The Case-Time-Control Design

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Assessing the known or intended effects of a drug using nonexperimental epidemiologic designs is often infeasible because of the absence of accurate data on a major confounder, the severity of the disease treated by this drug. To circumvent this problem of confounding by indication, I propose the case-time-control design, which does not require a measure of this confounder. Instead, the design uses subjects from a conventional case-control design as their own controls and thus requires that exposure be measurable at two or more points in time. I present a logistic model to estimate relative risks under this design and illustrate the method with data from a case-control study of 129 cases of fatal or near-fatal asthma and 655 controls. The exposure of interest was quantity of use of inhaled beta-agonists, drugs prescribed for the treatment of asthma. I found that the "best" estimate of relative risk for high *vs* low beta-agonist use using the conventional case-control approach is 3.1 [95% confidence interval (CI) = 1.8–5.4], which inherently includes the confounding effect of unmeasured severity. The corresponding estimate of drug effect using the proposed case-time-control approach is 1.2 (95% CI = 0.5–3.0), which excludes the confounding effect of unmeasured severity. This example indicates that the class of beta-agonists may not play the leading role attributed to it in the risk of fatal or near-fatal asthma, as had been previously suspected, except perhaps at excessive doses, as indicated by the dose-response analyses. (Epidemiology 1995;6:248–253)

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One of the principal challenges of nonexperimental designs is the choice of the reference group. In case-control studies, one is always faced with the difficulty of control selection. The case-base paradigm[1] proposes that controls be selected from the source population that gave rise to the cases, a principle that engenders some practical difficulties.[2,3] A necessary condition to avoid the inherent pitfalls associated with control selection is the measure of important confounding variables, which can then be controlled at the design or analysis stages.

This conventional approach can be problematic and even at times infeasible in the nonexperimental assessment of the known or intended benefits and risks of a drug. In pharmacoepidemiology, there is often a strong association between exposure to the drug under study, for which a good measure is available, and the underlying severity of the disease it is used to treat, for which a measure is rarely available. This association arises because the drug's effect of interest is known or intended and, consequently, is prescribed selectively to patients with specific disease severity profiles. Disease severity, or alternatively the spectrum of stages or degrees of a disease, is then clearly an important confounding factor, being an important predictor of the effect under study and strongly associated with drug use. The lack of a measure for severity makes conventional case-control studies vulnerable to substantial biases, and hence essentially invalid when the goal is inference about the drug's effect. This form of confounding by the indication of the drug[4] can be detrimental to such research:

It is natural to seek to measure this severity level. Yet, even if a precise measure of disease severity were available, cases can be so distinct from potential controls with respect to these severity measures that the search for appropriate control subjects can prove to be formidable, if not futile. If and when control subjects can be found, the disease severity can also be so highly correlated with the level of drug use that one would require tremendous numbers of cases and controls to have any hope of estimating the independent effect of the drug, particularly when the beneficial or adverse events under study are rare.

In this paper, I propose the case-time-control design to address this problem of confounding by indication. This design applies in situations where exposure varies over time and can be measured at two or more points in time. I use data from a nested case-control study of the association between the use of inhaled beta-agonists for the treatment of asthma and the risk of fatal or near-fatal

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asthma to present the problem and illustrate the approach.

Example of the Problem: The Asthma Drugs Study

The Saskatchewan Asthma Epidemiologic Project[5] was initiated to investigate the risks associated with the chronic use of inhaled beta-agonists in the treatment of asthma. Using databases from the universal health insurance plan of the Province of Saskatchewan, Canada, my colleagues and I identified a cohort of 12,301 asthmatic persons ages 5–54 years and followed during 1980–1987. We found that 129 of them experienced fatal or near-fatal asthma. In a nested case-control design, we selected 655 controls for these cases. Using as the exposure the amount of beta-agonist use in the year before the index date, we found an odds ratio for the adverse event of 1.9 [95% confidence interval (CI) = 1.6–2.4] for every unit increase in the average monthly number of canisters of inhaled beta-agonist used.

The use of inhaled beta-agonists is known to increase with asthma severity, which also augments the risk of fatal or near-fatal asthma. Thus, although use of this drug was found to be a powerful marker of risk, it was not possible to distinguish the contribution of the drug to the risk from that of disease severity. This problem occurred in spite of matching for important risk factors and performing all analyses with adjustment for the effect of several powerful markers of asthma severity, such as the concurrent use of oral corticosteroids and other asthma drugs, as well as the frequency of prior hospitalizations for asthma. Further adjustments for disease severity assessed from medical records did not alter the prior results, possibly because these measures were not sufficiently precise to isolate the drug effect.[6] Thus, even with this barrage of all possible conventional stratagems, the question of how much of this effect, if any, is actually due to the drug still lingers.

