Reanalysis of the Effects of Air Pollution on Daily Mortality in Seoul, Korea: A Case-Crossover Design

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We used the case-crossover design to identify any increase in mortality in Seoul, Korea, when there were higher levels of ambient air pollution on case-days than would be expected solely as a result of chance. This empirical study showed that either unidirectional retrospective (selecting only control days prior to death) or prospective (selecting only control days after death) control sampling could cause risk estimates to be confounded by seasonal waves as well as time trends in air pollution levels. In bidirectional control sampling in which exposures at death were compared with exposures both before and after death, the estimated mortality was resistant to confounding by time patterns of air pollution. Using a bidirectional control sampling approach, the results from a conditional logistic regression model controlling for weather conditions showed that the nonaccidental mortality associated with a 50-ppb increment over a 3-day moving average of SO_2 concentrations, including the concurrent day and preceding 2 days, was 1.023 [95% confidence interval (CI), 1.016–1.084]. The relative risk of death was 1.023 (CI, 0.999–1.048) per 50 ppb for 1-hr maximum O_3 and 1.010 (CI, 0.988–1.032) per 100 µg/m^3 or total suspended particulates. In conclusion, the findings of this study were 2-fold: given the consistency of the observed association between SO_2 and daily mortality across different analysis methods, the association reported here indicates that air pollution is a probable contributor to premature death; and bidirectional control sampling is needed in a case-crossover design applied to air pollution epidemiologic studies to control confounding by seasonal patterns of air pollution as well as time trends. *Key words*: air pollution, case–control studies, case-crossover designs, epidemiologic methods, mortality. *Environ Health Perspect* 107:633–636 (1999). [Online 25 June 1999]
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Numerous studies have observed associations between current ambient air pollution concentrations and various health outcomes, including mortality (*1–6*), hospitalization for respiratory and heart disease (*7,8*), aggravation of asthma (*9*), and incidence of respiratory symptoms and lung function (*10–12*). These recent studies evaluating the health effects of acute or short-term exposure to air pollution used contemporary time–series statistical analysis techniques or related types of analysis.

Studies in various geographic and ethnic situations have shown that the findings for each observation are consistent, which suggests a possible causal relationship between air pollution and mortality. The analytic methods used in these studies are time–series analysis or simple comparison analysis of cross-sectional data. We applied a case-crossover design, an innovative epidemio logic technique with distinct strengths, to estimate the air pollution effects on premature mortality.

The case-crossover design developed by Maclure (*13*) was applied to evaluate potential associations between ambient air pollution and mortality. This design requires no additional control subjects to be sampled and can control individual susceptibility by making comparisons within a subject (*14*). A number of alterations to the case-crossover design have been proposed, involving different strategies for selecting control information from a case (*13–16*). Mittleman et al. (*15*) described methods in which one or more control intervals (or dates) are selected at specified time lags before the event, providing analogs of one-to-one or many-to-one matched case–control studies. A recent paper by Navidi (*14*) describes a bidirectional case-crossover design in which exposures at the event of failure (death) are compared with exposures both before and after failure on the basis that subsequent exposures are not influenced by failures, as in air pollution epidemiologic studies.

In the present study we empirically illustrate how time trends (including seasonal patterns) in the levels of air pollutants can change case-crossover estimators of risk and present the results of a study comparing the bidirectional method with unidirectional case-crossover approaches. The other objective of this study was to estimate the effect of ambient air pollution on mortality, with control for weather conditions and individual susceptibility.

Materials and Methods

This study examined the daily variation in mortality in relation to ambient air pollution in Seoul, the capital city of Korea (population of approximately 12 million), over a 5-year period from 1991 through 1995. Some general background, including the methods used to measure ambient air pollutants in Seoul, the characterization of Korean pollution problems, and the collection of mortality data has been published (*6*). Briefly, vehicular traffic and domestic space heating are thought to be the prime sources responsible for ambient air pollution in Seoul.

