An Approach to Checking Case-Crossover Analyses Based on Equivalence With Time-Series Methods

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Abstract: The case-crossover design has been increasingly applied to epidemiologic investigations of acute adverse health effects associated with ambient air pollution. The correspondence of the design to that of matched case-control studies makes it inferentially appealing for epidemiologic studies. Case-crossover analyses generally use conditional logistic regression modeling. This technique is equivalent to time-series log-linear regression models when there is a common exposure across individuals, as in air pollution studies. Previous methods for obtaining unbiased estimates for case-crossover analyses have assumed that time-varying risk factors are constant within reference windows. In this paper, we rely on the connection between case-crossover and time-series methods to illustrate model-checking procedures from log-linear model diagnostics for time-stratified case-crossover analyses. Additionally, we compare the relative performance of the time-stratified case-crossover approach to time-series methods under 3 simulated scenarios representing different temporal patterns of daily mortality associated with air pollution in Chicago, Illinois, during 1995 and 1996. Whenever a model—be it time-series or case-crossover—fails to account appropriately for fluctuations in time that confound the exposure, the effect estimate will be biased. It is therefore important to perform model-checking in time-stratified case-crossover analyses rather than assume the estimator is unbiased.

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The case-crossover design has been increasingly applied to epidemiologic investigations of the association between short-term exposure to a risk factor and adverse health effects, notably in the area of ambient air pollution research.[1,2] The study population consists solely of cases who serve as their own controls in the analysis. Control exposure periods are chosen from each case's history as a substitute for the selection of an external comparison group. The case-crossover design is a form of the matched case-control design, making it inferentially appealing for epidemiologic studies.[3] Figure 1 illustrates the general framework of case and control exposure periods for air pollution studies when reference periods before and after the time of the event (bidirectional referent sampling) are used.[4] The set of event and referent periods established for each case's exposure history is the reference window. The self-matching approach allows for control of potential confounding by time-fixed factors—an often-cited benefit of the design.

Various referent sampling strategies have been employed to control for confounding by time-varying factors.[4–7] Janes et al[2] provide a comprehensive review of these strategies and assess the potential biases associated with each. The goal is to limit the referent selection interval to short-term periods that restrict time-varying factors (such as seasonal characteristics of health and exposure, day-of-the-week effects, or other long-term trends in air pollution patterns) to be essentially constant within the reference window.[8–10]

The case-crossover design has been viewed as an attractive alternative to a time-series model for studying the acute effects of transient exposures. By a time-series model, we refer to the log-linear regression model: $\log\mu_t = X_t\beta + S_t$, where Y_t is the number of events with $E(Y_t) = \mu_t$ and $Var(Y_t) = \phi\mu_t$, X_t is the exposure such as air pollution, and S_t is the value of a smooth function of time at time t. Time-series analysis allows for over-dispersion relative to the Poisson variance, where ϕ is the over-dispersion parameter. The current understanding is that the case-crossover approach controls for potential confounding by design, while time-series methods control for this source of bias by modeling.[9–11] However, important modeling assumptions must be recognized and addressed during data collection and analysis using the case-crossover approach.

In this article, we review the equivalence between case-crossover and log-linear time-series analyses, and detail the necessary analytic assumptions for both modeling ap-

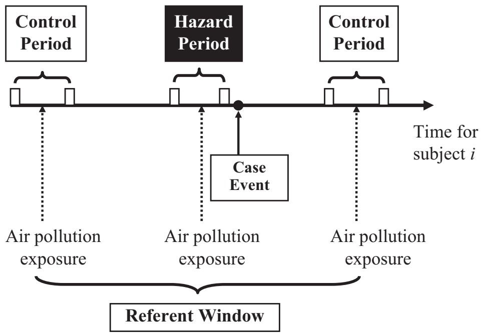

FIGURE 1. General design framework for a case-crossover study with bi-directional referent sampling.

proaches. We use the connection between the 2 approaches to propose model-checking criteria and to identify influential observations in data for case-crossover studies. We evaluate the potential for biased estimates due to time-varying risk factors for time-stratified case-crossover referent sampling schemes, and report simulation results that illustrate the potential for bias and the trade-off of bias and variance in a few specific cases. We then compare the relative performance of time-stratified case-crossover design with time-series methods when time-varying factors may confound risk estimates.