The Situation

Consider the simplest situation of a case-control study of the occurrence of an event in relation to a single dichotomous exposure that varies over time. For each study subject, case and control, the binary drug exposure E (= 1 for use and 0 for non-use) is measured for two time periods, which may or may not be consecutive, denoted as $j = 0,1$.

We call period $j = 1$, which corresponds to the current exposure of a study subject, the *current period*, and $j = 0$, which represents a period preceding this current period, the *reference period*. Thus, the interest of this paper is with specific situations where data on drug exposure are sufficiently variable and can be obtained not only for the current period but for a prior reference period as well. The actual length of the current period depends on the hypothesis under study. For example, in our asthma study, the scientific question of interest focused on the effect of "regular chronic use." Accordingly, we opted for a time window of 1 year because of the strong seasonal variations in disease and drug use, and because we judged that it was the duration of exposure needed for such a chronic effect to occur. The reference period was taken to be the year immediately preceding the 1-year current period. Alternatively, it may span a different period of the disease course. These issues are reviewed in greater detail in the Discussion.

The Proposed Approach

Because of their often higher level of disease severity, the cases may form a genuinely distinct group of patients. Despite a selection of controls from subjects with the same disease and matching for important prognostic factors, confounding by severity often cannot be controlled for. When no precise measure of this factor is available, the choice of controls is then clearly problematic, since there are no means of confirming that severity will be equally distributed in cases and controls. Using the case-base paradigm,[1] one could then infer that the most appropriate population source for these cases is not necessarily patients with the same disease and prognostic factors, but rather the cases themselves. This seemingly unorthodox deduction was made by Maclure[7] in his description of the case-crossover design for the study of short transient exposures and acute effects. On this basis, the best control for each case is the case itself with, as reference, exposure data from another point in time. By using, among cases, the same subject as his own control, underlying disease severity is automatically controlled for. This extension of the case-crossover design from short transient exposures to longer chronic exposures is addressed in the Discussion.

A caveat of this case-crossover approach in the present context is that these odds ratios, based solely on the cases, may be representing in part the natural increase in drug use over time and not just the increase associated with the event occurrence. This "natural increase" is common in epidemiologic studies of drug effects; it often reflects changing medical practice, greater recognition of the drug's benefits, more assurance with prescription of the drug, a wider spectrum of indications, increasing patient reliance on the drug, and aggressive marketing. Consequently, a portion of the effect of this natural time trend of medication use is present in the odds ratio obtained from the case-crossover analysis, and should be removed. The control subjects of the conventional case-control design can be used for this purpose. As I show below, each control subject may also be used twice, once for the current period and once for the reference period.

The Case-Time-Control Model

Because of the outcome-based sampling of the case-control data, which makes exposure the random variable, and the invariance of the odds ratio in this context, I focus solely on models based on logits of exposure. Accordingly, let $L_{ijk\ell} = \text{logit}[P(E_{ijk\ell} = 1)]$, where $E_{ijk\ell}$ represents the binary exposure for group i, period j, outcome k, and subject ℓ within group i. More specifi-

cally, $i = 0,1$ denotes the case/control group (1 = case subjects, 0 = control subjects); $j = 0,1$ denotes the period (1 = current period, 0 = reference period); $k = 0,1$ denotes the event occurrence (1 = event, 0 = no event); and $\ell = 1, \ldots, n_i$ designates the study subject within group i, with n_1 case subjects and n_0 control subjects. Note that $k = 1$ represents the case subjects ($i = 1$) at the current period ($j = 1$).

