the hypothesis, albeit with small numbers, that it is the time interval between diagnosis and contemporary magnetic field estimates that explains the difference between the results using historical calculations and spot measurements.

We have chosen to use relative risk estimates when comparing the different exposure estimates, since that is the type of effect measure commonly used in case-control studies. The results of this study might appear to differ from those of a study by Dovan *et al*,[15] based on the data of Savitz *et al*.[5] They found spot measurements to be rather stable over a 5-year period, with a correlation coefficient between low power spot measurements and measurements repeated after 5 years of 0.74. The apparent inconsistency with the results presented here perhaps can be explained by the lack of predictiveness between correlation coefficients and relative risks. In the Swedish residential study,[10] for example, the Pearson correlation coefficient between low power spot measurements and historical annual average calculations was found to be 0.79, similar to that observed by Dovan *et al*[15] and rather high. Despite this high correlation, an elevated relative risk for childhood leukemia was found only for historical calculations. The relative risk for spot measurements was below unity. This disparity is probably due to a large amount of misclassification of the exposure when spot measurements are used to assess an exposure that occurred several years earlier. In fact, 41% of those with spot measurements ≥0.2 μT had historical calculations <0.1 μT.[16] On the other hand, 91% of the subjects with historical calculations ≥0.2 μT also had spot measurements ≥0.2 μT. The extent of misclassification is further demonstrated by the low specificity and hence poor predictive value for spot measurements as a surrogate measure for historical fields.

These results have implications for the interpretation of some of the previous studies of magnetic field exposure and childhood cancer. The lack of an association with spot or 24-hour magnetic field measurements in the Savitz[5] and London[7] studies can, according to these results, be explained by the time interval between diagnosis and measurement, whereas the wire codes seem to capture better the exposure at the etiologically relevant time.

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Air Pollution and Daily Mortality in Amsterdam

Arnoud P. Verhoeff,[1] Gerard Hoek,[2] Joel Schwartz,[3] and Joop H. van Wijnen[1]

Few data are available on the association between the present low levels of air pollution in Western Europe and mortality. Daily mortality counts and the concentrations of black smoke, inhalable particles (PM_{10}), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3) were available for Amsterdam from 1986 to 1992. We used Poisson regression analysis to control for seasonal and other long-term temporal patterns. Black smoke and PM_{10} were positively associated with increased risk of mortality. The relative risk for a 100-μg per m^3 increase in black smoke on the same day was 1.19 [95% confidence interval (CI) = 1.02–1.38], and that for a 100-μg per m^3 increase in PM_{10} was 1.06 (95% CI = 0.99–1.14). The relative risk for individuals over 64 years of age was higher. We found no consistent association between the levels of SO_2 or CO and daily mortality, but ozone lagged 2 days was positively associated with daily mortality. The effect of particulates on acute mortality was independent of these pollutants. The results of the present study are consistent with the relation reported between particulate air pollution and daily mortality in other communities in Europe and the United States. (Epidemiology 1996;7:225–230)

Keywords: air pollution, mortality, Poisson regression, black smoke, particulate matter.

Episodes of extremely high levels of ambient air pollution in London in 1952,[1] the Meuse valley in 1930,[2] and in Donora, PA, in 1948,[3] have led to excess deaths. Since the London episode, a number of studies reported statistical analyses of fluctuations in daily mortality and daily ambient air pollution in different locations in Europe,[4–10] the United States,[11–20] and China.[21] In most of these studies, positive associations were found between daily mortality and daily air pollution levels, at levels substantially lower than those seen in London in 1952. Furthermore, most of these studies have reported that the levels of airborne particulate matter, not those of sulfur dioxide (SO_2), are correlated with daily mortality. Particulate air pollution has also been found to be associated with increased mortality in two prospective follow-up studies conducted in the United States.[22,23] Schwartz[24] reported the results of a meta-analysis including most of the daily time-series studies mentioned above. He reported a relative risk for a 100-μg per m^3 increase in total suspended particles (TSP) concentration of 1.06 [95% confidence interval (CI) = 1.05–1.07]. He demonstrated a dose-response relation between the concentrations of TSP and the risk of death, without any evidence for a threshold value.[24]