We used case-crossover analysis, a technique for assessing the brief change in risk associated with transient exposure (*13*). According to this method, each deceased person renders his or her own control information [control date(s)]; potential confounding due to age, sex, physiological status, personality, and other fixed characteristics is thereby eliminated. Methods of analysis of the case-crossover design are derived by considering a deceased person to be a stratum in a case–control study, where the cases and controls are times (calendar date when death occurred). Therefore, we defined that the dates of death are the cases and the other dates are the controls. We used the pair-matched analytic approach (conditional logistic regression) to contrast exposures (levels of air pollution) at the case dates with exposures at the control dates. In this instance, case-crossover analysis would identify an increase in risk of death if there were higher levels of ambient air pollution on the case-day than would be expected solely as a result of chance.

Based on previous research observations (*6*) we also considered a lead-lag relationship between air pollution and mortality. The results of previous studies indicated that the increased mortality occurred concurrently or within 1–5 days following an increase in air pollution.

We checked our estimated relative risks of death by repeating the calculations based on applying three control schemes, including a unidirectional retrospective and prospective control samplings and bidirectional control sampling (Figure 1). In unidirectional retrospective control sampling, we selected the

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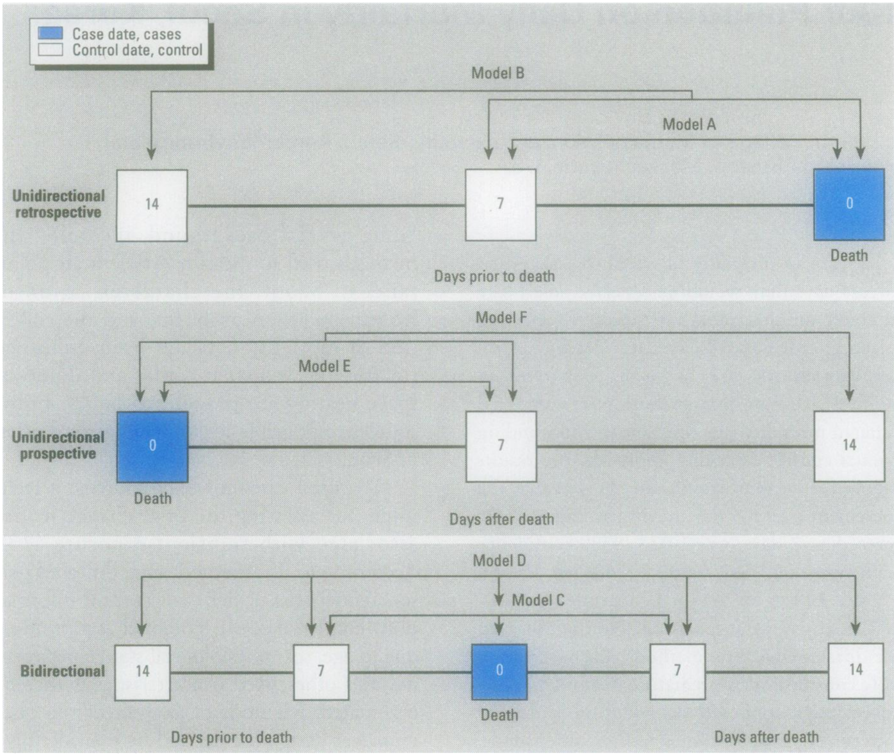

Figure 1. Schematic representation of six modeling (sampling) approaches. These models are analogous to case–control studies in which a variable number of controls are matched to each case (*M*-to-one matched, where *M* = 1, 2, 4).

Table 1. Descriptive statistics of mortality counts, weather, and air pollution in Seoul, Korea, 1991–1995.

