Sensitivity analyses to estimate the potential impact of unmeasured confounding in causal research

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Background The impact of unmeasured confounders on causal associations can be studied by means of sensitivity analyses. Although several sensitivity analyses are available, these are used infrequently. This article is intended as a tutorial on sensitivity analyses, in which we discuss three methods to conduct sensitivity analysis.

Methods Each method is based on assumed associations between confounder and exposure, confounder and outcome and the prevalence of the confounder in the population at large. In the first method an unmeasured confounder is simulated and subsequently adjusted. The other two methods are analytical methods, in which either the (adjusted) effect estimate is multiplied with a factor based on assumed confounder characteristics, or the (adjusted) risks for the outcome among exposed and unexposed subjects are adjusted by such a factor. These methods are illustrated with a clinical example on influenza vaccine effectiveness.

Results When applied to a dataset constructed to assess the effect of influenza vaccination on mortality, the three reviewed methods provided similar results. After adjustment for observed confounders, influenza vaccination reduced mortality by 42% [odds ratio (OR) 0.58, 95% confidence interval (CI) 0.46–0.73]. To arrive at a 95% CI including one requires a very common confounder (40% prevalence) with strong associations with both vaccination status and mortality, respectively OR 0.3 and OR 5.3 (OR 0.79, 95% CI 0.62–1.00).

Conclusions In every non-randomized study on causal associations the robustness of the results with respect to unmeasured confounding can, and should, be assessed using sensitivity analyses.

Keywords Bias, confounding, sensitivity analysis, unmeasured confounding

Introduction

Every non-randomized study on a causal association is threatened by potential confounding.1,2 For example, in daily medical practice, patients with a clear indication typically have a poorer prognosis and are, therefore, more likely to receive the (potentially beneficial) intervention. As a result, the observed effect of the intervention may be confounded (in this case typically diluted) by the clinical
condition of the patient. Several methods have been proposed to adjust for measured confounders, whereas unmeasured confounders may still bias the association under study. Although we cannot directly adjust for unmeasured confounders, their potential impact can be estimated by means of sensitivity analyses.

Over the years, several types of sensitivity analyses of the potential effect of unmeasured covariates on causal associations have been published. Even though some of these methods were proposed over 20 years ago, their application in clinical research is still limited. The aim of this article is to give an introduction to these methods and provide a sensitivity analysis that can easily be applied to clinical research. The sensitivity analysis we extensively present is based on previous work by Greenland and estimates the impact of an unmeasured binary confounder on the measured causal association between a binary exposure and a binary outcome.

To show how this method can be applied in clinical research we implemented it in a clinical study on the association between influenza vaccination and mortality risk among elderly. First, the example is introduced and analysed with adjustment for measured confounders (as is frequently done in epidemiologic research). Subsequently, the sensitivity analysis is introduced and applied. A secondary objective is to investigate to what extent a simulated unmeasured confounder resembles real unmeasured confounders. Finally, two other analytical methods are reviewed and applied to the same clinical example of influenza vaccine effectiveness. Hence, this article not only gives an introduction to methods to conduct sensitivity analyses of unmeasured confounders, but also illustrates how such methods can be applied in non-randomized studies.

Clinical example

We conducted a retrospective cohort study among community-dwelling elderly (age $\geq 65$ years) using the computerized medical database of the University Medical Center Utrecht General Practitioner Research Network. Medical information of seven influenza epidemic periods (1995/96–1999/2000, 2001/ 02, 2002/03) was pooled. We excluded the '2000/01' winter period because there was almost no influenza activity. Influenza epidemic periods were defined as periods of at least 2 consecutive weeks in which each week accounted for at least 5% of the season's total number of influenza isolates (national laboratory-based surveillance data). Vaccination status was ascertained through International Classification of Primary Care (ICPC)-coding (R44.1). Co-morbidity status was based on registration of ICPC-codes during the 12 months preceding each year’s influenza epidemic period: cardiovascular co-morbidity (myocardial infarction [K75], congestive heart failure [K77], other cardiovascular diseases [K74, K76, K78–K80, K82–K84] or stroke [K90]), pulmonary co-morbidity (lung cancer [R84, R85], asthma or chronic obstructive pulmonary disease [R91, R95, R96]), diabetes [T90] and cancer [B72, B73, B74, D74–77, S77, T71, U75–77, X75–77, Y77]. Furthermore, health care consumption [number of general practitioner (GP), visits] and medication use (cardiovascular medication [ATC code C01, C02, C03, C07, C08, C09, B01], pulmonary medication [R03] and diabetic medication [A10]) in the year preceding each influenza epidemic period were recorded. Vaccine effectiveness was estimated using logistic regression analysis adjusted for these measured confounders.

In total, 44,418 observations on influenza epidemic periods were pooled. Among 32,388 exposed subjects 266 died, whereas among 12,030 unexposed subjects 113 died, resulting in a crude odds ratio (OR) of 0.87 [95% confidence interval (CI) 0.70–1.09]. After adjusting for measured confounders (age, sex, health status and prior health care and medication use) influenza vaccination reduced all-cause mortality during influenza epidemics by 42% (adjusted OR 0.58, 95% CI 0.46–0.73).

Although several measured confounders were considered in this analysis, the adjusted effect estimate may be biased by unmeasured confounders. For example, functional health status has been suggested to be an important confounder of the association between influenza vaccination and mortality risk. Functional status measures were not available for this dataset. Sensitivity analyses can be used to estimate the potential impact of such an unmeasured variable on the estimated causal association.

Sensitivity analysis of unmeasured confounding

To analyse how sensitive the association between the exposure and the outcome is to unmeasured confounding, the characteristics of the unmeasured confounder can be varied over a range of values. This range of values can reflect predefined realistic confounder characteristics, which is referred to as bias-level sensitivity analysis. It is also possible to simulate a wide range of confounders to study when the association under study will have changed to some predefined point; for example, what characteristics are needed for the one to be included in the CI. Hence the range of the confounders depends on the results of the analyses. This is called target adjustment sensitivity analysis.