Here, we report on the association between daily mortality and daily levels of ambient air pollution in Amsterdam. Few studies describe the association between the present low levels of air pollution in Western Europe and mortality. Levels of SO_2 in Amsterdam are low, making confounding by this pollutant unlikely. Mortality data were available for the years 1986 through 1992. The major source of ambient air pollution in Amsterdam is long-range transport of air pollutants. The major local source contributing to ambient air pollution in the city is automobile exhaust.

Data and Methods

We obtained counts of total daily deaths within the city of Amsterdam (population 713,000 in 1992) from the Municipal Population Register for the years 1986–1992. These data do not contain cause of death.

We obtained air quality monitoring data from the Amsterdam Environmental Research Institute (OMEGAM), which manages the ambient air quality monitoring network of the city. Black smoke was measured every day at four sites. TSP was measured every 3 days at four sites during 1986–1988. Beginning in 1988, PM_{10} (particulates with an aerodynamic diameter of 10 μm or less) was measured every 3–4 days at the same locations as TSP. TSP and PM_{10} were both measured at one location for approximately 3 years (January 1984 to February 1987). SO_2 was measured continuously at 11 different sites, and carbon monoxide (CO) and ozone

From the [1]Department of Environmental Medicine, Amsterdam Municipal Health Service, Amsterdam, the Netherlands; [2]Department of Epidemiology and Public Health, University of Wageningen, Wageningen, the Netherlands; and [3]Department of Environmental Epidemiology, Harvard School of Public Health, Boston, MA.

Address correspondence to: Arnoud P. Verhoeff, Department of Environmental Medicine, Amsterdam Municipal Health Service, P.O. Box 20244, 1000 HE Amsterdam, the Netherlands.

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TABLE 1. Distribution of Daily Mortality, Air Pollution, and Meteorologic Variables in Amsterdam

	No. of Days	10%	25%	50%	75%	90%	Maximum	Mean
Mortality (deaths/day)								
Total	2,557	13	16	19	22	25	45	19
Age ≥65 years	2,557	10	13	15	18	21	35	16
Air pollutants ($\mu g/m^3$)								
Black smoke	1,737	4	6	9	16	23	81	12
PM_{10}	811	17	23	30	45	67	163	38
SO_2	2,224	4	7	11	16	25	139	13
CO	2,381	356	651	894	1,208	1,629	9,057	973
O_3, 1-hr maximum	2,030	8	20	39	59	81	301	43
Predicted								
Black smoke*	2,313	7	9	11	13	18	67	12
PM_{10}†	2,484	19	24	32	47	66	191	38
Weather								
Temperature (°C)	2,557	2	6	10	15	18	25	10
Relative humidity (%)	2,557	72	78	85	91	95	100	84

* Predicted using 24-hour averaged black smoke concentrations in Rotterdam.
† Predicted using 24-hour averaged TSP concentrations in Rotterdam.

(O_3) were measured continuously at five sites. In the analyses, we used 24-hour averaged concentrations (midnight to midnight), with the exception of O_3, for which we used the maximum 1-hour average concentrations for each day.

To calculate the citywide mean concentrations of air pollutants for Amsterdam, we used only data obtained from population-oriented monitoring sites. For black smoke, particulate matter, and the gaseous pollutants, three of the sampling sites were population oriented. The collocated TSP and PM_{10} measurements were highly correlated (Pearson correlation coefficient = 0.95, β = 0.90, standard error β = 0.03; constant = −3.60, standard error = 1.19). Therefore, before calculation of the citywide mean, we converted the TSP concentrations measured during 1986–1988 into PM_{10} levels, using linear regression.