Variable	Days (no.)	10%	25%	50%	75%	90%	Mean
Air pollutants							
TSP (μg/m^3)	1,646	45	61	85	115	149	92.5
SO_2 (ppb)	1,794	8	11	19	34	54	26.0
O_3 (ppb)	1,764	14	21	29	41	55	32.4
Weather							
Temperature (°C)	1,826	-1.1	3.6	13.7	21.6	24.9	12.6
Humidity (%)	1,826	46	56	66	76	84	65.5
Death (per day)	1,826	68	75	83	92	100	83.7

TSP, total suspended particulates.

same weekday(s) 1 or 2 weeks prior to death; for example, air pollution levels just before death on a Monday were compared with levels on Monday for the preceding 1 or 2 weeks. In unidirectional prospective control sampling, we selected the same weekday(s) 1 or 2 week(s) after death; for example, a death on Monday was compared with the following Monday(s). In the bidirectional control sampling, we simultaneously selected a pair of days—one from 1 week prior to death and the other from the following week.

Relative risks were estimated with methods for matched-pair studies on the basis of conditional logistic regression analyses. Synoptic weather variables (air temperature and relative humidity) were included to control for weather in the regression model. To control for seasonal variations, we did not select the control(s) any further than 2 weeks preceding/following the day of death. All *p*-values were two-tailed, and all relative risks were computed with 95% confidence intervals (CIs).

Results

The observed concentrations of ambient air pollutants during the study period were at levels below Korea's current ambient air quality standards (Table 1). A descriptive analysis showed that the correlation between total suspended particulates (TSP) and SO_2 levels (Pearson correlation coefficient, $r = 0.72$, $p \leq 0.001$) was the highest. O_3 levels were negatively correlated with SO_2 ($r = -0.34$, $p \leq 0.001$), but not with TSP ($r = 0.01$, $p > 0.05$). The 3-day moving averages (including the concurrent day death occurred) of SO_2 and TSP levels resulted in the highest relationship to daily mortality. Therefore, the regression model for daily mortality included air temperature, relative humidity, and levels of one of the air pollutants (3-day moving averages of SO_2 and TSP and 1-hr maximum O_3 levels).

In acute exposure studies, confounding due to temporal correlations between pollution, weather, seasonal variables, and calendar time was a concern. Figure 2 indicates that there were clear seasonal variations and shows the overall average trends over 5 years in two pollutants, TSP and SO_2. O_3 showed clear seasonal variations, but not an overall average trend over the years.

The conditional logistic model including only one of the air pollutants was regressed to compare the estimated risks of death for different control sampling schemes. The relative risks (odds ratio) with 95% CIs are shown in Table 2. Results for several matching ratios and schemes are shown. The results indicated that the estimates could be biased if control dates were selected only at antecedent or postmortem week(s). Because of improper control for seasonal patterns and time trends of air pollution, it is likely that our results would be underestimated or overestimated if we selected controls only in antecedent or postmortem week(s), respectively.

One pollutant model controlling for weather conditions (air temperature and relative humidity) shows similar patterns of estimation over the selection of different control schemes. Therefore, we reported the results using controls from a bidirectional sampling scheme for comparison (Table 3). The risk of all-cause mortality was estimated to increase by 5% (CI, 1.6%–8.4%), with an increase in 3-day moving average SO_2 levels equal to 50 ppb. The relative risk of death was 1.023 (CI, 0.999–1.048) per 50 ppb for 1-hr maximum O_3, and 1.010 (CI, 0.988–1.032) per 100 μg/m^3 for TSP.

Discussion

This empirical analysis was conducted to estimate an association between ambient air pollution and daily mortality using a case-crossover study design. We also compared relative risks calculated for six control selection schemes. This comparison gave us an idea of the necessity of control for seasonal waves and the overall average trend of air pollution over the study period.

We observed independent SO_2 effects on daily mortality even after using various approaches to control for weather conditions, seasonal variables, or long-term time trends in the logistic regression model. Our previous time–series analysis of the same data indicated that the mortality associated with a 50-ppb increment in a 3-day moving average of SO_2 concentrations was 1.078 (CI, 1.057–1.099) (*6*). The consistent finding of