REFERENT SAMPLING STRATEGIES FOR AIR POLLUTION STUDIES

Various sampling strategies are used to select reference periods to estimate the effect of air pollution exposures on a health outcome of interest. Referent sampling schemes specific to air pollution epidemiology use reference periods both before and after the time of the event (bidirectional referent sampling) as a method to reduce bias due to temporal trends in exposure and outcome variables.[4,12] Variations include the symmetric bidirectional design that matches referent periods by day of the week and establishes equivalent intervals between case and referent periods.[5,7,9] Due to concerns about potential overlap bias in the symmetric bidirectional design, the time-stratified design is considered the most generally valid approach for case-crossover studies of acute air pollution effects.[11]

In the time-stratified design, the follow-up period is partitioned a priori into disjoint reference windows.[8] The most common analytic approach employs conditional logistic regression to compare the exposure at the time of the event to the exposure for the remaining control periods within this prespecified window. The time-stratified design method maintains desirable multivariable modeling properties by restricting reference windows to brief intervals that minimize confounding by seasonal and short-term patterns in exposure measures. A typical strategy is to constrain the referent-period selection to exposures matched by day of the week during the same calendar month as the case event.[8,13] This allows for asymmetric reference windows in which the case event is not centrally located by design.

CONNECTION OF CASE-CROSSOVER AND TIME-SERIES MODELS

The case-crossover approach is often viewed as a parallel alternative to time-series analysis. Lu and Zeger[14] have shown that the case-crossover method using conditional logistic regression is a special case of a time-series log-linear model when there are common exposures across subjects in each time period. This is the case in ambient air pollution studies. The conditional logistic regression estimating equation of a time-stratified design is equivalent to Poisson regression with indicator variables for strata.[13,14] With the symmetric bidirectional design, the conditional logistic estimating equation is equivalent to Poisson regression using a locally weighted running-mean smoother to estimate the smooth function S_t.[14]

The case-crossover method is often described as adjusting for potential confounders by design instead of by modeling as in time-series analysis.[9,10,15] This connection makes it clear that both methods control for potential confounding in their respective regression models; however, different assumptions are made about the nuisance function S_t that represents potential temporal confounding influences. Hence, it is equally important for both methods to evaluate key modeling assumptions. The equivalence of case-crossover and time-series methods allows us to use standard log-linear model diagnostic tools[16] to check models inherent in case-crossover analyses.

MODEL-CHECKING FOR CASE-CROSSOVER ANALYSIS

Data Displays

A display of data is a first step to reveal unusual observations or patterns of interest. The equivalence of the time-series and case-crossover methods indicates that a time-series plot of observed and model-predicted responses against time is a natural display for case-crossover data as well. A plot of Pearson residuals versus time or against predicted values is another useful visual tool.

Over-Dispersion Relative to the Poisson Model

The equivalence of time-series and case-crossover estimating equations means that the 2 methods produce the same estimator of the relative risk. Most case-crossover analyses rely on conditional logistic regression and assume that all subjects are independent. For common exposures shared by subjects, such as in ambient air pollution studies, this is equivalent to assuming that Y_t, the number of events on day t, follows a Poisson distribution.[14] Hence the case-crossover approach is equivalent to a log-linear time-series model without over-dispersion, and it uses the Poisson variance to calculate the standard error (SE) of the log relative risk estimates.[17] In many applications, the Poisson assumption is not valid because there are unmeasured factors that produce variations in the risk of the event within matched sets of reference windows.

Time-series analysis does allow for over-dispersion relative to the Poisson variance. The variance estimator for the log relative risk is inflated by an estimator of the over-dispersion parameter $\hat{\phi}$ given by $\hat{\phi} = \sum_{t=1}^{N} \hat{r}_t^2 / N$, where $\hat{r}_t = (Y_t - \hat{\mu}_t) / \sqrt{\hat{\mu}_t}$ is the standardized residual. The over-dispersion parameter likely reflects the influence of unmeasured causes of mortality that vary over time in a manner that is not accounted for by the assumed model for S_t.