Notation

The sensitivity analysis we will first describe here is a generic sensitivity analysis, which means it can (theoretically) be applied to any epidemiological...
dataset. Therefore, we will use a general notation. Let $X$ indicate a dichotomous exposure measure (e.g. vaccination status), where $X=1$ indicates exposure and $X=0$ indicates the absence of exposure. Similarly, let $Y$ indicate a dichotomous outcome measure (e.g. mortality: $Y=1$ if a subject is dead and $Y=0$ if a subject is alive) and let $Z$ be an unmeasured potential dichotomous confounder (e.g. functional health status). Furthermore, $P_Z$ indicates the prevalence of the unmeasured confounder in the total population, $OR_{ZX}$ is the marginal (crude) association between the unmeasured confounder and exposure and $OR_{ZY|X}$ indicates the conditional association between the unmeasured confounder and the outcome (conditional on exposure status).

**Sensitivity analysis with an unmeasured confounder**

To assess the association between a dichotomous exposure measure ($X$) and a dichotomous outcome measure ($Y$) while taking a potential dichotomous confounder ($Z$) into account, we can implement the following approach. Let $n_{ijk}$ be the sample count of units for which $X=i$, $Y=j$ and $Z=k$. For example, $n_{110}$ indicates the number of exposed subjects ($X=1$) that have the outcome ($Y=1$) and in which the unmeasured confounder is absent. If we knew the cell counts for the three-way table in Table 1, we would be able to estimate the association between $X$ and $Y$ adjusted for $Z$.

In general, any set of assumptions that a researcher can make (based on experience or prior research) that allows for a solution for the three-way table is a good approach. There are multiple sets of assumptions that can be used to populate the three-way table. We will use the aforementioned assumptions, to be precise the assumptions about the prevalence of the unmeasured confounder, the marginal association between confounder and exposure and the conditional association between confounder and outcome.

To calculate the cell counts for the three-way table in Table 1, first consider the $2 \times 2$ table of the marginal association between the unmeasured confounder ($Z$) and the exposure ($X$), given in Table 2. The cell counts for this two-way marginal table (Table 2) can be generated by solving a system of equations generated by specifying the association between $Z$ and $X$ and including the prevalence of the unmeasured confounder. The number of exposed, unexposed and the total number of subjects (i.e. $N_{X1}$, $N_{X0}$ and $N$, respectively) can be observed in the data. The probability of presence of the confounder $Z$ among those exposed—i.e. $P_{1}=P(Z=1 \mid X=1)$—and among those not exposed—i.e. $P_{0}=P(Z=1 \mid X=0)$—can be set to satisfy the following set of equations:

$$P_{1} = P(Z=1 \mid X=1) = \frac{b_{11}}{b_{11} + b_{01}} = \frac{b_{11}}{N_{X1}} \quad (1)$$

$$P_{0} = P(Z=1 \mid X=0) = \frac{b_{01}}{b_{10} + b_{01}} = \frac{b_{10}}{N_{X0}} \quad (2)$$

$$P_{Z} = \frac{b_{10} + b_{11}}{N} \quad (3)$$

With a specified value of $OR_{ZX}=\frac{b_{10}}{b_{01}}$, combining equations (1) through (3) results in a second degree polynomial in $P_{1}$:

$$N_{X1}(OR_{ZX} - 1)P_{1}^2 + (NP_{Z}(1 - OR_{ZX}) + N_{X1}(1 - OR_{ZX}) - N)P_{1} + NP_{Z}OR_{ZX} = 0. \quad (4)$$

If we define $P_{X}=N_{X1}/N$, i.e. $P_{X}$ is the probability of exposure in the study population, equation (4) can be rewritten as:

$$P_{X}(OR_{ZX} - 1)P_{1}^2 + ((P_{Z} + P_{X})(1 - OR_{ZX}) - 1)P_{1} + P_{Z}OR_{ZX} = 0. \quad (5)$$

We can solve equation (5) for $P_{1}$ and derive the cell counts for the marginal $Z$-$X$ table. Although equation (5) has two solutions, only one will be plausible (i.e. between 0 and 1). This is the solution for which

$$P_{1} = \frac{(P_{Z} + P_{X})(OR_{ZX} - 1) + 1 + \sqrt{\Delta}}{2P_{X}(OR_{ZX} - 1)}$$

with

$$\Delta = [(P_{Z} + P_{X})(1 - OR_{ZX}) - 1]^2 - 4P_{X}(OR_{ZX} - 1)P_{Z}OR_{ZX} \quad (6)$$

A proof that a feasible solution is always obtained is given in Appendix 1.

Tables 1 and 2 are related, since $b_{00}=n_{000}+n_{010}$, $b_{01}=n_{001}+n_{101}$, $b_{10}=n_{010}+n_{101}$ and $b_{11}=n_{011}+n_{111}$. We can use the same approach to now calculate

| Table 1 Conditional associations between a dichotomous unmeasured confounder ($Z$) and a dichotomous outcome measure ($Y$) for strata of a dichotomous exposure measure ($X$) |
|--------|--------|--------|--------|--------|
| $X=0$  | $X=1$  | $X=0$  | $X=1$  |
| $Y=0$  | $n_{000}$  | $n_{010}$  | $n_{000}$  | $n_{010}$  |
| $Y=1$  | $n_{001}$  | $n_{011}$  | $n_{100}$  | $n_{110}$  |

| Table 2 Marginal associations between a dichotomous unmeasured confounder ($Z$) and a dichotomous exposure measure ($X$) |
|--------|--------|--------|
| $X=0$  | $X=1$  |
| $Z=0$  | $b_{00}$  | $b_{01}$  | $N_{Z0}$  |
| $Z=1$  | $b_{10}$  | $b_{11}$  | $N_{Z1}$  |
|        | $N_{X0}$  | $N_{X1}$  | $N$      |
the cell counts for the three-way table (Table 1). First, we start with the exposed subjects (the right side of Table 1):

\[ P_1 = P(Z = 1 \mid Y = 1, X = 1) = \frac{n_{111}}{n_{111} + n_{110}} = \frac{n_{111}}{N_{Y=1|X=1}} \]