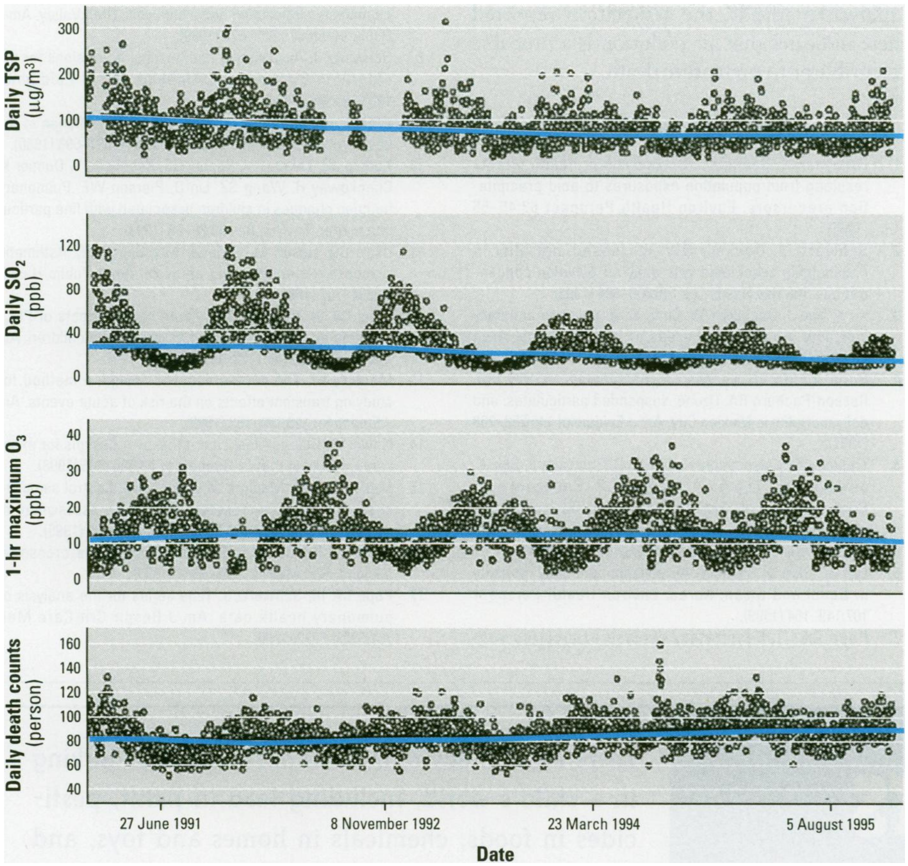

Figure 2. Distribution of daily death counts, daily mean SO_2 (ppb), daily mean TSP (μg/m^3), and 1-hr daily maximum O_3 (ppb) concentrations in Seoul, Korea, 1991–1995. TSP, total suspended particulates. The smoothed curve (loess) shows the substantial long-term time trends of air pollutants.

Table 2. Results of conditional logistic regression analyses without control for weather conditions using different selection schemes of controls, Seoul, Korea, 1991–1995 (one-pollutant model).

	Relative risks (95% confidence interval)					
Variable	A[a]	B[b]	C[c]	D[d]	E[e]	F[f]
TSP (100 μg/m^3)	0.948 (0.927–0.969)	0.983 (0.959–1.008)	1.021 (0.999–1.044)	1.020 (0.999–1.041)	1.035 (1.009–1.061)	1.058 (1.035–1.082)
SO_2 (50 ppb)	0.815 (0.787–0.844)	0.919 (0.884–0.956)	1.085 (1.048–1.123)	1.100 (1.067–1.135)	1.245 (1.195–1.297)	1.394 (1.346–1.444)
O_3 (50 ppb)	1.063 (1.037–1.089)	1.040 (1.011–1.070)	1.021 (0.996–1.046)	1.022 (1.000–1.045)	1.004 (0.976–1.033)	0.990 (0.966–1.015)

TSP, total suspended particulates.
[a]Two controls selected in the weeks before the week death occurred. [b]One control in the weeks before death occurred. [c]Two controls in the weeks before and after death occurred. [d]Four controls in the week before and after death occurred. [e]One control selected from the week after the week death occurred. [f]Two controls from 2 weeks after the week death occurred (see Figure 1).