Daily 24-hour averaged concentrations of black smoke and TSP measured in the city of Rotterdam (located about 80 km from Amsterdam) were also available for the entire period. The black smoke concentrations measured in both cities were positively correlated (r = 0.60, N = 1,558), as were the TSP and PM_{10} concentrations (r = 0.85, N = 786). To increase the number of observations, we used the Rotterdam data to predict daily concentrations of black smoke and PM_{10} in Amsterdam.

We obtained data on daily mean, maximum, and minimum temperature and daily mean relative humidity from the weather station at Amsterdam's Schiphol Airport. We obtained the weekly incidence of influenza-type illnesses in the Netherlands from the Dutch Institute for Research of Health Care in Utrecht.

The basic methodology used in this study is the same as that used in several recent studies addressing air pollution and mortality.[15–19,21] Daily mortality counts were regressed using Poisson regression. Daily mortality counts often show substantial seasonal and other long-term temporal patterns. Air pollution might explain part of that pattern. Other factors, such as season and infectious disease epidemics, are predominantly responsible for that pattern. We assessed the relation between air pollution and mortality only after controlling for these factors. The model has the form:

$$\log[E(Y_i)] = X_i \beta$$

where $E(Y_i)$ is the expected mortality count on day i, X_i is the matrix of covariates on day i, and β is the vector of the estimated regression coefficients. The relative risk estimates are given by exponentiation of the regression coefficients.

Mortality data may be overdispersed and positively autocorrelated. We estimated the overdispersion parameter as the ratio of the residual deviance and the residual degrees of freedom of the models. To check for serial correlation in the regression models, we calculated partial autocorrelation coefficients for the residuals of the models.

We performed a two-stage analysis. In the first stage, we used Poisson regression to filter out the seasonal and other long-term temporal patterns. The model included indicators for year of study, month, day of the week, epidemics of influenza-type illnesses, and weather terms (temperature and relative humidity). Kunst *et al*[25] reported that, in the Netherlands, mortality is lowest at an average daily temperature of 16.5°C and increases at both lower and higher temperatures. Following the approach of Mackenbach *et al*,[8] we created two dummy variables for temperature: "warm" (0 if temperature ≤16.5°C; temperature minus 16.5°C at higher values) and "cold" (0 if temperature ≥16.5°C; 16.5°C minus temperature at lower levels). We also considered lagged effects of temperature up to 2 days. We included indicators of quintiles of relative humidity in the model. We used diagnostics to ensure model fit, which included plots of residuals against day of study, temperature, and humidity, to ensure that there was no range of these variables where the model systematically misfit the data.

In the second stage, we examined air pollution for its additional contribution to predicting daily mortality by including it in the basic model. We treated pollutants as continuous variables in the Poisson regression analyses. To evaluate the presence of an exposure-response relation between daily mortality and black smoke or PM_{10}, we divided the concentrations of these pollutants into quintiles and used indicators for these quintiles in the regression. We considered the concurrent day's pollution levels as well as lags up to 2 days. All regression analyses were performed for total mortality counts and also stratified according to age.

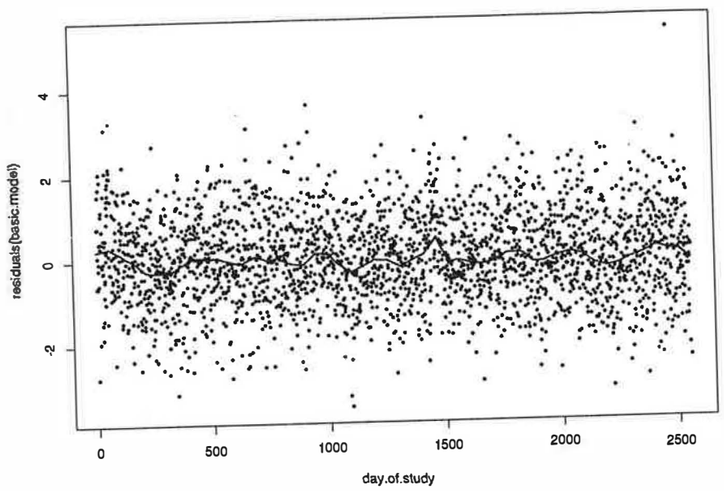

FIGURE 1. Plot of the residual number of deaths on each day in the study period controlling for all covariates except air pollution. The nonparametric smoothed line shows the absence of the seasonal pattern in these residuals.