(7)

\[ P_0 = P(Z = 1 \mid Y = 0, X = 1) = \frac{n_{101}}{n_{101} + n_{100}} = \frac{n_{101}}{N_{Y=0|X=1}} \]

(8)

\[ P_{Z|X=1} = \frac{n_{101} + n_{111}}{N_X} \]

(9)

where the number of cases and non-cases among the exposed (i.e. \( N_{Y=1|X=1} \) and \( N_{Y=0|X=1} \)) are observed in the data. \( P_{Z|X=1} \) (the prevalence of the unmeasured confounder among exposed subjects) is provided by the solution to Equation (4). With a specified value of \( \text{OR}_{ZY|X=1} = n_{111}/n_{101} \), (10) yields a second degree polynomial in \( P_1 \):

\[ N_{Y=1|X=1}(\text{OR}_{ZY|X=1} - 1)P_1^2 + (N_{X=1}P_{Z|X=1} - \text{OR}_{ZY|X=1})P_1 + N_{Y=1|X=1}(1 - \text{OR}_{ZY|X=1}) \]

(10)

\[ + N_{Y=1|X=1}(1 - \text{OR}_{ZY|X=1}) = 0 \]

Note the similarities between Equation (4) and Equation (10).

Solving Equation (10) provides \( P_1 \) and, consequently, the cell counts for the conditional Z–Y table (conditional on X). The cell counts for the Z–Y table for the unexposed subjects can be calculated similarly. The conditional associations between Z and Y, i.e. \( \text{OR}_{ZY|X=0} \) and \( \text{OR}_{ZY|X=1} \), can either be considered equal (no interaction) or unequal. The latter would indicate that the effect of the unmeasured confounder (Z) on the outcome (Y) differs for different levels of the exposure (X). Overall measures of association can be estimated from the derived three-way table of cell counts for X, Y and Z.

The general approach outlined above is quite flexible. For example, measures of the associations between the unmeasured confounder and exposure and the unmeasured confounder and the outcome other than ORs, e.g. risk ratios (RRs), can be considered. In Appendix 2 the approach is summarized for situations in which RRs or risk differences are

\[ \text{OR}_{adj} = \frac{n_{111}n_{010}}{n_{101}n_{011}} \]

In this adjusted OR, however, the measured confounders are not taken into account. To take the measured confounders into account, the following procedure can be followed. After calculating the cell counts for the three-way table (Table 1), a variable that meets the predefined confounder characteristics can be constructed. We can randomly generate values for the confounder within each exposure–outcome stratum of subjects satisfying the generated cell counts. For example, there are \( n_{110} + n_{111} \) exposed cases (for which \( X = 1 \) and \( Y = 1 \)) in the dataset of which in \( n_{111} \) the unmeasured confounder is present (\( Z = 1 \)) and in \( n_{110} \) the unmeasured confounder is absent (\( Z = 0 \)).

After constructing the dichotomous confounder, the dataset is similar to the initial dataset but includes the generated unmeasured confounder Z. We can then estimate the association between X and Y, after adjustment for the (unmeasured) confounder Z and the measured confounders in a multiple regression analysis. As the simulation of the unmeasured confounder is a random process, conditional on exposure and outcome, more accurate inference will be obtained by repeatedly applying this process and combining the resultant estimates of association using standard methods for multiple imputation.

In this method the unmeasured confounder is simulated independently of the measured confounders. In reality, however, confounders are often associated. Consequently, when using prior research results concerning the associations between the unmeasured confounder and the outcome and exposure but, for simplicity, ignoring the association of the unmeasured confounder with measured confounders, the sensitivity analysis can result in an over-adjustment for the confounder in the sense that to obtain the same adjusted association (adjusted for the unmeasured confounder), the real confounder characteristics would need to be stronger than that used in the sensitivity analysis. To demonstrate this phenomenon we implemented the following set of analyses. Prior health-care use was dichotomized at 12 GP visits (median). Subsequently, three models were fit: the first model included measured confounders, yet did not include the measured confounder prior health care use. The second model additionally included the measured (dichotomized) confounder prior health-care use, whereas the third model included prior health-care use as a (simulated) confounder that was simulated independently of other covariates.

### Clinical example continued

Influenza vaccination reduced mortality after adjusting for measured confounders (adjusted OR 0.58, 95% CI 0.46–0.73). To study the effect of potential unmeasured confounders on this estimated association we implemented sensitivity analyses. In these sensitivity analyses ranges of strengths of association were
Prevalence of unmeasured confounder = 20%

| Prevalence of unmeasured confounder | OR_{Z|X} |
|-------------------------------------|---------|
|                                    | 1.5     | 2.0     | 2.5     | 3.0     | 3.5     | 4.0     |
| OR_{ZX}                            |         |         |         |         |         |         |
| 0.3                                 | 0.64 (0.50–0.81) | 0.69 (0.54–0.88) | 0.74 (0.58–0.94) | 0.78 (0.61–0.99) | 0.82 (0.64–1.04) | 0.85 (0.66–1.08) |
| 0.4                                 | 0.63 (0.49–0.79) | 0.66 (0.52–0.84) | 0.70 (0.55–0.88) | 0.73 (0.57–0.92) | 0.76 (0.59–0.96) | 0.78 (0.61–0.99) |
| 0.5                                 | 0.62 (0.49–0.78) | 0.64 (0.51–0.81) | 0.67 (0.53–0.84) | 0.69 (0.54–0.87) | 0.71 (0.56–0.90) | 0.72 (0.57–0.92) |
| 0.6                                 | 0.61 (0.48–0.76) | 0.65 (0.50–0.79) | 0.64 (0.51–0.81) | 0.66 (0.52–0.83) | 0.67 (0.53–0.85) | 0.68 (0.54–0.87) |
| 0.7                                 | 0.60 (0.48–0.76) | 0.61 (0.49–0.77) | 0.62 (0.49–0.79) | 0.63 (0.50–0.80) | 0.64 (0.51–0.81) | 0.65 (0.51–0.82) |