A model for this situation is:

$$L_{ijk\ell} = \mu + s_{i\ell} + \pi_j + \theta_k, \quad (1)$$

where μ represents the overall exposure logit, $s_{i\ell}$ is the effect of study subject ℓ in group i, π_j is the effect of period j, and θ_k is the effect of event occurrence k, which is the parameter of interest. Note that the patient's underlying severity is inherently accounted for in $s_{i\ell}$. In our specific situation, the two terms for Model 1 are, for the group of case subjects,

$$L_{111\ell} = \mu + s_{1\ell} + \pi_1 + \theta_1 \quad (2)$$

and

$$L_{100\ell} = \mu + s_{1\ell} + \pi_0 + \theta_0, \quad (3)$$

while in the group of control subjects, the two terms of Model 1 are:

$$L_{010\ell} = \mu + s_{0\ell} + \pi_1 + \theta_0 \quad (4)$$

and

$$L_{000\ell} = \mu + s_{0\ell} + \pi_0 + \theta_0. \quad (5)$$

The net period effect is given by $\delta_\pi = \pi_1 - \pi_0$, whereas the net effect of exposure on event occurrence is given by $\delta_\theta = \theta_1 - \theta_0$. Logits 2 and 3 indicate that δ_θ and δ_π are aliased in the group of case subjects so that, in that group, only the sum $\delta_\theta + \delta_\pi$ is estimable. On the other hand, Logits 4 and 5 indicate that δ_π is estimable in the group of control subjects. Clearly, the net effect of exposure on event occurrence δ_θ is estimable by subtraction.

Note that estimability of δ_θ, the net effect of exposure on event occurrence, does not require that π_1 and π_0 be equal for $i = 1$ and 0 (case and control subjects), but only that their difference $\pi_1 - \pi_0$ be equal.

Estimation for the Case-Time-Control Model

To estimate the net effects of period and exposure on event occurrence, we may use existing techniques for matched binary data arising from case-control designs. Each subject forms a matched pair from the two periods. By assuming conditional independence of exposure within a pair, we may use the conditional logistic regression model to estimate the odds ratios for period and outcome effects. The conditional analysis automatically eliminates the nuisance parameters induced by the subject effects $s_{i\ell}$, which inherently also comprise the effects of disease severity. Although we should use exposure as the dependent variable to be compatible with Model 1, instead, to be consistent with standard techniques, we use exposure as an independent variable and the period (1 = current period, 0 = reference period) as the dependent variable. The two approaches are equivalent and produce identical results.

We define variables E, G, and T within the framework of the conditional logistic regression model. Variable E refers to the binary exposure (1 = yes, 0 = no), G refers to the subject's group (1 = case subjects, 0 = control subjects), and T refers to the time period of measurement within the matched pair (1 = current period, 0 = reference period). If we denote the probability of the outcome event by R, the regression model necessary to estimate the odds ratios of interest is:

$$\text{logit}\,(R) = \beta_0 + \beta_1 E + \beta_2 E \times G, \quad (6)$$

where T is the "outcome," which replaces the usual "case" (or "failure") designation of standard logistic regression models by the current period and the usual "control" (or "success") designation by the reference period.

The relative risk of interest, namely the one that measures the risk associated with exposure, above and beyond that of time (period), is given by $OR = \exp(\beta_2)$, obtained from the interaction term between the exposure of interest (E) and subject's group designation (G). The coefficient β_2 corresponds exactly to the difference between Logits 4, 5 and 2, 3. The portion of the risk associated with the period effect is given by $OR_{co} = \exp(\beta_1)$, corresponding to Logits 4 and 5 since it is specific to the control subjects (G = 0) who did not develop the event. On the other hand, the relative risk computed from the case subjects only (G = 1), namely $OR_{ca} = \exp(\beta_1 + \beta_2)$, corresponding to Logits 2 and 3, includes the effect associated with the drug itself. Therefore, $OR = \exp(\beta_2)$ is that portion exclusively associated with the drug, since the effect of the time trend is extracted.

Illustration

Data on the use of inhaled beta-agonists and other drugs were obtained for a 1-year current period and a 1-year reference period. The exposure of interest E, namely beta-agonist use in the prior year, was first dichotomized by defining a cutoff at 12 canisters for the year (low: ≤ 12, that is, ≤ 1 canister per month; high: >12, that is, >1 canister per month), with "high" use corresponding to $E = 1$. To assess dose-response, trichotomous (low: ≤ 12; moderate: >12 and ≤ 24; excessive: >24) and continuous forms of beta-agonist exposure were also used, the latter in terms of the number of canisters per month. These data may be analyzed by three approaches.

The Conventional Analysis

Under a conventional case-control strategy, the relative risk of interest is that associating drug exposure E during the current period with the probability of the event characterized by the case/noncase status, with adjust-

ment for potential confounder(s) measured during the current period, the baseline period, or both. The technique for this analysis is based on the unconditional logistic regression model. Although, in the original study, the controls were matched to the cases, we found that the effect of matching was practically negligible, thus justifying an unmatched analysis.