Results

Table 1 presents the distribution of daily mortality, air pollution, and meteorologic variables in Amsterdam during the study period. Black smoke, PM_{10}, and SO_2 were negatively correlated with temperature (r = −0.11, −0.13, and −0.36, respectively), and ozone was correlated positively (r = 0.61). Black smoke was positively correlated with PM_{10} (r = 0.51), SO_2 (r = 0.36), and CO (r = 0.50), but negatively with ozone (r = −0.15). PM_{10} was positively associated with SO_2 and CO (r = 0.59 and r = 0.41, respectively), but only weakly with ozone (r = 0.06).

We found a strong seasonal periodicity in daily counts of mortality. Figure 1 shows a plot of the residuals of the Poisson model, after controlling for year of study, month, day of the week, epidemics of influenza-type illnesses, same-day temperature, and relative humidity. There is no apparent temporal pattern left in the residuals, also illustrated by the nonparametric smoothed plot *vs* time. All covariates, except for relative humidity, were associated with daily mortality. Lagged effects of temperature up to 2 days showed only weak associations with daily deaths. The model showed little indication of overdispersion (estimated dispersion parameter = 1.07) or serial correlation (partial autocorrelation coefficients <0.04). The diagnostic plots of residuals against temperature and humidity showed no range of these variables where the model systematically misfitted the data.

When we included black smoke or PM_{10} in the above model, we found positive associations between current-day black smoke or PM_{10} concentrations and daily deaths (Table 2). Current-day black smoke and PM_{10} values were stronger predictors than those of prior days (Table 2). As black smoke concentrations are lower than those of PM_{10}, the proportion of total deaths attributed to black smoke during the study period is 2.1%, and that attributed to PM_{10} is 2.3%. For individuals older than 64 years, the relative risk estimates increased. For current-day black smoke, the relative risk became 1.26 (95% CI = 1.07–1.49), and for current-day PM_{10}, the relative risk was 1.07 (95% CI = 0.98–1.16).

We found weak associations between current-day concentrations of SO_2, or CO, or their lagged concentrations up to 2 days, and the number of daily deaths. For

TABLE 2. Relative Risk of Death and 95% Confidence Intervals for a 100-$\mu g/m^3$ Increase in Black Smoke, PM_{10}, SO_2, CO, and O_3 in Amsterdam, Adjusted for Seasonal and Other Long-Term Temporal Patterns

Pollutant	Relative Risk	95% Confidence Interval
Black smoke		
Current day	1.187	1.020–1.380
1-day lag	1.162	1.004–1.342
2-day lag	1.026	0.888–1.187
PM_{10}		
Current day	1.062	0.986–1.144
1-day lag	1.017	0.944–1.096
2-day lag	0.998	0.928–1.073
SO_2		
Current day	1.042	0.943–1.151
1-day lag	1.048	0.952–1.154
2-day lag	1.016	0.923–1.119
CO		
Current day	1.001	0.998–1.003
1-day lag	1.002	0.999–1.004
2-day lag	1.000	0.998–1.002
O_3 (1-hr maximum)		
Current day	1.018	0.962–1.078
1-day lag	1.001	0.953–1.051
2-day lag	1.049	1.001–1.100

TABLE 3. Relative Risk of Death and 95% Confidence Intervals for a 100-$\mu g/m^3$ Increase in Black Smoke or PM_{10} in Amsterdam, Adjusted for Gaseous Pollutants, and Seasonal and Other Long-Term Temporal Patterns