Prevalence of unmeasured confounder = 40%

| Prevalence of unmeasured confounder | OR_{Z|X} |
|-------------------------------------|---------|
|                                    | 1.5     | 2.0     | 2.5     | 3.0     | 3.5     | 4.0     |
| OR_{ZX}                            |         |         |         |         |         |         |
| 0.3                                 | 0.66 (0.52–0.83) | 0.71 (0.56–0.91) | 0.76 (0.60–0.96) | 0.79 (0.62–1.00) | 0.82 (0.65–1.04) | 0.84 (0.67–1.08) |
| 0.4                                 | 0.64 (0.50–0.81) | 0.68 (0.54–0.86) | 0.71 (0.56–0.90) | 0.74 (0.58–0.94) | 0.76 (0.60–0.96) | 0.78 (0.61–0.99) |
| 0.5                                 | 0.62 (0.49–0.79) | 0.66 (0.52–0.83) | 0.68 (0.54–0.86) | 0.70 (0.55–0.88) | 0.72 (0.57–0.90) | 0.73 (0.58–0.92) |
| 0.6                                 | 0.61 (0.49–0.77) | 0.64 (0.50–0.80) | 0.66 (0.52–0.83) | 0.67 (0.53–0.84) | 0.68 (0.54–0.86) | 0.69 (0.54–0.87) |
| 0.7                                 | 0.60 (0.48–0.76) | 0.62 (0.49–0.78) | 0.63 (0.50–0.80) | 0.64 (0.51–0.81) | 0.65 (0.51–0.82) | 0.65 (0.52–0.83) |

Numbers represent ORs (including 95% CIs). OR_{ZX} indicates the association (OR) between the unmeasured confounder and vaccination status. OR_{Z|X} indicates the association (OR) between the unmeasured confounder and mortality conditional on exposure status. The 95% CIs of the ORs in the grey area (upper right corner) include one (i.e. influenza vaccination was not significantly associated with mortality).

Sensitivity analysis of the effect of an unmeasured confounder on the association between influenza vaccination and mortality risk

Influence of assumption of independence of the unmeasured confounder

The effect of simulating a measured confounder independently of other covariates was assessed by simulating prior health-care use (in the year preceding each epidemic period). This variable was dichotomized at 12 GP visits (median). In the original dataset the measured variable prior health-care use was related to other covariates, e.g. cardiovascular co-morbidity status (OR 1.88, 95% CI 1.74–2.04) and cancer (OR 1.40, 95% CI 1.19–1.65). In a model that included age, sex, co-morbidity status and prior medication use but not health-care use, influenza vaccination reduced mortality risk by 33% (OR 0.67, 95% CI 0.54–0.85). Subsequent inclusion of the measured covariate prior health-care use as a dichotomized confounder in the model increased vaccine effectiveness to 40% (OR 0.60, 95% CI 0.48–0.76). In the original dataset the measured variable prior health-care use was associated with vaccination status (OR_{ZX} = 2.16), and mortality (OR_{Z|X} = 5.00). The observed prevalence of high prior health-care use (more than 12 visits) was 46%. Using these confounder characteristics, prior health-care use was simulated independently of other covariates, which resulted in 49% vaccine effectiveness (OR 0.51, 95% CI 0.40–0.64). Clearly, simulating prior health-care use independently of other covariates led to an overestimation of the impact of this confounder, indicated by the larger change in estimated vaccine effectiveness (33–49% vs 33–40%). Careful consideration of this phenomenon should be given when using prior research results about associations of outcome and exposure with unmeasured confounders in these sensitivity analyses.

Other sensitivity analyses

Several other methods to conduct sensitivity analyses of unmeasured confounding have been used in epidemiologic research. We would like to review two other methods briefly.

In 1998, Lin et al. presented a method for binary outcomes and censored survival outcomes. This method multiplies intervention effects estimated from regression models incorporating exposure and measured confounders by a factor based on posited associations between an unmeasured confounder and both exposure and outcome. Under the assumption that the unmeasured confounder (Z) is independent of measured confounders (conditional on X), the true RR and the RR obtained without the unmeasured confounder (RR*) are related via RR = RR*/A, with A = \{RR_{Z|X=1}P_1 + (1 - P_1)\}/\{RR_{Z|X=0}P_0 + (1 - P_0)\}.
Here, \( \text{RR}_{ZY|X=1} \) and \( \text{RR}_{ZY|X=0} \) are the RRs for the outcome associated with the unmeasured confounder among the exposed and unexposed, respectively. Hence, the effect of the unmeasured confounder can vary among subgroups of exposure. \( P_1 \) and \( P_0 \) are the prevalence of the unmeasured confounder among the exposed and unexposed, respectively. If the outcome is rare, this method can be used to approximate the impact of unmeasured confounding on ORs as well using a similar adjustment term where the RRs are replaced with the corresponding ORs.