Standardized Residuals

For the case-crossover approach, we treat individual-level baseline risks as nuisance parameters; hence we do not typically calculate fitted values. Using the equivalence to time-series, we can calculate standardized residuals $\hat{r}_t$ to check whether the model provides an adequate description of the data. We can plot the residuals as a time plot to reveal outliers, autocorrelation, or cyclic effects.[18] If the Poisson assumption is valid, $\hat{r}_t$ has mean 0 and variance 1. The spread of the standardized residuals can provide a visual estimate of the degree of over-dispersion. If the model is correctly specified for a larger Poisson mean, the standardized residuals are also approximately Gaussian. Hence when the number of events for each day is large (eg, greater than 5), Q-Q plots of $\hat{r}_t$ can be used to check the Poisson assumption.[19,20]

Dffits

Outliers for either the dependent or independent variables may excessively influence model fit and statistical inferences derived from regression coefficients. It is therefore important to check for influence points by calculating a measure such as Cook's distance, Dffits, or DfBeta.[21–23] We will use Dffits to illustrate how to check for highly influential events in case-crossover studies. Dffits represents the change in the predicted model estimate when each observation is omitted from the analysis. The Dffits can be calculated using equation $Dffits(t) = \dfrac{\hat{y}_t - \hat{y}_t(-t)}{s_t(-t)\sqrt{h_t}}$, where $\hat{y}_t$ and $\hat{y}_t(-t)$ are the predicted outcomes at time t with or without the observation y_t in the regression, $s_t(-t)$ is the SE estimated without y_t.[21] We use h_t to denote the leverage statistic for time t, which is the tth diagonal elements of the projection matrix.[16] A large absolute value for Dffits indicates an influential observation.

Example

We illustrate model-checking for the case-crossover method with an analysis of mortality in Chicago for persons over 75 years of age using PM_{10} data for the period 1995 to 1996. Data for this application are available at the Internet-based Health and Air Pollution Surveillance System website.[24] These data are typical of an air pollution time-series to which case-crossover analyses are applied. The data were analyzed using the time-stratified case-crossover design and time-series methods with the statistical programs R.[25] Sample codes are available online.[26] Figure 2 illustrates the daily mortality in Chicago for people 75 years and older. Most notable is the period with a very high mortality rate in July 1995, corresponding to an extreme heat event lasting several days.[27]

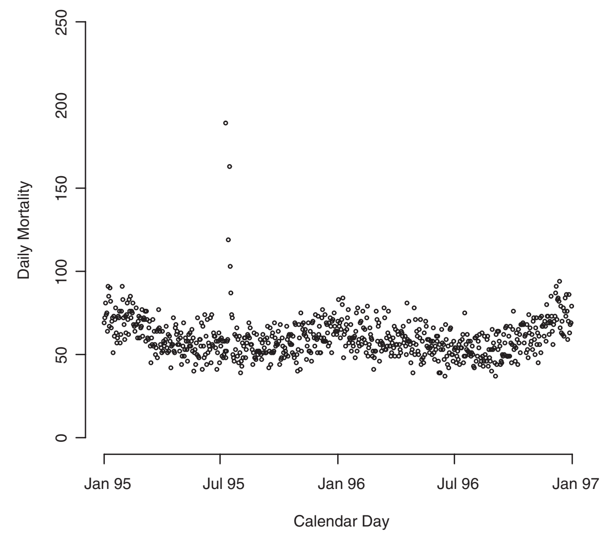

FIGURE 2. Daily mortality in Chicago for persons 75 years and older.

Four modeling approaches are applied to the data. To control for the J-shaped effect of temperature on mortality, we included natural splines of temperature and dew-point temperature with 3 degrees of freedom in all the 4 models. Method A is a time-stratified case-crossover design that selects control periods occurring on the same day of the week in the same calendar month and year as the case-event day. Method B is a time-series model that uses indicator variables for day of the week in each calendar month and year. Methods A and B give identical estimators. Method C is the same as method B, except that it uses indicator variables for day of the week in each season of the year (7×4/yr rather than 7×12/yr). Method D is a time-series model with a smooth function of time (natural spline) with 4 degrees of freedom per year times the indicator variables for day of the week. Method D has similar degrees of freedom as method C but allows the day-of-the-week effect to vary as a smooth function of time rather than as a step function.