Pollutant	Relative Risk	95% Confidence Interval
Black smoke + SO_2		
Black smoke	1.265	1.073–1.491
SO_2	0.876	0.743–1.033
Black smoke + CO		
Black smoke	1.203	1.005–1.441
CO	1.000	0.997–1.003
Black smoke + O_3		
Black smoke	1.178	1.011–1.373
O_3	1.029	0.967–1.096
PM_{10} + SO_2		
PM_{10}	1.023	0.928–1.129
SO_2	1.129	0.906–1.406
PM_{10} + CO		
PM_{10}	1.100	1.005–1.203
CO	0.982	0.995–1.002
PM_{10} + O_3		
PM_{10}	1.034	0.944–1.131
O_3	1.050	0.947–1.165

the concentrations of O_3 lagged 2 days, we found a positive association with mortality (Table 2).

We then considered black smoke and PM_{10} in combination with other pollutants, to investigate whether the associations between particulate air pollution and daily mortality were confounded by other pollutants. As presented in Table 3, the association between black smoke and daily mortality remained, considering black smoke together with SO_2, CO, or O_3. Including O_3 lagged 2 days did not change the relative risk estimates for both black smoke and O_3. For PM_{10}, the relative risk estimates decreased after including SO_2 or O_3 in the models but increased after including CO. Including PM_{10} and O_3 lagged 2 days in the same model reduced the relative risk estimates for both pollutants. We observed the same changes in relative risk estimates if the number of daily deaths of individuals over 64 years of age was taken as the dependent variable.

We conducted separate analyses for the low-temperature months (November through April), and the high-temperature months (May through October). For black smoke, 817 observations were available for the low-temperature months. The relative risk estimate of black smoke for these months was 1.08 (95% CI = 0.89–1.30). For the high-temperature months, 920 observations were available, giving a relative risk estimate of 1.35 (95% CI = 1.04–1.75). For PM_{10}, 398 observations were available for the low-temperature months and 413 for the high-temperature months. The relative risk estimates were 1.08 (95% CI = 0.98–1.18), and 1.10 (95% CI = 0.97–1.25), respectively. For ozone (1-hour maximum) lagged 2 days, we performed a separate analysis for the high-temperature months only. The relative risk estimate was 1.04 (95% CI = 0.99–1.09).

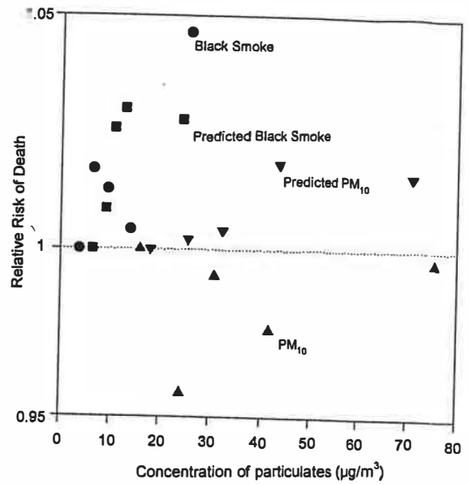

FIGURE 2. Relative risk of death by quintile of black smoke, PM_{10}, and predicted black smoke and PM_{10}.

The association between black smoke and daily mortality counts was confounded by daily temperature, epidemics of influenza-type illnesses, and day of the week. The estimated relative risk for black smoke without controlling for these variables (1.21; 95% CI = 1.06–1.39) was higher than that from the complete model estimate. Likewise, the association between PM_{10} and daily mortality was confounded by the same variables. The estimated relative risk for PM_{10} without controlling for these variables was 1.11 (95% CI = 1.04–1.19).

Using the predicted black smoke concentrations based on the black smoke concentrations in the city of Rotterdam, and thus increasing the number of observations from 1,737 to 2,313, gave a very similar relative risk (1.19; 95% CI = 1.00–1.43). For the predicted PM_{10} concentrations based on the TSP concentrations measured in the city of Rotterdam, the estimated relative risk was 1.06 (95% CI = 1.01–1.11). This value is similar to that based on the measured PM_{10} concentrations.