Suppose the association between the unmeasured confounder and the outcome is indicated by an OR \( \text{OR}_{ZY|X} \). Furthermore, suppose subjects with the unmeasured confounder to be half as likely to be vaccinated as subjects without the unmeasured confounder. In the original data on the effects of influenza vaccination the numbers of vaccinated subjects with and without the unmeasured confounder were estimated to be 0.0071 and 0.0123, respectively. This method can accommodate the presence of measured confounders by stratifying on the propensity for exposure given the measured confounders and applying the methodology above within strata. Within strata effects estimates can then be aggregated in a strata-weighted average.

Another method, first published in 1983 by Rubin and Rosenbaum, to conduct sensitivity analysis of unmeasured confounding, is based on maximum likelihood estimation.\(^{11}\) The maximum likelihood estimate of the risk for the outcome among exposed and unexposed subjects is estimated based on four parameters: prevalence of the unmeasured confounder \( (P_Z) \), the association between the unmeasured confounder and the outcome among exposed \( \text{OR}_{ZY|X=1} \) and unexposed \( \text{OR}_{ZY|X=0} \) and the association between the unmeasured confounder and the exposure \( \text{OR}_{ZX} \). This method then takes the following steps. First, the log(odds) the treatment is absent in subjects in which the unmeasured confounder is absent, i.e. \( \Gamma = \text{log}(\text{odds}(X = 0 | Z = 0)) \), is calculated by solving the quadratic equation

\[
[P_X \cdot \text{OR}_{ZX}]w^2 + [(P_X - P_{Z=0}) \text{OR}_{ZX} + P_X - P_{Z=1}]w + (P_X - 1) = 0,
\]

in which \( w = \exp(\Gamma) \). This quadratic equation has one positive solution, which provides \( \Gamma \). Secondly, the probability of absence of the unmeasured confounder, given exposure status, \( P_{Z=0|x} = P(Z = 0 | X = x) \) can be calculated by solving the equation

\[
P_{Z=0|x} = P_{Z=0}/[P_{Z=0} + P_{Z=1} \cdot \exp(X \cdot \text{ln(OR}_{ZX}))]
\]

(1 + exp(\( \Gamma \)))/(1 + exp(\( \Gamma + \text{ln(OR}_{ZX}) \))].

The risk for the outcome among the exposed \( (R_{Y|X=1}) \) and unexposed subjects \( (R_{Y|X=0}) \) can then be used to calculate the effect estimate, e.g. the RR \( (R_{Y|X=1}/R_{Y|X=0}) \). This method can accommodate the presence of measured confounders by stratifying on the propensity for exposure given the measured confounders and applying the methodology above within strata. Within strata effects estimates can then be aggregated in a strata-weighted average.

We estimated the impact of an unmeasured confounder on the association between influenza vaccination and mortality risk using this method. In the original article, the risks for the outcome were calculated for different strata of the study population. These strata were quintiles of the propensity score, based on 74 observed confounders. We will illustrate the method by assessing the impact of unmeasured confounding on the effects of influenza vaccination among elderly. For insightfulness, we estimate this impact as if the total population consists of one stratum. Mortality risks (after adjustment for observed confounders) among vaccinated and non-vaccinated subjects were estimated to be 0.0071 and 0.0123, respectively (OR = 0.58). An unmeasured confounder was assumed to be present in 40% of the population, to be a risk factor for mortality \( \text{OR}_{ZY|X=1} = \text{OR}_{ZY|X=0} = 2 \), and subjects with the unmeasured confounder to be half as likely to be vaccinated as subjects without the unmeasured confounder \( \text{OR}_{ZX} = 0.5 \). Such a confounder would reduce influenza vaccine effectiveness from OR 0.58 (95% CI 0.47–0.71) to OR 0.65 (95% CI 0.53–0.79), which is similar to the results of the other sensitivity analyses we discussed.

**Discussion**

We have illustrated a method, based on generating cell counts, where an unmeasured confounder is simulated independently of measured covariates for exposed and unexposed subjects (i.e. for the situations that \( X = 0 \) and \( X = 1 \)). Thirdly, again for exposed and unexposed subjects (i.e. for \( X = 1 \) and \( X = 0 \)), the log(odds) for the absence of the outcome, given exposure status, \( \beta_X \), can be calculated by solving the quadratic equation

\[
[P_X \cdot \text{OR}_{ZY|X}]w^2 + [(P_X - P_{Z=0}) \text{OR}_{ZY|X} + P_X - P_{Z=1}]w + (P_X - 1) = 0,
\]

in which \( P_X = P(Y = 0 | X = x) = N_{Y=0|x}X \), and \( w = \exp(\beta_X) \). This quadratic equation also has one positive solution. Finally, the risk for the outcome given the exposure \( (R_{Y|X}) \) is calculated:

\[
R_{Y|X} = \frac{P_{Z=0} \exp(\beta_X + \text{ln(OR}_{ZY|X}))}{1 + \exp(\beta_X + \text{ln(OR}_{ZY|X}))} + \frac{P_{Z=1} \exp(\beta_Y)}{1 + \exp(\beta_Y)}
\]
to conduct sensitivity analyses of the impact of unmeasured confounding on the estimation of causal effects. These sensitivity analyses were applied in a clinical example on influenza vaccine effectiveness. In principle, if the unmeasured confounder was collinear with measured confounders, then adjusting for this unmeasured confounder would not affect the causal association. Therefore, in these sensitivity analyses our interest lies in that part of an unmeasured confounder that is not related to the measured confounders. However, since covariates are often related to other covariates (e.g. cardiovascular co-morbidity is related to health-care use), simulating unmeasured confounders independent of measured confounders can overestimate the impact of unmeasured confounders on the association under study for settings where the associations between the unmeasured confounder and the outcome and exposure are based on prior research results. This was demonstrated in the simulation of the measured confounder ‘prior health-care use’ in the influenza vaccine effectiveness data.