Table 1 displays the results of these analyses for our data. For the dichotomous form of exposure, identified by Row a in Table 1, the crude odds ratio for high beta-agonist use is 4.4 (95% CI = 2.9–6.7). Adjusting for concurrent (during the current period) oral corticosteroid use and the number of prior asthma hospitalizations as confounding factors lowers the odds ratio to 3.4 (95% CI = 2.2–5.3). Additional adjustment for beta-agonist and oral corticosteroid use during the reference period further lowers the odds ratio, albeit minimally, to 3.1 (95% CI = 1.8–5.4). Since this model "adjusts" the effect of drug exposure for differences in the baseline and concurrent severity markers, we can deduce that 3.1 is the "best" estimate one can derive from these case-control data using conventional tools.

Rows b and c of Table 1 display corresponding results for the trichotomous and continuous forms of beta-agonist exposure, respectively. The dose-response relation between the amount of beta-agonist use and the risk of fatal or near-fatal asthma is clearly evident from these two analyses. These results conform with those previously reported.[5]

The Case-Crossover Analysis

Using this strategy, based solely on the cases, we may use techniques for matched-pairs data to estimate the relative risk by contrasting *E* during the current period with *E* during the reference period in these same cases. The Mantel-Haenszel estimate of the odds ratio in this situation is simply given by the ratio of the number *B* of cases exposed during the current period and unexposed during the reference period to the number C unexposed during the current period and exposed in the reference period. This odds ratio in the cases, denoted by OR_{ca}, can also be obtained from a conditional logistic model. In our example, for the 129 cases of the asthma study, *B* = 29 and C = 9, so that OR_{ca} = 3.2 (95% CI = 1.5–6.8).

The Case-Time-Control Analysis

The case-crossover strategy applied to a situation of chronic effects, by using case subjects as their own controls, permits control for severity but does not account for general time trends in drug use. The case-time-control model does account for time trends. The results of this latter approach, applied to the asthma data, are displayed in Table 2. For Row a, corresponding to the dichotomous form of beta-agonist exposure, we find the effect associated with the drug itself to be OR = 1.2 (95% CI = 0.5–3.0), as obtained from the interaction term of Model 6. The effect of natural time trends in beta-agonist use is given by an odds ratio of 2.6 (95% CI = 1.6–4.1). Time trend accounts for much of the excess relative risk found by the approach based solely on the cases (case-crossover), namely OR = 3.2 (95% CI = 1.5–6.8).

Rows b and c of Table 2 display the corresponding results of the analysis based on the trichotomous and continuous forms of beta-agonist use. For the continuous form, the relative risk from the case-crossover analysis is OR = 2.8 (95% CI = 1.6–4.5) per canister of beta-agonist per month, whereas the portion due to time trends is 1.6 (95% CI = 1.2–2.2). Therefore, the residual effect due to the drug is OR = 1.7 (95% CI = 0.9–3.0). The corresponding best estimate from the conventional approach is OR = 2.1 (95% CI = 1.6–2.9).

For the trichotomous exposure, the net drug effect odds ratios are 1.1 (95% CI = 0.4–2.5) and 3.1 (95% CI = 0.7–12.9) for 1–2 and >2 canisters per month, respectively, when contrasted with ≤1 canister. These arise from corresponding combined (case-crossover) effects of 2.7 (95% CI = 1.2- 5.8) and 6.4 (95% CI = 1.9–21.7), of which period effects of 2.7 (95% CI = 1.7- 4.2) and 2.1 (95% CI = 1.0–4.3) are removed.

TABLE 1. Results of Conventional Approach: Unconditional Logistic Regression Analysis for Asthma Case-Control Study of 129 Cases and 655 Controls with Three Models and Three Forms of Exposure

	Crude		Adjusted for Covariates in: Current Period Only		Adjusted for Covariates in: Current and Reference Period†	
	OR	95% CI	OR	95% CI	OR	95% CI
Beta-agonist use during current period (canisters/year)						
a. Dichotomous >12 *vs* ≤12	4.4	2.9–6.7	3.4	2.2–5.3	3.1	1.8–5.4
b. Trichotomous						
13 –24 *vs* ≤12	2.9	1.8–4.7	2.3	1.4–3.9	2.2	1.3–3.8
>24 *vs* ≤12	7.3	4.5–11.8	5.4	3.3–9.0	4.9	2.3–10.2
c. Continuous‡ number/month	1.9	1.6–2.2	1.7	1.5–2.0	2.1	1.6–2.9

* Adjusted for number of prior asthma hospitalizations and oral corticosteroid use during the current period.
† Adjusted for number of prior asthma hospitalizations, oral corticosteroid use during the current period, and beta-agonist and oral corticosteroid use during reference period.
‡ Odds ratio is per canister per month.