To assess a possible exposure-response relation between particulate air pollution and daily mortality, we evaluated the association of mortality with indicators of quintiles of black smoke and PM_{10} compared with the lowest quintile for both the measured and the predicted concentrations. The results are presented in Figure 2.

Discussion

The magnitude of the association between black smoke and mortality in Amsterdam is not directly comparable with that found in studies that used linear regression analysis.[4,6,7,10] Three studies investigating the relation between PM_{10} and daily mortality used the same approach as in the present study. In these studies, an

increase in PM_{10} levels of 100 μg per m^3 was associated with an increase of daily mortality ranging from 11% to 17%.[15,16,19] The increase in daily mortality in Amsterdam associated with a 100-μg per m^3 increase in PM_{10} is in the lower range of that found in studies in the United States. In the studies addressing TSP levels and daily mortality, an increase of the TSP concentrations of 100 μg per m^3 has been associated with a relative risk of approximately 1.06.[24] The reason for the lower coefficient in the Amsterdam data is unknown. In the U.S. studies, sulfates represented a substantial part of the fine particle mass. The yearly averaged sulfate concentrations in Amsterdam over the study period, however, ranging from 8.5 μg per m^3 for 1990 to 13.1 μg per m^3 for 1992, are similar to those in the U.S. studies.[15,22,23] Other explanations, including random variation, are possible.

The lack of association between daily mortality and 24-hour average SO_2 concentrations agrees with the results of Mackenbach *et al*,[8] who reported on the relation between SO_2 concentrations and mortality in the Netherlands. It also agrees with the results of most other time-series studies considering both SO_2 and particulates and supports the findings of others that the effect of particulates on mortality is independent of SO_2.[7,15,17,18]

The finding that current-day ozone does not predict daily mortality well was also reported in two other studies.[14,15] Nevertheless, O_3 lagged 2 days was a stronger predictor of daily mortality. The effect of ozone largely remained if considered together with black smoke or PM_{10}. This finding has not been reported earlier in relation to mortality, although an association was reported between daily mortality and total oxidants lagged 1 day in Los Angeles.[13] Furthermore, in recent studies, hospital admissions for respiratory symptoms have been associated with ozone concentrations lagged for 1 or 2 days rather than with the concurrent day's concentrations.[26–30]

Touloumi *et al*[10] reported a positive association between ambient CO levels and daily mortality in Athens, but this association was reduced considerably after including CO and black smoke or SO_2 in the same model. CO was not considered as a copollutant in other time-series analyses.

In the season-specific analyses, black smoke and mortality were more strongly associated for the warmer months (May through October), although both black smoke concentrations and mortality peaked in winter. A similar result was obtained for PM_{10}. Season-specific analyses have not been reported in the other studies considering black smoke or PM_{10}. Possible explanations for a stronger association between particulates and mortality during the warmer months may be differences in particle composition (more traffic related in summer), more time spent outdoors, and a different ratio of fine particles to smoke/PM_{10}.

Exposure-response relations between daily mortality and black smoke and PM_{10}, respectively, became apparent only using the predicted black smoke and PM_{10} concentrations instead of the measured levels. Schwartz and Marcus[7] reported an exposure-response relation between black smoke and mortality in London. Exposure-response relations for PM_{10} and daily mortality were reported in all three time-series studies addressing PM_{10}[15,16,19] and in most studies assessing the relation between TSP levels and mortality.[14,17,20]

The association between black smoke and daily mortality in Amsterdam seems more robust then the association between PM_{10} and daily mortality. The black smoke sampler collects only fine particles. If the smaller fraction of particulate is the most important with regard to health effects, that would explain the stronger association between black smoke and mortality than that between PM_{10} and mortality. Alternatively, black smoke may be more strongly related with the relevant chemical component(s) of particles causing the observed health effects. In a prospective cohort study, Dockery *et al*[22] found a stronger association of mortality with fine particles ($PM_{2.5}$) than with PM_{10}.

