Index event bias—a numerical example

Luc J.M. Smits, Sander M.J. van Kuijk, Pieter Leffers, Louis L. Peeters, Martin H. Prins, Simone J.S. Sep

Department of Epidemiology, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre, Peter Debyeplein 1, 6229 HA Maastricht, The Netherlands
Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Peter Debyelaan 25, 6229 HX Maastricht, The Netherlands
Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Lundlaan 6, 3584 EA Utrecht, The Netherlands
Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Peter Debyelaan 25, 6229 HX Maastricht, The Netherlands
Department of Internal Medicine, Maastricht University Medical Centre, Peter Debyelaan 25, 6229 HX Maastricht, The Netherlands

Accepted 12 June 2012

Abstract

Studies of determinants of recurrent disease often give unexpected results. In particular, well-established risk factors may seem not to have much influence on the recurrence risk. Recently, it has been argued that such paradoxical findings may be because of the bias caused by the selection of patients based on the occurrence of an earlier episode of the disease. This bias was referred to as index event bias. Here, we give a theoretical quantitative example of index event bias, showing that, as a result of selection of patients on the basis of previous disease: (1) risk factors become inversely associated when they are not in the unselected population, and (2) the crude association between the risk factor of interest and disease becomes biased toward the null.

© 2013 Elsevier Inc. Open access under the Elsevier OA license.

Keywords: Recurrence; Epidemiologic methods; Bias (epidemiology); Multifactorial causality; Risk factors; Models, theoretical

1. Introduction

Many medical disorders can recur within individuals. If the risk of developing a disorder is increased after its first occurrence, previously affected individuals constitute a risk group for the disorder and target for prevention. As prevention can be accomplished by manipulating causal factors, studies have been devoted to identifying causal factors of recurrence and estimating their strength.

Such studies often give unexpected results. In particular, factors that have been well established as determinants of the first occurrence of a disease may seem not to influence the risk of recurrence much. For instance, factor V Leiden is an established strong risk factor of first-time venous thrombosis, with reported relative risks (RRs) of up to 80 for homozygous individuals vs. noncarriers [1]. However, among patients with a previous thrombotic event, its effect on the recurrence is not clear [2]. Another example is that hypertension, although increasing the risk of first-time stroke about fourfold [3], has turned out to be a much weaker risk factor for stroke recurrence, with RRs ranging from 0.9 to 1.6 [4–8].

Dahabreh and Kent [9] have recently argued that such paradoxical findings can be the result of selection of a study population on the basis of previous occurrence of an event. Because of conditioning on this event, an inverse association between (known and unknown) risk factors may arise, when these risk factors are not mutually associated within the general population. As a consequence, the association between the individual risk factors and recurrence of the event will be biased toward the null (“index event bias”). In the example of hypertension and stroke, experimental studies show that the reduction of hypertension has strong beneficial effects on stroke recurrence rates [10,11], further indicating that the apparent weakness of the association in observational studies is indeed a result of bias.

Although Dahabreh and Kent make a strong case for index event bias as an explanation of the paradoxical findings in recurrence risk research, they do not adduce quantitative examples to show the mechanism of the bias. In the present article, we will illustrate the operation of the bias by the use of a numerical example.

2. Simulation in short

We present hypothetical data for a study intending to measure the association of a particular risk factor with...
Assumptions
To enhance transparency of the example, we make a number of simplifying assumptions, namely
1. all women who experience a pregnancy complication proceed to a next pregnancy,
2. experiencing the complication for the first time does not in itself increase the risk of a new instance of the complication, and
3. individual risk profiles (i.e., the combination of risk factors) do not change over the course of the two consecutive pregnancies.

In an additional analysis, we relax the latter assumption by allowing risk factor status to change between the two pregnancies.

the recurrence of a particular pregnancy complication. To demonstrate the effects of the selection on the basis of a prior complication, we start with a population of first-time pregnant women, let part of them develop the complication, and then focus on second pregnancies among those who developed the complication. In the population of first-time gravids, the risk factor of interest is unassociated (by design) to other risk factors of the complication. We will demonstrate that, after the selection on the basis of prior complication

1. the risk factor of interest becomes inversely associated with other risk factors of the complication and
2. the crude association between the risk factor of interest and complication becomes biased toward the null.

3. Simulation study
3.1. First pregnancy
Let us consider an initial cohort of 100,000 first-time pregnant women and assume that there are four risk factors involved in the etiology of the pregnancy complication (C), namely the risk factor of interest (R), two other unmeasured risk factors (U1 and U2), and pregnancy (P). We set the marginal frequencies of R, U1, and U2 during the first pregnancy to 0.2, 0.2, and 0.2, respectively, and ensure that the occurrence of each factor is independent of that of each of the other two (Table 1). For instance, the likelihood that U1 = 1 is 0.20, whether R = 1 or R = 0.

