

## Original article

## Sensitivity analysis for the effects of multiple unmeasured confounders



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## ARTICLE INFO

## Article history:

Received 25 April 2016

Accepted 23 July 2016

Available online 3 August 2016

## Keywords:

Bias

Confounding

Sensitivity analysis

## ABSTRACT

**Purpose:** Observational studies are prone to (unmeasured) confounding. Sensitivity analysis of unmeasured confounding typically focuses on a single unmeasured confounder. The purpose of this study was to assess the impact of multiple (possibly weak) unmeasured confounders.

**Methods:** Simulation studies were performed based on parameters estimated from the British Women's Heart and Health Study, including 28 measured confounders and assuming no effect of ascorbic acid intake on mortality. In addition, 25, 50, or 100 unmeasured confounders were simulated, with various mutual correlations and correlations with measured confounders.

**Results:** The correlated unmeasured confounders did not need to be strongly associated with exposure and outcome to substantially bias the exposure–outcome association at interest, provided that there are sufficiently many unmeasured confounders. Correlations between unmeasured confounders, in addition to the strength of their relationship with exposure and outcome, are key drivers of the magnitude of unmeasured confounding and should be considered in sensitivity analyses. However, if the unmeasured confounders are correlated with measured confounders, the bias yielded by unmeasured confounders is partly removed through adjustment for the measured confounders.

**Conclusions:** Discussions of the potential impact of unmeasured confounding in observational studies, and sensitivity analyses to examine this, should focus on the potential for the joint effect of multiple unmeasured confounders to bias results.

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## Introduction

Associations between exposures and health outcomes estimated in observational studies are prone to confounding. Observed confounders can be adjusted for in the analysis, but unmeasured and residual confounding can still bias estimated effects. For example, in a large cohort study, ascorbic acid (vitamin C) was found to reduce all-cause mortality by 52% (relative risk 0.48, 95% confidence interval 0.33–0.70, comparing highest with lowest quintile of ascorbic acid intake) [1], after adjustment for measured confounders (age, sex, body mass index, smoking status, systolic blood pressure, serum cholesterol, diabetes, and vitamin C supplement use). Because this effect was not found in randomized trials (e.g.,

relative risk 1.00, 95% confidence interval 0.94–1.06, for vitamin C supplementation vs. placebo) [2], it was disputed whether the observational study result was biased by unmeasured confounding by, for example, socioeconomic status or dietary habits [3–5].

Publications describing methods for sensitivity analysis of unmeasured confounding typically focus on the impact of a single confounding variable [6–15]. It is often assumed that only a variable with a strong association with both exposure and outcome can materially confound the association under study. For example, in an observational study of influenza vaccine effectiveness, sensitivity analysis of unmeasured confounding was conducted by simulating a single unmeasured confounder under a wide range of scenarios. The authors concluded that “... our sensitivity analyses indicate how our estimates of vaccine effectiveness would be lower, though still significant, after adjustment for the effect of a strong hypothetical unmeasured confounder” [16]. Similarly, a sensitivity analysis suggested that odds ratios between a confounder and both exposure and outcome would need to be at least 2.8 to nullify a

All authors declared that they do not have any conflict of interest.

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<http://dx.doi.org/10.1016/j.annepidem.2016.07.009>

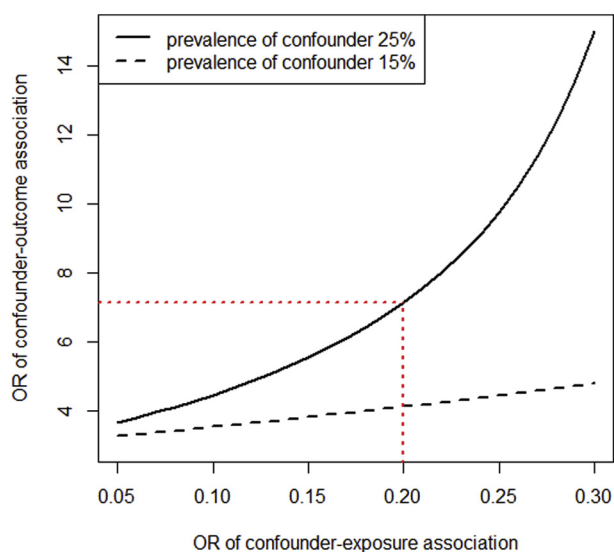
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positive association between use of a telephone health coaching service and hospital emergency admission rates. The authors concluded that unmeasured confounding was an unlikely explanation because "... the amount of unobserved confounding would have had to be greater than is realistic for clinical variables" [17].