The estimated regression coefficients agree to 2 significant digits ($\hat{\beta} = -0.17$) for case-crossover method A and time-series method B (results not shown). Methods A and B use the same estimating equation; hence they generate the same estimates of relative risk. However, the SEs are 0.42 for method A and 0.57 for method B. Note that for method A, conditional logistic regression does not take into account over-dispersion in the Poisson variance of the dependent variable, while we allow for over-dispersion in the log-linear regression models. The estimated over-dispersion parameter, $\hat{\phi}$, equals 1.8, indicating that there is greater variation in the numbers of deaths within matching strata than can be explained by the model. Much of this variation can be explained by a few outliers in the time-series (as we detail below), so that the inferences based upon the full data set are to be interpreted with caution. The estimates of β are -0.05 (SE = 0.52, $\hat{\phi} = 2.0$) and -0.23(SE = 0.53, $\hat{\phi} = 1.9$) for methods C and D, respectively. The large degree of over-dispersion indicates that the models did not completely capture the structure of S_t, again because of a few outliers.

We can use deletion diagnostics to quantify the influence of these points. Figure 3 shows the Dffits for methods A and D. The top 2 graphs in Figure 3 indicate that the Dffits are mostly in the range of (-1.5 to 1.5) for method A and (-1 to 1) for method D. There are several points with high Dffits for both models, corresponding to the high mortality event in July 1995. In the lower graphs, we set aside influential points and refit both models. After deleting observations from July 14th to 18th, the regression estimates for methods A through D, respectively, are 0.57 (SE = 0.43), 0.57 (SE = 0.45, $\hat{\phi}$ = 1.1), 0.88 (SE = 0.40, $\hat{\phi} = 1.2$), and 0.59 (SE = 0.40, $\hat{\phi}$ = 1.1). Although the estimated relative risks are not statistically significant, the magnitude of the estimate changed greatly after moving the highly influential points. Both the case-crossover and time-series methods produced biased estimators in the presence of those outliers. The high over-dispersion came mostly from the outliers, an observation that agrees with previous findings that mortality data tend to have small over-dispersion.[28,29] After removing highly influential points, method C has a slightly higher estimate of over-dispersion ($\hat{\phi} = 1.2$) than the other methods, which suggests that, after controlling for temperature and dew point, it is not appropriate to assume baseline risk is constant within the same day of the week during the same season of the year. The degree of over-dispersion in this mortality data is relatively modest. However, taking proper account of over-dispersion in inferences can be essential for outcomes such as hospitalization and infectious disease events, where the degree of dispersion is much greater.[30–32] In such cases, allowing for over-dispersion of the Poisson variance provides a more robust variance estimator and more valid inferences in case-crossover studies.

Figure 4 displays the Q-Q plots of the standardized residuals for methods A and D before and after removing influential points. Because the time-averaged predicted values are large (around 60), the standardized residuals $\hat{r}_t = (Y_t - \hat{\mu}_t)/\sqrt{\hat{\mu}_t}$