Several methods have been developed to estimate the effect of unmeasured confounding in non-randomized studies.7–12 We reviewed two additional methods, first published by Lin et al.12 and Rosenbaum et al.11 These analytical methods provided results similar to those yielded by the method based on generating cell counts. The method by Lin et al. is easy to apply and more readily incorporates measured confounders than the other methods but relies on the assumption of conditional independence of the unmeasured and measured confounders given exposure. The method developed by Rosenbaum and Rubin is more complicated but does not rely upon rarity of outcomes to be applicable in the estimation of ORs. This methodology proposes to reduce measured confounders to a stratification measure using methods such as propensity scores. A similar approach could be taken with the method based on generating cell counts for the three-way table. After stratification on the propensity score this method could be applied within strata and results averaged over strata in some sensible fashion.

Nelson and Noorbalooci discuss how reducing the measured confounders using propensity with the existence of unmeasured confounders depends on the same assumption of conditional independence of the unmeasured confounder and the measured confounders given exposure used by Lin et al.25 Hernan and Robins discuss how this assumption can be easily violated in practice.26 In particular, this assumption will be violated when the measured and unmeasured confounders are independent. However, this technical limitation does not appear to limit use of these methods given the observed correspondence of results among the three methods considered here, only one of which relies on this conditional independence assumption.

All three methods discussed utilize the same confounder characteristics (i.e. the prevalence of the unmeasured confounder, the marginal association between the unmeasured confounder and exposure and the association between the unmeasured confounder and outcome conditional on exposure status). Information on such associations for common unmeasured confounders can often be found in the existing literature. The method of Lin et al. is the simplest method to implement but is limited in flexibility in that the associations between the confounder and the other measure must be on the same scale, i.e. ORs or RRs, as the association of interest between the exposure and outcome. Similarly, mixing different scales of association in the method outlined by Rosenbaum and Rubin would be expected to greatly complicate derivation of the maximum likelihood estimates. The method based on generating the cell counts for the three-way contingency table for X, Y and Z offers a good combination of ease and flexibility.

In the sensitivity analyses applied to the influenza vaccination data, the conditional association between the unmeasured confounder and the outcome was assumed to be similar for exposed and unexposed subjects. A different association between the confounder and outcome for exposed and unexposed subjects implies interaction between exposure and the unmeasured confounder, i.e. the effect of exposure on outcome differs for different levels of the unmeasured confounder. Although such interactions can be included in sensitivity analyses, it seems inconsistent with the intent of sensitivity analyses since our primary interest is in the confounding of the main effect of exposure on the outcome, rather than subgroup effects. The potential usefulness of letting the causal associations vary between levels of the unmeasured confounder in the generation of cell counts would be to mimic some sampling variation. However, small variations of the association between confounder and outcome across groups of exposed and unexposed subjects will minimally affect the estimated causal association. For example, suppose in the clinical example of influenza vaccination the association between an unmeasured confounder and outcome differs 10% between exposed and unexposed subjects (i.e. either OR_{Z|X=1} = 1.9, OR_{Z|X=0} = 2.1 or OR_{Z|X=0} = 2.1, OR_{Z|X=0} = 1.9). Furthermore, the confounder is present in 40% of the population, and reduces the likelihood of vaccination (OR_{ZX} = 0.5). A stable association of the confounder with outcome across exposed and unexposed subjects (OR_{Z|X=2}) results in OR 0.65 (95% CI 0.52–0.82), unstable associations result in comparable effect estimates: OR 0.61 (95% CI 0.49–0.77) and OR 0.69 (95% CI 0.55–0.87).

Multiple unmeasured confounders with small associations with exposure and outcome may, together, have as large an impact on the studied relation than as one strong confounder alone, possibly even one
with extraordinarily large associations with exposure and outcome.\textsuperscript{27} Adjusting for several unmeasured confounders is a challenging problem, since with increasing numbers of unmeasured confounders the number of characteristics grows enormously and possible correlations between such confounders need to be addressed. This is beyond the scope of this article and for new methods on this, we refer to recent work by others.\textsuperscript{28,29} Alternatively, it can sometimes be argued that a single binary unmeasured confounder may approximate several confounders.\textsuperscript{30} Consideration of a single confounder is a useful compromise, but careful consideration should be given to the possibility of multiple unmeasured confounders in the specification of associations for the single utilized unmeasured confounder.

Conflicting results from non-randomized epidemiologic studies are often attributed to unmeasured confounding. With respect to the controversies in influenza vaccination studies,\textsuperscript{31} we showed, as was previously shown by Nichol \textit{et al.},\textsuperscript{32} that it is unrealistic to assume that a single unmeasured confounder could result in the observed mortality reduction by influenza vaccination. Functional health status, which is most often not measured in influenza vaccine effectiveness studies, has been proposed as a potential confounder responsible for the observed vaccination effectiveness.\textsuperscript{21,22} Poor functional health status was shown to be inversely related to influenza vaccination status ($OR_{X} \approx 0.5$), whereas it increased mortality risk ($OR_{Y}$ ranged 2.8–13.4), and was present in 10–15% of the elderly population.\textsuperscript{21} In our data, an unmeasured confounder with the same characteristics as functional health status would, at most (in the case of $OR_{Y|X} = 13.4$), result in a reduction of influenza vaccine effectiveness to 3% ($OR = 0.97$, 95% CI 0.77–1.21), according to the method by Lin \textit{et al.} However, this method can overestimate the effects of unmeasured confounders by ignoring the correlation of functional status with the measured confounders. As an association with mortality as strong as that given by an OR of 13 seems unlikely, it therefore seems likely that vaccine is effective or that there are other unmeasured confounders of vaccine effectiveness. Such additional unmeasured confounders, however, have not been widely identified.