Table 3. The RR, CI, and SE for ambient air pollution as a determinant of death, from conditional logistic regression models, controlling for weather conditions (air temperature and relative humidity), in Seoul, Korea, 1991–1995.

	Control days sampled					
	1:2[a]			1:4[b]		
Pollutant	RR	CI	SE	RR	CI	SE
TSP (100 μg/m^3)	1.009	0.984–1.034	0.0126	1.010	0.988–1.032	0.0112
SO_2 (50 ppb)	1.013	0.975–1.052	0.0195	1.049	1.016–1.084	0.0164
O_3 (50 ppb)	1.015	0.988–1.042	0.0148	1.023	0.999–1.048	0.0123

Abbreviations: CI, 95% confidence interval; RR, relative risk; SE, standard error of the log relative risk; TSP, total suspended particulates.
[a]Two controls were matched; one was selected from the preceding week and the other from the following week. [b]Four controls were matched; two were selected from the two preceding weeks and the remainder from the two following weeks.

SO_2 effects on mortality suggests the possibility that SO_2 may act as a better indicator of fine particles in Seoul. Further study is needed to clarify this finding by looking at the effect of fine particles on mortality in Seoul.

Time–series analysis can be a useful tool in evaluating short-term or acute health effects of time-varying exposures (*17*). Nearly all of the currently available mortality studies of air pollution are typically population-based time–series studies where the units of comparison are composed of the entire population of communities.

In this paper, we have shown empirically that the validity of relative risks (odds ratios) in case-crossover studies varies greatly depending on the strategy used in control sampling, particularly if confounding by time trends (or seasonal waves) of exposure existed. A simulation study showed that unidirectional control sampling (selecting control days only prior to or after death) could cause risk estimates to be confounded by time trends in exposure (*14*). Figure 3 shows the relative risks of death associated with a 50-ppb increment in a 3-day moving average of SO_2 levels and their 95% CIs calculated for six control samplings. The clear trend of SO_2 levels may play a critical role in explaining this pattern of estimates for different control samplings. This empirical observation indicated that the validity of estimators in case-crossover studies greatly depends on proper control for the time trends of risk factors. Pope and Schwartz (*17*) pointed out the necessity of control for seasonal conditions as well as time trends in estimating short-term associations. We selected controls within the 2 weeks prior to or after the day when each death occurred. Our finding indicated that this could not control for seasonal patterns. To control for time trends and seasonal waves, we applied bidirectional control sampling in which air pollution levels at the

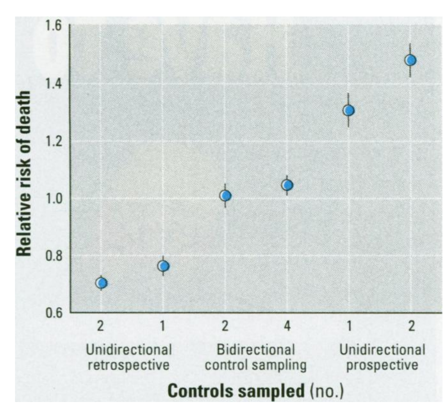

Figure 3. The estimated relative risk of premature death for different control samplings. The relative risks are for a 50-ppb increase in SO_2. The vertical lines indicate 95% confidence intervals. Bars that do not overlap with 1.0 indicate statistically significant associations ($p < 0.05$).

time of death were compared with exposures both before and after death. As Navidi (*14*) pointed out, when subsequent levels of air pollution were not influenced by failure (death), it was possible to determine postfailure what a subject's level of exposure would have been had the subject not failed. He also showed that unidirectional control sampling could be severely biased when time trends in exposures were strong and proposed the bidirectional case-crossover method because control information was assessed in both directions from the failure time. This method allows consistent estimators of risk to be computed regardless of time trends in exposure.

Elaborate models and statistical techniques cannot compensate for inadequate study design or poor data collection. However, consistent and coherent findings play an important role in establishing the causal pathway in mortality and air pollution. Given the consistency of the observed association between SO_2 and daily mortality across different analysis methods, the association reported here indicates that air pollution is a probable contributor to premature death.

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