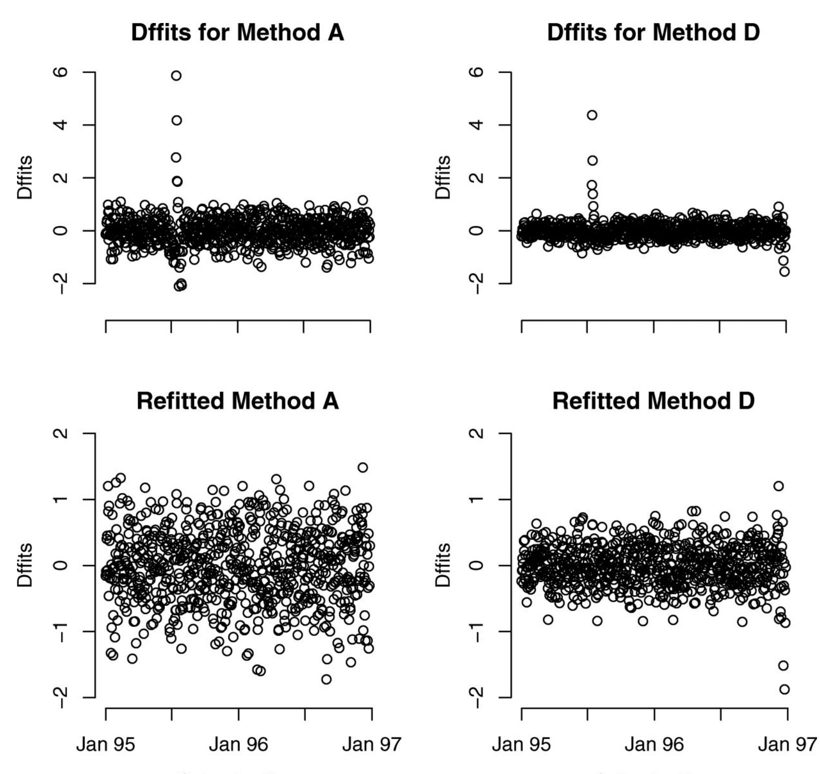

FIGURE 3. The Dffits statistics for method A and method D before (top) and after (bottom) removing influential points. Method A is a time-stratified case-crossover design time-stratified design using the days with the same day of the week in the same month and year of the event day as control days. Method D is a time-series method using a natural spline with 8 degrees of freedom.

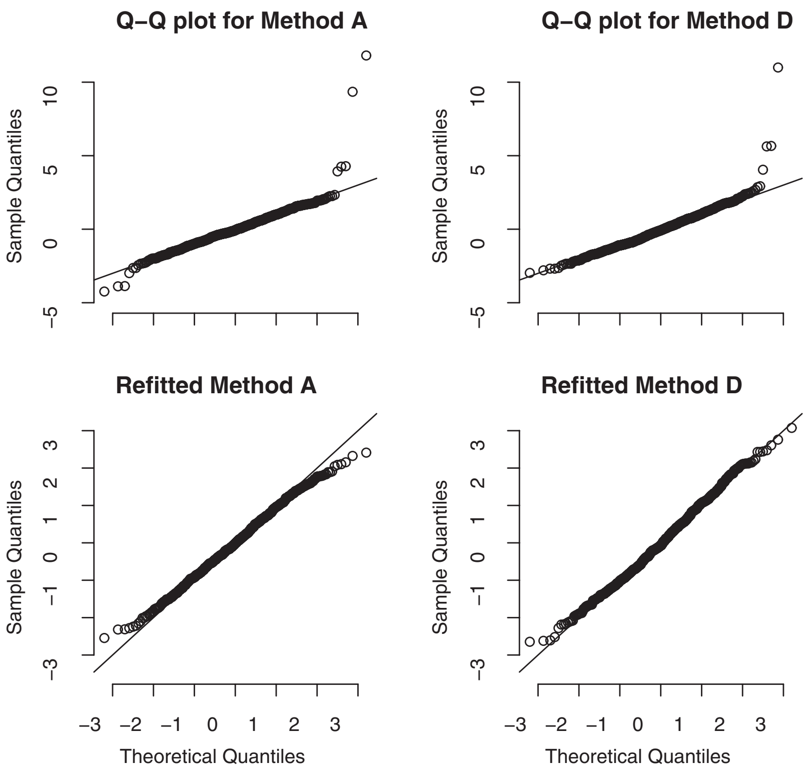

FIGURE 4. The Q-Q plot of standardized residuals for method A and method D before (top) and after (bottom) removing influential points. Method A is a time-stratified case-crossover design time-stratified design using the days with the same day of the week in the same month and year of the event day as control days. Method D is a time-series method using a natural spline with 8 degrees of freedom.

should approximate a standard Gaussian distribution if the model is correctly specified. Figure 4 suggests that the standardized residuals are skewed to the right before influential points are removed, indicating a violation of the Poisson assumption. After removing the influential points, the standardized residuals are very close to the Gaussian distribution for both models.