Unmeasured confounding is a major threat to the validity of non-randomized studies. This type of confounding cannot be addressed using standard statistical methods such as regression, matching or stratification. To assess the validity of results of non-randomized studies, the potential impact of an unmeasured confounder on the studied association should be quantified. Sensitivity analyses, such as those presented in this article, assess the sensitivity of the observed relation for ‘clinically plausible’ unmeasured confounding. They do not, however, provide an answer to the question whether unmeasured confounding is actually present and cannot give a single precise estimate of a causal effect. It remains up to the researcher and the critical reader to judge the potential for unmeasured confounding. Although methods for assessing the sensitivity of estimated causal associations to unmeasured confounders have been available for several years,\textsuperscript{22,23} they have not been implemented in routine epidemiologic methodology for observational studies and are infrequently used. In a recent review we estimated <3% of observational intervention studies published in leading medical journals used such sensitivity analyses.\textsuperscript{16} We showed how such analyses can be implemented in every observational study.

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**KEY MESSAGES**

- The impact of unmeasured confounders on causal associations can be studied by means of sensitivity analyses.
- Three reviewed methods of sensitivity analysis of unmeasured confounding provided similar results when applied to a dataset on influenza vaccine effectiveness.
- The assumption of conditional independence between measured and unmeasured confounders underlying these methods can overestimate the impact of unmeasured confounders on the association under study.
Sensitivity analyses of unmeasured confounding

References


Appendix 1

To show that the second degree polynomial in $P_{1}$,

$$P_{X}(OR_{ZX} - 1)P_{1} + ((P_{X} + P_{Z})(1 - OR_{ZX}) - 1)P_{1} + P_{Z}OR_{ZX} = 0,$$

(A1)

has real solutions for any combination of $P_{Z}$ in $(0,1)$, $P_{X}$ in $(0,1)$ and $OR_{ZX}$ in $(0,\infty)$ consider the discriminant of the quadratic solution:

$$\Delta = \{(P_{X} + P_{Z})(1 - OR_{ZX}) - 1\}^{2} - 4P_{X}(OR_{ZX} - 1)P_{Z}OR_{ZX},$$

(A2)
Equation (A1) has real solutions, only if $\Delta \geq 0$. For $OR_{ZX}$ in $(0, 1)$ it is clear that $\Delta > 0$. To see that $\Delta > 0$ for $OR_{ZX}$ in $(1, \infty)$ we can rewrite Equation (A2) as

$$
\Delta = OR_{ZX}(P_Z - P_X)^2 + 2(P_X + P_Z - P_X^2)(OR_{ZX}) + \{(P_Z + P_X) - 1\}^2
$$

(A3)

As $P > P^2$ for any $P$ in $(0,1)$, all three terms in Equation (A3) are positive and, hence, $\Delta \geq 0$.

Now, $P_1$ in Equation (A1) is a probability. Thus at least one of the solutions needs to lie in $(0,1)$. The solution

$$
P_1 = \frac{\left[(P_Z + P_X)(OR_{ZX} - 1) + 1 - \sqrt{\Delta}\right]}{2P_X(OR_{ZX} - 1)}
$$

(A4)

always falls in $(0,1)$. To demonstrate this, it suffices to show $P_1 < 1$ and $P_1 > 0$ for any $P_Z$ in the interval $(0,1)$, $P_X$ in the interval $(0,1)$ and $OR_{ZX}$ in the interval $(0,\infty)$. Note, when $OR_{ZX} = 1$, l'Hôpital’s rule yields $P_1 = P_Z$.

Let us first show $P_1 > 0$. For any $OR_{ZX}$ in the interval $(0,1)$ the denominator of Equation (A4) is negative, so for $P_1 > 0$ the numerator must be positive. This requires

$$(P_Z + P_X)(OR_{ZX} - 1) + 1 - \sqrt{\Delta} > 0, \text{or}
$$

$$(\{(P_Z + P_X)(OR_{ZX} - 1) + 1\})^2 > \Delta, \text{ for}
$$

$$
\Delta = OR_{ZX}^2(P_Z - P_X)^2 + 2(P_X + P_Z - P_X^2)(OR_{ZX}) + \{(P_Z + P_X) - 1\}^2.
$$

This can be re-expressed as

$$
OR_{ZX}^2 - OR_{ZX} < 0, \text{ which is true for any OR}_{ZX} \text{ in the interval (0, 1). A similar argument yields } P_1 > 0 \text{ when OR}_{ZX} \text{ is in (1, } \infty).\n$$

Now, let us show $P_1 < 1$. The inequality $P_1 < 1$ can be written as $P_1 - 1 < 0$. Thus

$$
(P_Z + P_X)(OR_{ZX} - 1) + 1 - \sqrt{\Delta} - 2P_X(OR_{ZX} - 1) < 0
$$

(A5)

For any OR_{ZX} in the interval (0, 1) the denominator in inequality Equation (A5) is negative, so for $P_1 < 1$ the numerator must be positive. Hence, we need

$$(P_Z + P_X)(OR_{ZX} - 1) + 1 - \sqrt{\Delta} - 2P_X(OR_{ZX} - 1) > 0.
$$

This can be re-expressed as

$$
\{(P_Z - P_X)(OR_{ZX} - 1) + 1\}^2 > \Delta. \text{ This can be further reexpressed as}
$$

$$
OR_{ZX}^2P_Z - P_Z - OR_{ZX} + 1 > 0, \text{ or } (P_Z - 1)(OR_{ZX} - 1) > 0, \text{ which is true for any OR}_{ZX} \text{ in the interval (0, 1), since P_Z is in (0, 1). Again, similar arguments yield P_1 < 1 for OR}_{ZX} \text{ in the interval (1, } \infty).\n$$

**Appendix 2**

**RRs**

Suppose the marginal association between an unmeasured dichotomous confounder (Z) and a dichotomous exposure (X) is given by the RR: $RR_{ZX} = P(X = 1|Z = 1)/P(X = 1|Z = 0)$. Then, as given in Table 2,

$\theta_{11} = N_PX_{PZ}(1 + P_Z)(RR_{ZX} - 1),$  
$\theta_{10} = N_PZ - PXPZ(RR_{ZX} - 1),$  
$\theta_{01} = N_{1 - P_Z} - PXPZ/(1 + P_Z)(RR_{ZX} - 1),$  
$\theta_{00} = N_{1 - P_Z} - PXPZ/(1 + P_Z)(RR_{ZX} - 1),$  

for $P_X = N_{1X}/N$ (i.e. $P_Z$ is the probability of exposure in the study population), and $P_Z = N_{Z}/N$ (i.e. $P_Z$ is the prevalence of the unmeasured confounder in the study population).

