the pre-event, actual event, and post-event time intervals strongly influences the remaining variance of the data. The duration of the three time intervals is essential in determining if a significant difference exists between the various time intervals (pre- or post-event, or whatever time interval is under investigation) and in relation to the independent and the dependent variable. The method applied in this study does not lend itself to such subjective manipulations.

To eliminate this time effect, all time periods for at least one variable (generally the dependent variable, i.e., changes in morbidity rate) were analyzed, using the Fourier analysis. To assess a possible association, the time-adjusted morbidity data were correlated with measures of the air pollution indicator component SO_2.

The time-adjusted morbidity, ΔM, is the difference between the raw morbidity data, $M(t)$, which were adjusted for temporal inhomogeneity, and the Fourier-analyzed morbidity data, $Mf(t)$ (Fig. 2). This means that the observed increase in the number of calls on weekends and holidays (not due to the independent variable, namely, an increase in the level of SO_2, but due to the lack of other available services)

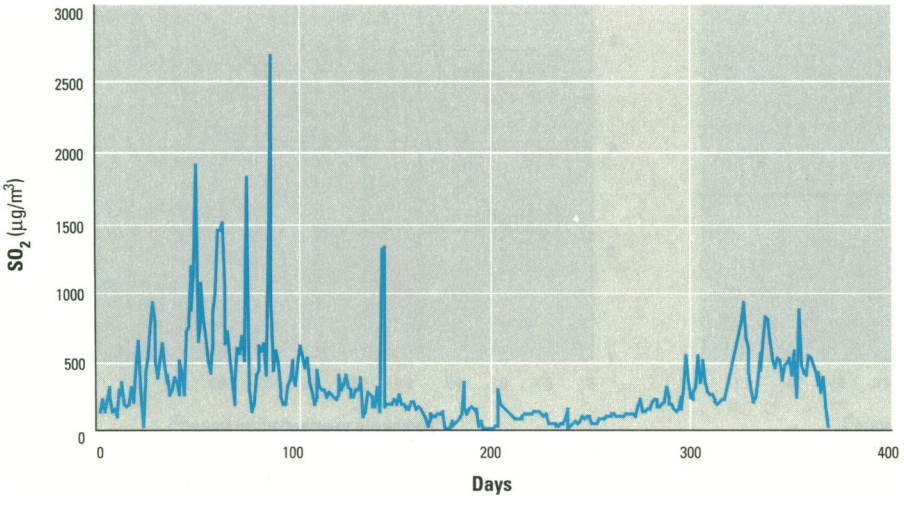

Figure 1. Daily mean sulfur dioxide levels for 1984 (24-hr averages).

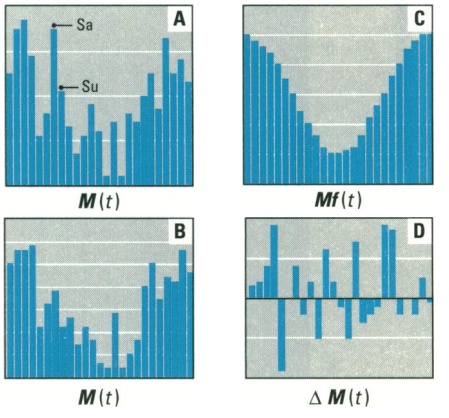

Figure 2. Controlling for temporal inhomogeneities and pseudocorrelations using morbidity measurements: (A) original data (Sa, Saturday; Su Sunday), (B) normed data, (C) Fourier-transformed data, and (D) deviation.

was adjusted by the daily average number of calls (averaged according to the weekly average number of calls). The adjustment was based on the mean of the relationship between the weekly average (Monday–Friday) and the mean value on Saturday and Sunday, respectively. Adjusting these data to the weekly average assured that extreme values remained in the data pool. This process prevents a pseudocorrelation caused by the normal, yearly temporal course of the dependent and independent variables. Using the Fourier analysis, it does not matter which of the variables, the independent, the dependent, or both, are used. In this study, the hypothesis was posed so that the Fourier analysis determined the morbidity to derive at threshold values. This requires that the data for the independent variable (pollutant concentration) are not transformed but numerically maintain their true value.

Figure 2 illustrates the different steps of the method. Figure 2A shows the raw daily morbidity data, i.e., the daily frequency of responses to calls to the MMES. Figure 2B shows the adjusted data, with weekends adjusted according to the weekly mean. The study also revealed that the frequency of calls to the MMES remained fairly constant throughout the week (Monday to Friday) with no significant difference in the frequency of calls between the different week days. Figure 2C shows the Fourier curve. Figure 2D shows the difference between the adjusted and the Fourier-analyzed data and corresponds well to the actual variance of the now time- and season-independent morbidity rate. These data were then used to determine the threshold values.

