



Invited Commentary

Invited Commentary: Application of Case-Crossover Methods to Investigate Triggers of Preterm Birth

Lyndsey A. Darrow*

* Correspondence to Dr. Lyndsey A. Darrow, Department of Environmental Health, Rollins School of Public Health, Emory University, 1518 Clifton Road, NE, Atlanta, GA 30322 (e-mail: ldarrow@sph.emory.edu).

Initially submitted July 20, 2010; accepted for publication July 22, 2010.

Properties of the case-crossover design have appeal for investigation of acute triggers of preterm birth. Measured and unmeasured time-invariant risk factors are controlled by design, such that maternal race, socioeconomic status, and other personal factors will not confound the exposure–preterm birth association. In this issue of the *Journal*, Basu et al. (*Am J Epidemiol.* 2010;172(10):1108–1117) apply the case-crossover approach to assess the short-term relation between ambient apparent temperature and preterm birth. Novel application of the design to preterm birth, a “fatal” event exhibiting dramatic within-subject changes in risk, merits a review of the assumptions underlying the design. Implications of the referent time periods selected and the potential for confounding by seasonal patterns of conception are discussed in this commentary. The provocative associations observed by Basu et al. between high ambient apparent temperature and preterm birth should stimulate follow-up analyses and could ultimately have important public health implications. Future research can also help delineate the relative strengths and weaknesses of different temporal analytic strategies for investigating short-term associations between various exposures and preterm birth.

air pollution; epidemiologic methods; infant, premature; parturition; pregnancy outcome; premature birth; temperature

Preterm birth and its consequences continue to be an enormous public health problem, and identification of modifiable triggers of preterm labor is a research priority. Several exposures of interest lend themselves well to a temporal analytic approach, because temporal variation in factors such as air pollution levels, allergen levels, pesticide applications, water quality, various types of infection, and meteorology can be examined in relation to short-term changes in the rate of preterm birth. In this issue of the *Journal*, Basu et al. (1) investigate short-term associations between ambient apparent temperature and preterm birth using a novel implementation of the case-crossover approach, a case-only design in which subjects serve as their own matched controls. Their approach to the study question yields provocative results that, if borne out, could ultimately have important public health implications. Application of the case-crossover approach to the new context of preterm birth merits revisiting the assumptions underlying the case-crossover design and assessing how short-term changes in the underlying risk of preterm birth might affect the analysis.

The case-crossover design was introduced by Maclure in 1991 to be used “when brief exposure causes a transient change in risk of a rare acute-onset disease” (2, p. 144). The general approach is to compare exposure immediately prior to the case-defining event with the same individual’s exposure at referent time periods when he or she did not experience the event. The relevant lag period for exposure is specified (e.g., exposure in the week prior to the event), and exposures are assumed not to have carryover effects beyond the specified period. By making within-person comparisons, all measured and unmeasured time-invariant confounders are controlled by design.

Not surprisingly, a principal challenge of the design is selecting appropriate referent time periods representative of the distribution of exposure when the subject was at risk but did not experience the event. Over the past 2 decades, several strategies for selecting referent periods have been proposed, including approaches to accommodate situations with strong temporal trends in exposure (i.e., nonstationary exposures) (3, 4). Much of this methodological work has

occurred in the arena of air pollution, an exposure similar to ambient apparent temperature with respect to seasonality and autocorrelation. Lumley, Levy, and others (3, 5, 6) have shown that the time-stratified approach, in which time is partitioned a priori into disjoint strata, or “windows,” yields unbiased conditional logistic regression estimates. This approach is in contrast to referent selection using functions of the observed event day (e.g., symmetric bidirectional).

In this issue of the *Journal*, Basu et al. (1) implement the time-stratified approach: time windows are defined a priori as calendar months within year, and “case” days (defined by the preterm birth date) are matched to “control” days by day of the week. For example, if the preterm birth occurred on Monday, June 26, 2006, then the control periods selected are all other Mondays in June 2006. Depending on when in the month the preterm birth occurred, the control days could be all after the case day (when the subject would have been at an older gestational age), all before the case day (when the subject was at a younger gestational age), or a mix of before and after the case day. The exposure of interest is the ambient apparent temperature in the week prior to each observation day.