In line with contemporary disease causation theory, we assume that the development of disease is the result of the combined action of multiple component causes. We stipulate that causation of C needs the presence of P together with at least two other risk factors. Table 2 lists all combinations of values of risk factors sufficient for C to develop.

Table 1. Joint distribution of risk factors R, U1, and U2 in 100,000 first-time pregnant women

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>U1 = 1</th>
<th>U1 = 0</th>
<th>U1 = 0</th>
<th>U1 = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = 1</td>
<td>800</td>
<td>3200</td>
<td>3200</td>
<td>12800</td>
</tr>
<tr>
<td>R = 0</td>
<td>3200</td>
<td>12800</td>
<td>12800</td>
<td>51200</td>
</tr>
<tr>
<td>Total</td>
<td>4000</td>
<td>16000</td>
<td>16000</td>
<td>64000</td>
</tr>
</tbody>
</table>

Italic numbers indicate women developing C because of a combination of risk factors (Table 2).

Application of this scheme to our population of primigravids means that 10,400 women (10.4%) develop the pregnancy complication (Table 1, italic numbers). Risks of developing the complication among individuals with R = 1 and R = 0 are 0.36 (7,200/20,000) and 0.04 (3,200/80,000), respectively, and the RR is 9.00 (0.36/0.04).

3.2. Second pregnancy
In Table 3, frequencies of combinations of R, U1, and U2 are displayed for the second pregnancy among the 10,400 women who experienced the complication in their first pregnancy. Now, the three risk factors have become negatively associated. For instance, if R = 1, the likelihood that U1 = 1 is 0.56, whereas it is 1.00 if R = 0.

Because only women with a previous complication are included and no changes in determinant status across pregnancies occur, all women in both strata of R develop the complication during their second pregnancy, and the crude RR for R = 1 vs. R = 0 is 1.00 ((7,200/7,200)/(3,200/3,200)).

This value of the (crude) RR is the result of extreme bias toward the null, caused by the introduction of a negative association between R and the other risk factors. The real (causal) RR can be calculated by means of a counterfactual approach [12]. That is, instead of comparing the observed complication risks of women with R = 1 and R = 0, the observed complication risk among women with R = 1 is compared with the hypothetical risk that would apply if the same women would have R = 0 instead of R = 1. Computed in this way, the RR amounts to 9.00 because its denominator is 0.11 (800/7,200) instead of 1.00 (3,200/3,200).

3.3. Effect of risk factor change across pregnancies
In the example described previously, we did not allow individual risk factor status to change between pregnancies.
We carried out some additional calculations to see how such intraindividual changes in the presence of $R$, $U_1$, and $U_2$ would influence the amount and direction of bias. Fig. 1 displays crude and counterfactual RRs for a simulation in which women exposed to $R = 1$ during the first pregnancy can change to $R = 0$ before the start of the second pregnancy. Such change would occur, for instance, in case of a preventive intervention on risk factor $R$. When the probability of $R = 1$ changing to $R = 0$ increases from 0.0 to 0.5, crude RRs increase from 1 to about 2, whereas real (counterfactual) RRs remain equal.

Fig. 2 shows crude and counterfactual RRs for a simulation in which women with $R = 0$ can change to $R = 1$, mimicking a situation in which the probability of being exposed to the risk factor increases over time (e.g., advanced age). When the probability of $R = 0$ changing to $R = 1$ increases from 0.0 to 0.5, crude RRs remain 1, whereas real RRs change from 9.0 to about 3.5.

Figures 3 and 4 show crude and counterfactual RRs for simulations in which women with $U_1 = 1$ can change to $U_1 = 0$ (Fig. 3) or from $U_1 = 0$ to $U_1 = 1$ (Fig. 4). These simulations mimic variability of risk factors other than the risk factor of interest. The figures show that the transition from $U_1 = 1$ to $U_1 = 0$ leads to an increase of both crude and real RRs, whereas the transition from $U_1 = 0$ to $U_1 = 1$ leads to a decrease in real RR while crude RR remains 1. Across the observed range of probabilities of transition from $U_1 = 1$ to $U_1 = 0$ or vice versa, crude and real RRs never cross, and hence, bias remains present.

4. Discussion

Our simulation study illustrates how restriction to individuals with previous disease can lead to biased estimates of the strength of risk factors of disease recurrence. This type of bias has earlier been referred to as index event bias and is a form of “collider-stratification bias” [13]. As the bias is attributable to the selection of a study population on the basis of a common effect of two (or more) factors, it can be considered a form of selection bias [14].

Table 3. Joint distribution of risk factors $R$, $U_1$, and $U_2$ during the second pregnancy of 10,400 women who developed the pregnancy complication during the first pregnancy

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>$U_1 = 1$</th>
<th>$U_1 = 1$</th>
<th>$U_1 = 0$</th>
<th>$U_1 = 0$</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R = 1$</td>
<td>800</td>
<td>3,200</td>
<td>3,200</td>
<td>0</td>
<td>7,200</td>
</tr>
<tr>
<td>$R = 0$</td>
<td>3,200</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3,200</td>
</tr>
<tr>
<td>Total</td>
<td>4,000</td>
<td>3,200</td>
<td>3,200</td>
<td>0</td>
<td>10,400</td>
</tr>
</tbody>
</table>

Italic numbers indicate women developing recurrent $C$ because of a combination of risk factors (Table 2).