The standardized residual plots are useful for checking a case-crossover model. Recall that method A is a time-stratified design that assigns control periods by selecting the same day of the week in the same calendar month and year for each reference window; hence there are 4 or 5 exposure-days in each case-defined stratum. Figure 5 illustrates the standardized residuals versus day in case strata for Sunday through Monday. Outliers corresponding to the heat wave event can be easily detected. After removing the influential points, the standardized residuals have mean 0 and constant variance close to 1, which suggests that this model more adequately describes the data.

ISSUES OF BIAS

In this section, we discuss issues of bias based on a general framework for the case-crossover design applied to air pollution investigations. We define X_{it} as the exposure for subject i at time t and let Y_{it} indicate whether person i has the event at time t (1 = event; 0 = no event). The probability that subject i has an event at time t is given by the relative risk model $\lambda_i(t, X_{it}) = \lambda_{0it} \exp(\beta X_{it}) = \lambda_{0i} \exp(\beta X_{it} + \gamma_{it})$. We assume that each subject has a baseline risk λ_{0it} that consists of a time constant frailty, λ_{0i}, and unmeasured time-varying factor, $\exp(\gamma_{it})$. For air pollution studies, the population is often assumed to have a common exposure during each interval so that $X_{it} = X_t$. Lu and Zeger[14] have discussed the equivalence between time-series and case-crossover estimates in this situation. The person-specific relative risk assumptions above imply a model for the relation between daily mortality events and air pollution concentrations of the form $\log\mu_t = X_t\beta + S_t$, where $\exp(S_t) = \sum\lambda_{0i}\exp(\gamma_{it})$, summing over all the individuals in the population.

For case-crossover studies, control of confounding by time-varying factors is addressed by referent sampling strategies as discussed above. The time-stratified design has been described as the referent sampling scheme that has an unbiased estimating equation for case-crossover analyses.[2,11] As noted by these authors (Janes, Sheppard, and Lumley[2,11]) this is true only when γ_{it} is actually constant within the reference window, implying that the function of time, S_t, will also be constant within the reference window so that it is a step-function of time. In this section, we quantify the bias for case-crossover models employing the most common approach to referent selection time-stratified design from the perspective that a true S_t exists, and that this function can be incorrectly modeled with either a case-crossover or time-series approach (see online Appendix 1 for details). The bias of the

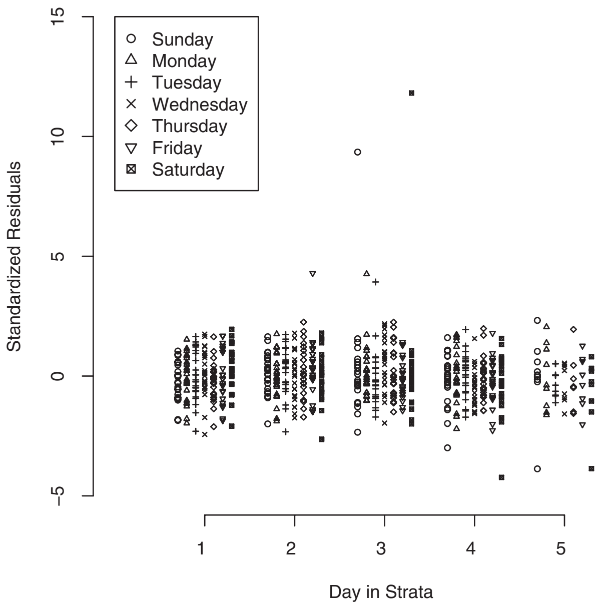

FIGURE 5. The standardized residuals of method A by day in each reference window strata before removing influential points. Method A is a time-stratified case-crossover design time-stratified design using the days with the same day of the week in the same month and year of the event day as control days.

estimating equation will depend on the exposures and the true parameter β, as well as the true S_t.

To demonstrate the potential bias using case-crossover or time-series methods, we report a brief simulation study in a specific air-pollution-mortality example (see online Appendix 2 for details).

The simulation results illustrate that when the time-stratified design case-crossover model cannot capture the smoothness of S_t, there can be a bias produced in the estimate of $\hat{\beta}$. The degree of bias is generally smaller than the standard deviation in the cases considered. The mean squared errors from the simulation suggested that using too many degrees of freedom could make the time-series estimator worse than the case-crossover method due to the bias-variance trade-off. There are several articles regarding the topic of model choice in the time-series analysis literature.[33,34] In summary, whenever a model—be it time-series or case-crossover—fails to appropriately account for fluctuations in time that confound the exposure, the effect estimate is biased. It is therefore important to perform model-checking to time-stratified design case-crossover analyses rather than assume that the estimator is unbiased.