One characteristic of the case-crossover design in this context is the inclusion of control periods when the subject was not technically at risk of the outcome (after the case day) and when the subject was at much lower risk of the outcome (before the case day). The control days selected after some case days correspond to a gestational age greater than 37 weeks, and, had the subject been born on that day, he or she would not have been counted as a case. Furthermore, because birth is a “fatal” event in the sense that an infant, once born, is no longer at risk of birth, *all* control days selected after the case day are from a period when the subject was not at risk of the outcome.

Analogous situations arise in case-crossover studies of mortality. As Lumley and Levy (5) show, the use of referent periods after fatal events is not entirely free of bias, but, under the rare disease assumption, the bias is generally ignorable. In fact, exclusion of referent time periods after the case event would typically introduce the greater problem of selection bias when there are within-window trends in exposure. Lumley and Levy conclude “that there is a bias from treating dead subjects as if they were still at risk, but that this bias is very small if the population rate of death is small, even when there is a trend in the exposure” (5, p. 700).

This conclusion begs the question, is preterm birth a rare disease? Basu et al. (1) report that the highest unconditional risk of birth on any gestational day was 4%. However, the most likely birth day is at 40 weeks’ gestation (i.e., the due date), and the highest risk of birth on any gestational day before 37 weeks (i.e., the disease definition) is certainly much lower. Hence, any bias arising from the use of referent time periods when the subject was not at risk of preterm birth is probably minimal.

Further, it is well known that gestational age is a strong risk factor for parturition; a fetus at 36 weeks’ gestation has roughly twice the risk of birth compared with a fetus at 35 weeks’ gestation. Thus, for many of the case days, control days are sampled when the subject was at a dramatically lower risk of the outcome. Justification for this approach

relies on a key assumption: within a month window, the distribution of gestational ages among the population at risk of preterm birth is not systematically related to day of the month. Stated more broadly, no risk factors for preterm birth, apart from the exposure under study, should vary systematically within the time window, unless these time-varying factors are controlled in the analysis. Basu et al. (1), for example, control for day-of-week differences in risk of preterm birth by matching. Problems arise when this assumption is not satisfied and baseline risk of preterm birth varies systematically by day of the month.

The existence of both exposure trends and uncontrolled trends in the underlying risk of the outcome within the time windows is a recipe for confounding. Clearly, there are within-window trends in ambient apparent temperature: as the authors point out (1), in California, temperatures generally rise during May and June, level off in July and August, and decline in September. Within-window trends in the outcome of preterm birth are less conspicuous, but a prime concern is the influence of seasonal patterns of conception. If conceptions are not uniformly distributed throughout the year, then preterm births, and births more generally, will not be uniformly distributed throughout the year because of the fundamental relation between gestational age and birth: the number of expected births at any given point in calendar time is proportional to the number of fetuses at risk at each gestational age. More concretely, in Atlanta, Georgia, the number of fetuses in late gestation at risk of preterm birth increases from May through August each year, presumably because conceptions increase from September through December (7).

To illustrate the implications of this phenomenon, consider 2 scenarios. In the first scenario, suppose that solely because of the seasonal patterns of conception, more preterm births occurred at the end of June than at the beginning of June (i.e., because more fetuses were at risk in the population at the end of June compared with the beginning of June). If temperature is generally higher in late June compared with early June, we would expect to find an association between temperature and preterm birth, even in the absence of a causal effect of temperature. In the second scenario, assume there is no seasonal pattern of conception (or spontaneous abortion, etc.) such that preterm births would be expected to be uniformly distributed throughout the month of June. In this scenario, any departure from a uniform pattern of preterm births in the month of June would not be due to seasonal patterns of conception and could be explained by temperature or some other external trigger of preterm birth exhibiting within-month variation.