Fig. 1. Crude and counterfactual relative risks (RRs) for the association between $R$ and $C$ during the second pregnancy, as a function of the probability ($P$) that women with $R = 1$ during the first pregnancy change to $R = 0$ before the start of the second. Crude RR, solid line and counterfactual RR, dashed line.

Fig. 2. The crude and counterfactual relative risks (RRs) for the association between $R$ and $C$ during the second pregnancy, as a function of the probability ($P$) that women with $R = 0$ during the first pregnancy change to $R = 1$ before the start of the second. Crude RR, solid line and counterfactual RR, dashed line.

Fig. 3. The crude and counterfactual relative risks (RRs) for the association between $R$ and $C$ during the second pregnancy, as a function of the probability ($P$) that women with $U_1 = 1$ during the first pregnancy change to $U_1 = 0$ before the start of the second. Crude RR, solid line and counterfactual RR, dashed line.

Fig. 4. The crude and counterfactual relative risks (RRs) for the association between $R$ and $C$ during the second pregnancy, as a function of the probability ($P$) that women with $U_1 = 0$ during the first pregnancy change to $U_1 = 1$ before the start of the second. Crude RR, solid line and counterfactual RR, dashed line.
The study design considered in this article, in which the study population is restricted to individuals with a first episode of disease and followed until recurrence of the disease, has frequently been applied in a wide range of medical (and nonmedical) disciplines. Until now, the possibility of index event bias (or collider-stratification bias) has not been mentioned in any of these studies, even when the associations that were found were unexpectedly weak. As a consequence, the importance of risk factors of recurrence, and therefore the potential effectiveness of prevention aimed at risk factors, may have been underestimated.

In our simulation, we made some simplifying assumptions that merit attention. First, we assumed that all women with the complication in the first pregnancy conceived again. In the real world, a second pregnancy may not occur for a number of reasons. For instance, women with a previous complicated pregnancy may choose to prevent a new pregnancy to avoid the risk of a recurrent complication. If the probability of a second pregnancy is unrelated to risk factors of the complication or only related to the risk factor of interest, the degree of bias will not be different from that in our simulation (because the numerator and denominator for the RR do not change). If the probability of a second pregnancy is related to other risk factors of the complication ($U_1$ or $U_2$ in our simulation), the degree of bias may differ from that in the simulation.

Second, in our example, we assumed that the pregnancy complication in itself did not affect recurrence risk. This assumption may often not hold because many disorders, during their first instance, can induce immunity, organ damage, or other long-term effects that may influence the risk of recurrence. We chose not to incorporate this effect in our simulations to preserve simplicity and focus on the core mechanism of the bias. Further methodological studies could explore the effects of adaptations of the model, making it comply better with specific real-world situations.

It should be noted that the numerical results obtained in our example depend on the particular risk model assumed. The strength of the bias may vary with the number of different sufficient causes and their composition. For a theoretical elaboration of modeling approaches of the effects of conditioning on a collider within a sufficient-component cause framework, we refer to VanderWeele and Robins.

Our additional analyses show that the degree of bias decreases when intra-individual variability of the risk factor of interest increases. On the basis of this result, we expect that index event bias tends to be stronger when unmodifiable factors (such as genetic factors) are studied. We also found that, when intra-individual variability of other (unknown) risk factors increases, the degree of bias can decrease as well as increase.

In addition to complicating causal research, the selection on an index event may affect the accuracy of predictive models of recurrence risk. Because of the introduction of negative associations between measured and unmeasured risk factors, the predictive value of the measured risk factors will decrease. This may lead to the seemingly contradictory finding that a factor proven to be a target for effective recurrence prevention turns out to be a weak predictor of the outcome in a recurrence risk prediction model. More research is needed with respect to the consequences of index event bias for prediction studies.

In our simulation, we used a counterfactual approach to calculate correct RRs (i.e., unaffected by index event bias). Obviously, this approach is not feasible in the real world because values of all component causes (and their interaction in causing the outcome) need to be known. For now, we are not aware of any method by which all bias can be removed in practice. As Darabreh and Kent have noted, partial control may be achieved by adjusting for important risk factors of the outcome. Residual bias will however always be a concern because generally many causal factors remain unknown.

In conclusion, the possibility of index event bias should be a reason for extra caution in the causal interpretation of results of recurrence risk factor studies. The absence of any strong or consistent association of a determinant with recurrence risk should not be the reason to discard the factor as a potential focus for preventive action, as exemplified by hypertension and stroke recurrence.

References


196