Results

Threshold Values

Pilot studies have revealed a temporal delay of human health effects associated with extreme pollution exposure levels. If these adjustments are applied to the raw morbidity data, health effects or variations in morbidity are observed 1 day (24 hr) later (*7–10,13*). This 1-day lag period is based on the assumptions that a response has to take place first and that health effects are only recorded on a 24-hr basis.

Taking this lag period into account, the exposure interval day 1 to day 14 and the effect intervals are temporally offset by 1 day, resulting in an integration interval. The observed effect is then the average deviation of the morbidity rate, calculated for the integration interval using the Fourier-transformed curve. Assuming a dose–response effect, a nonlinear dependence can be expected between frequency of morbidity and dose of exposure. This dependency is also supported by the results obtained from environmental epidemiologic studies shown in Figure 3.

The time-independent morbidity rate and exposure measurements (with SO_2 as the indicator variable) were further analyzed by calculating continuous means. For example, for every 2 days, means were calculated by averaging the exposure measurements. These 2-day means were then sorted into a series of exposure concentration levels. Each 2-day mean was then compared with the corresponding observed 1-day delayed morbidity variation and sorted according to the 2-day-averaged concentration levels. This resulted in a table that

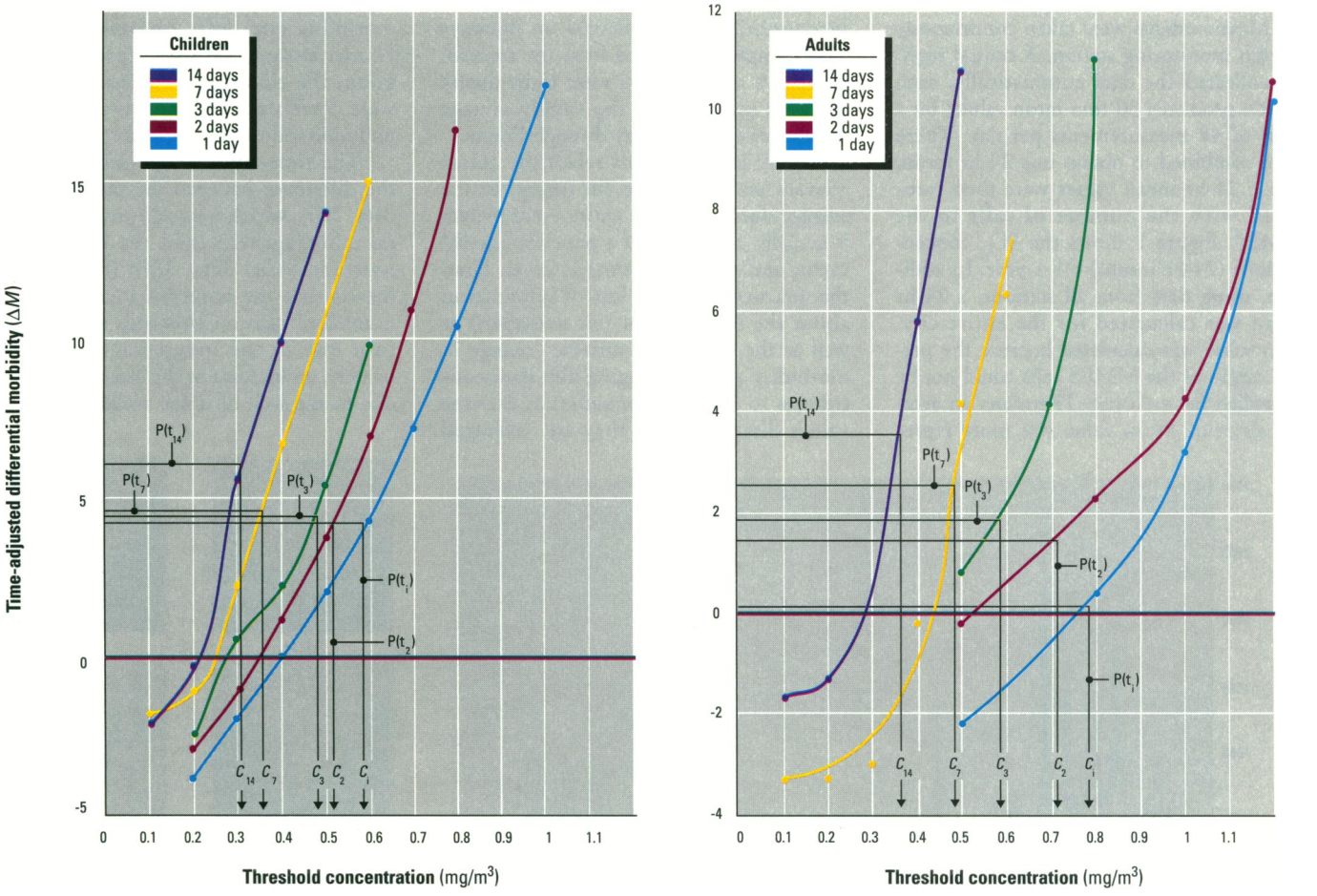

Figure 3. Derivation of threshold values (derived from the time-series analysis of time-adjusted morbidity). ΔM, time-adjusted differential morbidity [$M(t) = \Delta Mf(t) - M(t)$]; $Mf(t)$, Fourier-analyzed data; $M(t)$, raw data; $P(t_i)$, test variable for the ith integration interval; t_i, integration interval with length i; c_i, threshold concentration (if $c > c_i$ the greater the chance of increase in morbidity at exposure time $t = t_i$).

could be used to derive the (1-day delayed) morbidity rate for a specific exposure level. The same procedure was applied to the 3-day, 7-day, and 14-day averaged exposure measurements. Figure 3 illustrates this method. The expected trend is apparent: increased morbidity with increasing concentration within the same temporal integration interval and increased morbidity with increasing duration of the integration interval but constant level of exposure. Assuming a dependence between morbidity and exposure concentration allows one to derive threshold values.

Having established threshold values, one problem remains: above which point does the deviation from the mean morbidity rate become significant? To determine whether a significant deviation from the normal morbidity frequency occurred, a test variable was introduced. This test variable corresponds to the upper limit of the confidence interval of the morbidity frequency not attributable to the air pollution exposure. As the frequency of cases contributing to the estimate determines the Student's t-value, each temporal integration interval requires an individual test variable, $P(j)$:

$$P(j) = \Delta M_{\text{summer},\,j} + t_{\alpha} \cdot \delta(\Delta M_{\text{summer},\,j})/\sqrt{n}$$

where δ is the standard deviation and n is the number of variables.

Results indicate that effect-dependent threshold values for respiratory tract diseases differed in children and adults (Fig. 4). With the help of the test variable, $P(t_j)$, the exposure levels corresponding to the integration intervals were determined for the data depicted in Figure 3. Figure 4 presents the corresponding exposure concentrations and the integration intervals, which are essentially based on the exposure duration. Children were found to have an increase in morbidity at a level of 0.6 mg SO_2/m^3 air, whereas for adults this level was 0.8 mg SO_2/m3 air.

The shaded area in Figure 4 corresponds to the noncritical zone. As long as the level of exposure dependent on the duration of the exposure remains within this zone, the morbidity frequency is not expected to increase above background. However, should the concentration level measured and the duration of the exposure change and move outside this area, an increase in the morbidity of respiratory illnesses above normal background. Figure 4 also indicates that a child is more sensitive to lower concentrations of the pollutant than adults. This can be observed within all integration intervals.

Assessment of Attributable Risk

After determining threshold values, the next questions are what is the attributable risk associated with a pollution level beyond the threshold level and what increase in the burden can be expected?

Environmental epidemiologic studies always necessitate certain assumptions. The most critical assumption is associated with the confounding variables. In determining the threshold level, it was assumed that any confounding effect was virtually eliminated because the Fourier analysis rendered the morbidity time independent, particularly since cases not related to environmental effects were eliminated (e.g., respiratory distress conditions due to aspiration of foreign objects, not a negligible event in small children).

Allowing again for a lag period of 1 day and temporally adjusting the morbidity with the respective exposure measures, the number of cases were sequentially categorized according to concentration levels, for example, 0.6–0.8, 0.8–1.0, and 1.0–1.2 mg SO_2/m^3 air. Because the MMES was the only such service in Leipzig during the study period and because in case of respiratory distress the MMES was called without exception, the number of all children under 18 years of age living in Leipzig were used as a reference group. Like the frequency of calls (morbidity) among the population under investigation, the risk of respiratory disease increased above 0.6 mg SO_2/m^3 air (threshold level for children), as shown in Figure 5.