Discussion

The problem of confounding by indication is the source of major criticisms, and often rightfully so, regarding the value of nonexperimental epidemiologic research in the study of the known or intended effects of drugs. In several instances, however, the alternative randomized trial approach advocated by these critics is simply an unacceptable solution. Indeed, by its prospective nature, by the rarity of the events under study and, most importantly, in view of the rapid evolution

TABLE 2. Results of Case-Time-Control Approach: Conditional Logistic Regression Analysis for Asthma Case-Control Study with Two Models and Three Forms of Exposure

	Case-Crossover		Case-Time-Control	
	OR	95% CI	OR	95% CI
Beta-agonist use (canisters/year)				
a. Dichotomous				
>12 *vs* ≤12	3.2	1.5–6.8	2.6	1.6–4.1
Beta-agonist × G*			1.2	0.5–3.0
b. Trichotomous				
13–24 *vs* ≤12	2.7	1.2–5.8	2.7	1.7–4.2
>24 *vs* ≤12	6.4	1.9–21.7	2.1	1.0–4.3
Beta-agonist × G*				
M13–24 *vs* ≤12			1.1	0.4–2.5
>24 *vs* ≤12			3.1	0.7–12.9
c. Continuous†				
Number/month	2.8	1.6–4.5	1.6	1.2–2.2
Beta-agonist × G*			1.7	0.9–3.0

* G denotes the subject's group: G = 1 for case subjects and G = 0 for control subjects.
† Odds ratio is per canister per month.

of drug development in general, this experimental approach would generate obsolete data and, in a field where decisions regarding drug safety are made swiftly, would become essentially inapplicable. The proposed case-time-control design offers a solution to the problem of confounding by indication. By using subjects as their own controls within the familiar case-control strategy and adjusting for natural time trends in drug utilization, the case-time-control design permits the separation of the effect associated with the drug from that of disease severity, even if this severity is not measured.

In our study of the risk of fatal or near-fatal asthma associated with the use of inhaled beta-agonists, we found that the "best" estimate of relative risk for high *vs* moderate beta-agonist use using the conventional case-control approach is 3.1 (95% CI = 1.8–5.4). Since no direct measures of disease severity were available, this "relative risk" of 3.1 is believed to comprise both the effects of the drug and of disease severity, with no possibility of quantifying the relative contribution of each. The corresponding estimate using the case-time-control approach is 1.2 (95% CI = 0.5–3.0). The effect due to disease severity, assuming that 1.2 is the actual drug effect and that 3.1 is the combined effect, and from the multiplicative nature of the measure, can be estimated to be 2.6. Thus, it appears that the effect due to disease severity overwhelms that of the drug in this study. On the other hand, the corresponding dose-response analysis, using the trichotomous form of beta-agonist exposure, indicates that there may be a drug effect from excessive use (>2 canisters per month), with an odds ratio of 3.1, but not with moderate use (1–2 canisters per month), with an odds ratio of 1.1.

The proposed method appears to have two consequences on the effect measure. First, it produces an estimate of effect systematically lower than the one based on the conventional approach. This result is not surprising if disease severity confounds in the usual way. Indeed, the case-time-control method, by using subjects as their own controls, is expressly designed to *remove* the effect due to severity from the measure resulting from the conventional approach. Second, it appears that the measure of effect resulting from the case-time-control method is less precise than the corresponding conventional one. This loss in precision results partly from the within-subject correlation induced by this proposed design, which reduces the effective study size of the one-to-one matched analysis required by its analysis. The apparent loss in precision is an artifact, however, since the conventional approach produces biased estimates of drug effects, as they are confounded by disease severity. The precisions are thus not comparable.