CONCLUSIONS

The case-crossover design has undergone rapid theoretical and methodologic development since its introduction, especially for the study of acute adverse health effects associated with air pollution. An often-claimed rationale for use of the case-crossover design is that it provides self-matched data at both case and control periods and removes confounding by time-fixed characteristics.[35,36] Another claimed advantage is that it controls time-varying confounders such as seasonal and day of the week factors by design through short-interval reference-window specification; hence the conditional logistic regression model includes fewer terms than time-series models.[37] Lu and Zeger[14] have previously shown that each case-crossover conditional logistic regression model is equivalent to a particular time-series log-linear model without over-dispersion.

Methods for addressing time-varying risk factors in case-crossover analyses have relied on the assumption that S_t is constant within the reference window. When this assumption is not satisfied, estimates from case-crossover models can also be biased, just as in any model when the predictors are incorrectly specified. These assumptions should be verified using the model-checking procedures discussed here, which assess the influence of time-varying factors on the association between health outcomes and air pollution.

Plotting the data is an important first step in revealing unusual data points and time-varying patterns of interest. The equivalence of the case-crossover approach to time-series methods makes visual display of data readily interpretable for case-crossover analyses. Further, the over-dispersion parameter in a time-series model reflects the influence of unmeasured time-varying factors that is not accounted for by the assumed model for S_t. The over-dispersion parameter indicates a violation of assumptions necessary for the use of the case-crossover design. When the Poisson assumption is valid, the standardized residuals should have mean 0 and variance 1.

Another cited advantage of the case-crossover design is that more extensive personal information may be used in the analysis; for example, subject-specific characteristics and time-activity patterns that influence individual exposures or the timing of case periods.[38,39] The use of individual-level measures in a case-crossover analysis permits the researcher to estimate directly the effect of personal exposures, and to assess effect modification of exposure by individual attributes. The equivalence of time-series and case-crossover methods still holds for subject-specific exposure or covariate data.[40] Therefore, it is possible to estimate appropriate SEs and to check model assumptions using log-linear time-series methods for case-crossover analyses.

REFERENCES

1. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133:144–153.
2. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology*. 2005;16:717–726.
3. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health*. 2000;21:193–221.
4. Navidi W. Bidirectional case-crossover designs for exposures with time trends. *Biometrics*. 1998;54:596–605.
5. Bateson TF, Schwartz J. Control for seasonal variation and time trend in