If the concentration doubles from 0.6 to 1.2 mg SO_2/m^3, respiratory diseases are increased above background to 3/10,000. It should be emphasized that this result is based on the number of all children under the age of 18 in Leipzig.

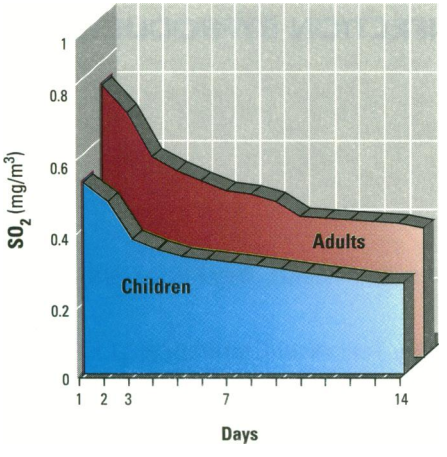

Figure 4. Dose–effect curve of respiratory illnesses for adults and children. The red and blue areas are the noncritical zones for adults and children, respectively.

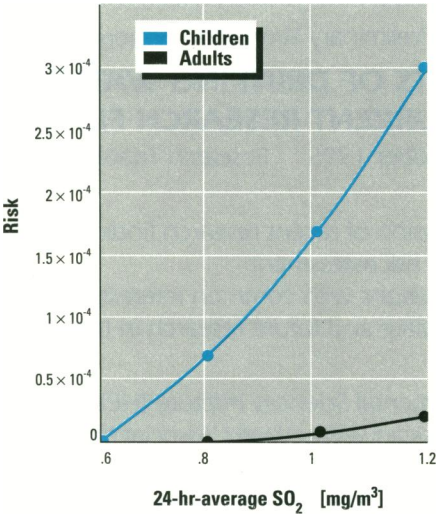

Figure 5. Attributable risk of respiratory illnesses (attributable risk indicates that risk above the expected level).

Discussion

Results of the methodology described here show that environmental epidemiologic studies can be used to quantify threshold values after controlling for confounding variables. The threshold value for excess respiratory illness among children due to environmental exposure was determined to be 0.6 mg/m^3 air (24-hr mean) for the indicator variable SO_2.

An attributable risk associated with a given change in the level of the pollution burden was estimated. The attributable increased risk associated with a doubling of the exposure burden from 0.6 to 1.2 mg SO_2/m^3 air was 3/10,000 children.

This method obviously has its limitations. For one, measuring an indicator variable precludes the determination of causality. An indicator variable does point toward an association between exposure to a pollutant and subsequent adverse respiratory health effects, but the potential of other air pollution constituents that may contribute to the same effect cannot be excluded. Nevertheless, the epidemiologic investigation presented here has the advantage that it occurs under real conditions in comparison to toxicological experiments.

Assessing threshold values and attributable risks should be considered when setting regulations. The preliminary model for smog regulation in Germany (*14*) established criteria for an early warning situation. One criterion is the presence of a low-exchange inversion weather front during which the level of SO_2 rises above 0.6 mg SO_2/m^3 (3-hr mean). Another one is that the low-exchange weather front should remain in effect for 24 hr, which virtually

establishes a 24-hr mean of 0.6 mg SO_2/m^3 air. Since this is an early warning stage, no consequences are expected. This study, however, shows that levels at and above 0.6 mg SO_2/m^3 air do indeed affect the health of susceptible population groups, such as children. Whether these levels affect only predisposed or vulnerable individuals cannot be determined with this method. Nevertheless, to prevent any undue adverse health effects among any individuals of the general population, the public should be advised that physical exertion (e.g., outdoor activities) be avoided, especially by vulnerable population groups such as children, when the early warning stage has been reached.

The purpose of this study was twofold: to investigate the methodological problem of determining threshold values and to derive at attributable risks based on environmental epidemiological studies. The results are a function of the same assumptions and limitations inherent in other studies. This also applies to problems associated with using an indicator component. Nevertheless, if the same conditions are applied as in other environmental epidemiology studies, such as correlation and regression as measures of the strength of the presumed association, identification of a temporal and spatial sequence in the relationship between the agent and morbidity, and comparability of the results with other studies, the statistical method presented here appears to be valid for determining threshold values and assessing the increased risk of respiratory tract morbidity associated with an increase in an air pollution constituent. Under these assumptions, the results show that environmental epidemiology can be used to assess a dose–response relationship and to estimate the attributable risk associated with a relative increase in the air pollution level.

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