The mechanism by which airborne particles increase mortality is still not understood. Nevertheless, the literature on the relation between particulate air pollution and daily mortality is fairly consistent. Furthermore, there is considerable evidence that airborne particulates are a risk factor for outcomes such as hospitalization for respiratory disease,[28,29,31–35] acute respiratory symptoms,[36–38] and decreased lung function.[36,38] Thus, there is a large body of evidence that particulate air pollution at the present (low) levels is associated with a variety of related health effects, including acute mortality. The effect may involve the exacerbation of preexisting conditions.

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Confounding and Exposure Trends in Case-Crossover and Case-Time-Control Designs

Sander Greenland

As with ordinary studies, both case-crossover and case-time-control studies can suffer from confounding, including confounding by indication. In a case-crossover analysis, confounding by fixed (constant) characteristics is eliminated by pairing of cases to themselves, at the possible cost of introducing bias due to time trends in exposure. A case-time-control analysis can correct case-crossover results only for bias due to such time trends. If an uncontrolled confounder (such as disease severity) is present, the use of time controls can introduce new confounding, and the case-time-control results may end up either more or less confounded than the ordinary and case-crossover results. The relative confounding in the different approaches depends on details of the relations among the unmeasured confounder, the study exposure, the study disease, and any trend in these variables or their effects. Like an ordinary study, a case-time-control study must assume absence of unmeasured confounders, whether fixed or time-varying. Like a case-crossover study, it must also assume absence of carryover effects and can be more prone to misclassification bias than an ordinary study. (Epidemiology 1996;7:231–239)

Keywords: exposure trends, confounding, case-crossover studies, case-time-control studies, data analysis, bias.

In a recent article, Suissa[1] introduced the case-time-control design as an extension of the case-crossover design. Suissa asserted that this design could circumvent the problem of confounding by an indication (such as disease severity), and it "does not require a measure of this confounder." I here provide a series of counterexamples to show that the case-time-control design does *not* adjust for unmeasured confounding (such as confounding by fixed severity indicators) and can be either more or less confounded than the ordinary case-control and case-crossover[2,3] analyses. I also discuss differences in the conditions for no confounding in ordinary studies, case-crossover studies, and case-time-control studies. I show that none of the designs is always less biased than the others, although, because of their pair-matched structure, both case-crossover and case-time-control studies can be more sensitive to misclassification than ordinary studies.

Because subjects serve as their own matched controls in the case-crossover design, this design automatically controls for confounders that remain constant (fixed) over time. For example, if an indication for a treatment is constant over time, then the treatment-effect estimate from a case-crossover study would not be confounded by this indication. If, however, the indication changes over the study period and is a risk factor for the study disease, the case-crossover design would be confounded by this indication if the latter was not controlled in the analysis.

Because comparisons are made at different time points, the case-crossover analysis implicitly depends on an assumption that the distribution of the study exposure is stable over time. The case-time-control analysis does not depend on this assumption, but it does depend on an additional assumption of no confounding of exposure trends. This is because the case-time-control analysis adjusts only for crude trends in exposure prevalence. When these crude trends are confounded, such adjustments may either worsen or lessen net confounding. The net confounding in the case-time-control analysis may be in the same or opposite direction from that in the ordinary case-control and case-crossover analyses, and it may be either toward or away from the null. Furthermore, bias due to trends in exposure measurement quality (as opposed to trends in true exposure) may be either lessened or worsened in the case-time-control analysis.

In all of the examples, the outcome will be uncommon enough so that the distinction between risk ratios and odds ratios will be immaterial. Also, the examples involve only expected counts and functions of these, so that issues of sample size and random error will not enter into the discussion. All expected estimates will be first-order (asymptotic) approximations. All of the examples will involve only a single fixed confounder C, so that the confounding is produced by uncontrolled differences among individuals ("between-person confounding") rather than uncontrolled differences within individuals ("within-person confounding"). In all examples, the joint effects of the exposure and confounder will be

From the Department of Epidemiology, UCLA School of Public Health, Los Angeles, CA 90095-1772.

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