The case-time-control design is an extension of the case-crossover design from short transient exposures to longer chronic exposures. In fact, it reduces to the case-crossover design if we find no natural time trends in drug utilization, except for considerations of longer time windows. The length of the exposure period, that is, the duration of exposure necessary to produce the effect under study, depends on the hypothesized mechanism of action and epidemiologic knowledge about drug exposure. The case-crossover design deals with exposures that are transient and of such brief duration that they are not an issue in the design. They are in fact incorporated within the effect period, the time period during which the risk of the event is presumed to be elevated after exposure to the agent under study. In Maclure's examples, the durations of sexual activity and coffee drinking (exposure periods) were incorporated within the 1-hour effect period during which the risk of a cardiovascular event was hypothesized to increase following the start of performing these activities. In our situation, the exposure period is long (1 year), since it was originally hypothesized that continuous exposure to 12 consecutive months of high use of inhaled beta-agonist medication was necessary to produce an increased risk of these adverse outcomes. The current period defined in this paper incorporates this information about the exposure period. Thus, an accurate specification of the length of the exposure period is crucial to the validity of the analysis. We propose that, in the absence of a precise period, various suitable durations could be attempted and their results interpreted *a posteriori*.

The reference period is an antecedent period of the subject's disease course, during which exposure will be determined, that serves as the source of "control" or reference information. It must be the same length as the current period and is here taken to be the time period immediately preceding the start of the current period. It can also be selected as a more remote point in time, leaving a gap with the current period, but this would impose strict selection criteria to the study population, such as, for example, that all subjects must be at least 5 years into their disease. The proposed approach of adjacent periods is thus the simplest, although the proximity of the current and reference periods may impinge upon the appropriateness of the assumption of conditional independence of exposures. On the other hand, this

proximity protects against possibly confounding changes in disease severity that are more likely to occur if the gap between the current and reference periods is too long. In this case, the resulting relative risk may not be free of confounding by disease severity. In essence, the choice of the reference period must be made by judiciously weighing these considerations.

Maclure[7] discussed the possible limitations of the case-crossover design, which are similar to those of the proposed case-time-control approach. First, within-subject confounding from the underlying constant severity is automatically accounted for by this technique, by using subjects as their own controls. Nevertheless, if severity, which is associated with drug use, also increases (or decreases) within subjects over time, and does so differently for case and control subjects, what is believed to be the residual effect associated with the drug could well remain confounded to some extent. This effect may be unimportant if the odds ratios are near one. For example, in our illustration, even if the severity of case subjects increased faster than that of control subjects over the 2-year span, the relative risk of 1.2 for the drug effect would indicate that the true value can only be lower, thus not changing the conclusions. This problem will not occur if the increase in severity is equal for case and control subjects. Nevertheless, it is important to have a good understanding of disease mechanisms when applying this design and, for example, to match case and control subjects on disease duration or similar factors.

Second, the model is based on the assumptions that the exposures within a subject during the current period and reference period are conditionally independent and that there is no carryover effect from the reference period to the current period. Although there is no quantitative means of verifying these assumptions, the latter can be taken into account in interpreting the exposure odds ratio by understanding that such a carryover effect would more likely increase the odds ratio. Thus, here again, this effect is inconsequential if the odds ratio is near one.

Third, selection bias, unlike in the case-crossover design, can be as problematic as for any standard case-control study, since the control subjects play a determining role in the case-time-control design. Consequently, the same precautions must be used with this design. An important consideration with the selection of control subjects in the case-time-control design is that exposures must be measured at the same points in calendar time as their respective case subjects.

Fourth, information bias may turn out to be less of a concern than for the case-crossover design. Indeed, if exposure measures are obtained in the same way for case and control subjects, any bias induced by time should cancel out. Finally, an accurate specification of the lengths of the current and reference periods is as crucial here as it is for conventional case-control studies.

In conclusion, the case-time-control design can, in the absence of confounders, provide unconfounded relative risk estimates for an exposure of interest. It thus offers a solution to the problem of confounding by indication,[4] which is a major obstacle in pharmacoepidemiology when assessing the known or intended effects of a drug using nonexperimental designs. In our example from a study of the risk of fatal or near-fatal asthma associated with the use of inhaled beta-agonists, the conventional case-control analysis suggests an important adverse effect of the drug, although the confounded yet unmeasured disease severity could explain some or all of this effect. A re-analysis of these data by the case-time-control approach indicates that the effect of asthma severity is the principal part of the risk, whereas the actual effect of the drug is small, if not nil. It would be useful to validate this case-time-control approach by re-analyzing data from other studies with suspected confounding by indication and possibly uncover similar contrasts.

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