case-crossover studies of acute effects of environmental exposures. *Epidemiology*. 1999;10:539–544.
6. Checkoway H, Levy D, Sheppard L, et al. A case-crossover analysis of fine particulate matter and out-of-hospital cardiac arrest. *Res Rep Health Eff Inst.* Cambridge, MA: Health Effects Institute, 2000;99:5–28.
7. Navidi W, Weinhandl E. Risk set sampling for case-crossover designs. *Epidemiology*. 2002;13:100–105.
8. Lumley T, Levy D. Bias in the case-crossover design: implications for studies of air pollution. *Environmetrics*. 2000;11:689–704.
9. Bateson TF, Schwartz J. Selection bias and confounding in case-crossover analyses of environmental time-series data. *Epidemiology*. 2001;12:654–661.
10. Janes H, Sheppard L, Lumley T. Overlap bias in the case-crossover design, with application to air pollution exposures. *Stat Med*. 2005;24: 285–300.
11. Mittleman MA. Optimal referent selection strategies in case-crossover studies: a settled issue. *Epidemiology*. 2005;16:715–716.
12. Greenland S. Confounding and exposure trends in case-crossover and case-time-control designs. *Epidemiology*. 1996;7:231–239.
13. Levy D, Lumley T, Sheppard L, et al. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology*. 2001;12:186–192.
14. Lu Y, Zeger S. On the equivalence of case-crossover and time series methods in environmental epidemiology. *Biostatistics*. 2007;8:337–344.
15. Zanobetti A, Schwartz J. The effect of particulate air pollution on emergency admissions for myocardial infarction: a multicity case-crossover analysis. *Environ Health Perspect*. 2005;113:978–982.
16. McCullagh P, Nelder JA. *Generalized Linear Models.* 2nd ed. London: Chapman & Hall/CRC; 1989.
17. Agresti A. *Categorical Data Analysis.* 2nd ed. Hoboken: John Wiley & Sons, Inc; 2002.
18. Chatfield C. *The Analysis of Time Series: An Introduction.* 4th ed. London: Chapman and Hall; 1989.
19. Wilk MB, Gnanadesikan B. Probability plotting methods for the analysis of data. *Biometrika*. 1968;55:1–17.
20. Casella G, Berger RL. *Statistical Inference.* 2nd ed. Pacific Grove: Thomson Learning; 2002.
21. Belsley DA, Kuh E, Welsch RE. *Regression Diagnostics.* New York: John Wiley & Sons, Inc.; 1980.
22. Cook RD, Weisberg S. *Residuals and Influence in Regression.* London: Chapman and Hall; 1982.
23. Williams DA. Generalized linear model diagnostics using the deviance and single case deletions. *Appl Stat*. 1987;36:181–191.
24. The Internet-based Health and Air Pollution Surveillance System website [database online]. Available at http://www.ihapss.jhsph.edu/data/data.htm. Accessed September 1, 2005.
25. R [computer program]. Available at http://www.r-project.org/. Accessed July 8, 2007.
26. Lu Y. Sample code to perform model-checking for case-crossover analyses. Available at http://www.biostat.jhsph.edu/~ylu. Updated November 12, 2007.
27. Semenza JC, Rubin CH, Falter KH, et al. Heat-related deaths during the July 1995 heat wave in Chicago. *N Engl J Med*. 1996;335:84–90.
28. Jordan P, Brubacher D, Tsugane S, et al. Modelling of mortality data from a multi-centre study in Japan by means of Poisson regression with error in variables. *Int J Epidemiol*. 1997;26:501–507.
29. Mar TF, Norris GA, Koenig JQ, et al. Associations between air pollution and mortality in Phoenix, 1995–1997. *Environ Health Perspect*. 2000; 108:347–353.
30. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA*. 2006;295:1127–1134.
31. Katz J, Carey VJ, Zeger SL, et al. Estimation of design effects and diarrhea clustering within households and villages. *Am J Epidemiol*. 1993;138:994–1006.
32. Katz J, Zeger SL, West KP, et al. Clustering of Xerophthalmia within households and villages. *Int J Epidemiol*. 1993;22:709–715.
33. Dominici F, Dermott AMC, Hastie TJ. Improved semiparametric time series models of air pollution and mortality. *JASA*. 2004;99:938–948.
34. Peng RD, Dominici F, Louis TA, Model choice in time series studies of air pollution and mortality. *J R Stat Soc Ser A: Stat Soc.* 2006;169:179–203.
35. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am J Epidemiol*. 1995;142:91–98.
36. Redelmeier DA, Tibshirani RJ. Interpretation and bias in case-crossover studies. *J Clin Epidemiol*. 1997;50:1281–1287.
37. Fung KY, Krewski D, Chen Y, et al. Comparison of time series and case-crossover analyses of air pollution and hospital admission data. *Int J Epidemiol*. 2003;32:1064–1070.
38. Sheppard L, Levy D, Checkoway H. Correcting for the effects of location and atmospheric conditions on air pollution exposures in a case-crossover study. *J Expo Anal Environ Epidemiol*. 2001;11:86–96.
39. Symons JM, Wang L, Guallar E, et al. A case-crossover study of fine particulate matter air pollution and onset of congestive heart failure symptom exacerbation leading to hospitalization. *Am J Epidemiol*. 2006;164:421–433.
40. Lu Y, Zeger S. On the equivalence of case-crossover and time series methods in environmental epidemiology. *Johns Hopkins University, Dept. of Biostatistics Working Papers.* 2006;Working Paper 101. Available at: http://www.bepress.com/jhubiostat/paper101.