In reality, how within-month trends in gestational age and temperature relate to one another can be complex and may differ by calendar month. In some months, the pattern of conception could induce a spurious association with temperature; in other months, the pattern of conception could mask a true association with temperature; and in yet other months, the 2 patterns could be uncorrelated and yield unbiased estimates, albeit with a loss of power. Further complicating matters, the seasonal patterns of birth can actually differ among population subgroups (7), which could lead to the false appearance of effect modification by factors such

as maternal race and ethnicity. Basu et al. (1) conducted a number of sensitivity analyses that indirectly touched on these issues, including month-specific analyses, analyses stratified by population subgroup, and the creation of 2-week time windows instead of calendar months to more tightly control for seasonal trends. The authors also conducted separate analyses for all full-term infants and for infants born between 37 and 38 weeks' gestation; these births should exhibit the same seasonal pattern as the 34- to 36-week births, except shifted forward in time by a few weeks. However, Basu et al. did not directly explore how the seasonal patterns of conception might be operating in these data.

The optimal way to directly account for any associations between gestational age and day of the month in case-crossover analyses of preterm birth is unclear. In a time-series analysis, one could model the daily count of preterm births within strata of gestational week using the risk set of ongoing gestations, thereby controlling for seasonal trends in gestational age (8). However, in a case-crossover analysis, controlling directly for gestational week could be problematic because some gestational weeks (i.e., those after 36 weeks) will never have a case day and will not be estimable. An alternative is to include within-window smoothers, such as splines, to compensate for the within-month trend in the outcome. However, there are challenges to choosing the form of the smoother. Besides, adding explicit control for time to a case-crossover analysis seems to stray from the spirit of the design, namely that, within short-enough time windows, baseline risk of the outcome can be assumed constant.

Although application of the case-crossover design to the study of preterm birth poses several challenges, its significant advantages should be emphasized. Temporal methods are ideally suited to investigate the acute effects of short-term exposures on preterm birth, yet they are uncommon in the literature. As the authors note (1), the case-crossover approach eliminates the potential for confounding by time-invariant risk factors such as genetic predisposition, maternal race-ethnicity, and several socioeconomic characteristics because comparisons are made within person. Just imagine the potential sources of confounding to contend with if the authors had compared pregnant women living in the hotter counties of California with those living in the cooler counties. From this perspective, concerns about confounding by within-window temporal patterns seem relatively modest. Future work can help delineate the strengths and weaknesses of the case-crossover approach relative to

other temporal analytic strategies for investigating short-term associations between various transient exposures and preterm birth. The provocative findings reported by Basu et al. warrant further investigation, particularly because even small effects of a ubiquitous exposure on a common health outcome can have large public health impacts.

ACKNOWLEDGMENTS

Author affiliation: Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, Georgia.

The author is grateful to Mitchel Klein and Matthew Strickland for several clarifying conversations during composition of this commentary. The author also thanks Paige Tolbert, Sarah Tinker, and Dana Flanders for their helpful comments.

Conflict of interest: none declared.

REFERENCES

1. Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. *Am J Epidemiol*. 2010;172(10):1108–1117.
2. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133(2):144–153.
3. Levy D, Lumley T, Sheppard L, et al. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology*. 2001;12(2):186–192.
4. 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(6):717–726.
5. Lumley T, Levy D. Bias in the case-crossover design: implications for studies of air pollution. *Environmetrics*. 2000; 11:689–704.
6. Janes H, Sheppard L, Lumley T. Overlap bias in the case-crossover design, with application to air pollution exposures. *Stat Med*. 2005;24(2):285–300.
7. Darrow LA, Strickland MJ, Klein M, et al. Seasonality of birth and implications for temporal studies of preterm birth. *Epidemiology*. 2009;20(5):699–706.
8. Darrow LA, Klein M, Flanders WD, et al. Ambient air pollution and preterm birth: a time-series analysis. *Epidemiology*. 2009; 20(5):689–698.