With a specified value of $RR_{ZX}$, the probability $Z$ takes value 1 among those exposed (i.e. $P_1 = b_{11}/(b_{01} + b_{11}))$, can be written as:

$$
P_1 = \frac{RR_{ZX}P_Z}{1 + P_Z(RR_{ZX} - 1)}
$$

(A6)

As both the numerator and the denominator of equation (A6) are positive for any $P_Z$ in $(0,1)$ and $RR_{ZX}$ in $(0,\infty)$, $P_1 > 0$. Furthermore, $P_1 < 1$, i.e. $RR_{ZX}P_Z/(1 + P_Z(RR_{ZX} - 1)) < 1$, since this can be reexpressed as $P_2 < 1$, which is true for any $P_Z$ in $(0,1)$.

If the association between the unmeasured confounder (Z) and the dichotomous outcome (Y) is specified for each level of the exposure (X), the three-way table cell counts (Table 1) must satisfy:

$$
RR_{ZY|X=0} = [n_{011}/(n_{001} + n_{011})]/[n_{010}/(n_{000} + n_{010})],
$$

with $b_{11} = n_{110} + n_{111}$, $b_{01} = n_{010} + n_{010}$ and $n_{011} + n_{010}$ is the number of unexposed cases. Also,

$$
RR_{ZY|X=1} = [n_{111}/(n_{101} + n_{111})]/[n_{110}/(n_{100} + n_{110})],
$$

with $b_{11} = n_{110} + n_{111}$, $b_{01} = n_{010} + n_{110}$ and $n_{111} + n_{110}$ is the number of exposed cases.

To populate Table 1, we first calculate the probability $Z$ takes value 1, given $X = 1$ and $Y = 1$, i.e. $P_1 = n_{111}/(n_{111} + n_{110})$:

$$
P_1 = \frac{RR_{ZY|X=0}P_{1|X=1}}{1 + P_{Z|X=1}(RR_{ZY|X=1} - 1)},
$$

for which $P_{1|X=1}$ is provided by the solution to Equation (A6).

**Risk differences**

Suppose the marginal association between an unmeasured dichotomous confounder (Z) and a dichotomous exposure (X) is given by the risk difference:

$$
RD_{ZX} = P(X = 1|Z = 1) - P(X = 1|Z = 0).
$$

Then, as given by Table 2,

$$
\theta_{11} = N_{RD_{ZX}P_Z}(1 - P_Z) + P_XP_Z,
$$

$\theta_{10} = N_{RD_{ZX}P_Z} + P_XP_Z(1 - P_Z),
$$

$\theta_{01} = N_{P_Z}(1 - P_Z) - RD_{ZX}P_Z(1 - P_Z),
$$

$\theta_{00} = N_{1 - P_Z} - P_X(1 - P_Z) + RD_{ZX}P_Z(1 - P_Z),
$$

for $P_X = N_{1X}/N$ (i.e. $P_Z$ is the probability of exposure in the study population), and $P_Z = N_{Z}/N$ (i.e. $P_Z$ is the prevalence of the unmeasured confounder in the study population).
With a specified value of $RD_{ZX}$, the probability $Z$ takes value 1 among those exposed (i.e. $P_1 = \frac{b_{11}}{b_{01} + b_{11}}$), can be written as:

$$P_1 = \frac{RD_{ZX} P_Z (1 - P_Z) + P_X P_Z}{P_X} \quad (A7)$$

As both the numerator and the denominator of Equation (A7) are positive for any $P_Z$ in $(0, 1)$, $P_X$ in $(0, 1)$, and $RR_{ZX}$ in $(0, \infty)$, $P_1 > 0$. $P_1 < 1$, only if $P_X > P_ZRD_{ZX}$.

If the association between the unmeasured confounder ($Z$) and the dichotomous outcome ($Y$) is specified for different levels of the exposure ($X$), the three-way table cell counts (Table 1) must satisfy:

$$RD_{ZY|X=0} = \frac{n_{011}}{n_{001} + n_{011}} - \frac{n_{010}}{n_{000} - n_{010}},$$

with $b_{10} = n_{001} + n_{011}$, $b_{00} = n_{010} + n_{000}$, and $n_{011} + n_{010}$ is the number of unexposed cases.

Also,

$$RD_{ZY|X=1} = \frac{n_{111}}{n_{101} + n_{111}} - \frac{n_{110}}{n_{100} - n_{110}},$$

with $b_{11} = n_{101} + n_{111}$, $b_{01} = n_{100} + n_{110}$, and $n_{111} + n_{110}$ is the number of exposed cases.

To populate Table 1, we first calculate the probability $Z$ takes value 1, given $X=1$ and $Y=1$, i.e., $P_1 = \frac{n_{111}}{(n_{111} + n_{110})}$:

$$P_1 = \frac{RD_{ZY|X=1} P_{Y|X=1} (1 - P_{Z|X=1}) + P_{Y|X=1} P_{Z|X=1}}{P_{Y|X=1}},$$

for which $P_{Z|X=1}$ is provided by the solution to Equation A7 and $P_{Y|X=1}$, i.e. the probability of the outcome given $X=1$, is observed in the data.