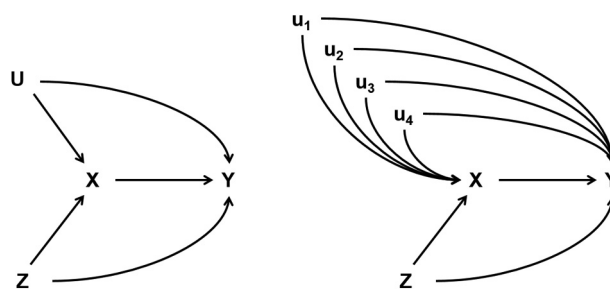
In the example of ascorbic acid intake and mortality, one can evaluate scenarios of a single binary unmeasured confounder that could cause the observed relation (odds ratio [OR] 0.48) between ascorbic acid intake and mortality, if there were in truth no association. Several of such scenarios are shown in Figure 1 (based on the method described by Lin et al. [8]). For example, an unmeasured binary confounder that is present in 25% of the population increases the odds of the outcome seven times (OR 7) and is negatively associated with exposure (OR 0.2) would lead to an observed relation of OR 0.48, although there were no association. Confounders that have such strong relations with exposure and outcome and are relatively common are probably known. Therefore, it may be hard to imagine that such a confounder exists, yet is unmeasured. This may therefore suggest that it is unlikely that the observed relation between ascorbic acid intake and mortality is due to unmeasured confounding.

However, multiple unmeasured "weaker" confounders (i.e., each with a small association with both exposure and outcome) may, together, yield considerable confounding bias. These different representations of unmeasured confounding are displayed in Figure 2. The sufficient set of variables to control for confounding includes the set of measured confounders (Z) as well as the set of unmeasured confounders (U) [18]. The set of unmeasured confounders could consist of multiple variables (e.g.,  $u_1$ – $u_4$ ). The possibility that there could be multiple (unmeasured) confounders for any given association has been confirmed by the finding that many measured subject characteristics and/or confounders in cohort studies are associated with one another, much more than would be anticipated by chance [19]. Although multiple unmeasured confounders can be summarized into a single variable [6,8], this may be hard to conceptualize and the literature provides little guidance on how to construct such a summary.

We argue that focusing on a single unmeasured confounder may distract from the possibility that multiple (possibly weak)



**Fig. 1.** Scenarios of unmeasured confounding of the relation between ascorbic acid intake and mortality that nullify the observed relation (OR 0.48). Based on the method described by Lin et al. [10]. The dotted line indicates a scenario in which an unmeasured confounder increases the odds of the outcome seven times, is negatively associated with exposure (OR 0.2), and is present in 25% of the population.



**Fig. 2.** Causal diagrams of unmeasured confounding. X represents exposure, Y outcome, Z the set of measured confounders, and U represents the set of unmeasured confounders (which may consist of multiple "weaker" confounders,  $u_1$ – $u_4$ ).

unmeasured confounders can have a large joint effect. Therefore, methods or sensitivity analyses to quantify the impact of unmeasured confounding should also consider scenarios of multiple unmeasured confounders. Here, guidance is provided, and sensitivity analysis of multiple unmeasured confounders is illustrated by an example of ascorbic acid intake and mortality.

### The bias due to multiple confounders

The magnitude of the bias due to a confounder of the exposure–outcome association depends on (1) the strength of the association between confounder and exposure; (2) the strength of the association between confounder and outcome; and (3) the prevalence of the confounder in the population (for categorical confounders) or its variance (for continuous normally distributed confounders) [8]. The direction of the bias depends on the signs of the association between the confounder and the exposure and outcome [20]. As the variance of a continuous confounder increases, so does the magnitude of the bias due to confounding.

The joint confounding effect of two continuous confounders depends on (1) the strength of the associations with exposure for each of the confounders; (2) the strength of the associations with the outcome for each of the confounders; (3) the variance of each of the confounders; and (4) the covariance between the confounders. This follows from the fact that the variance of the combination of two continuous confounders is given by

$$var_{A+B} = var_A + var_B + 2cov_{AB}$$

where  $var_A$  and  $var_B$  indicate the variance of the continuous confounders A and B, respectively, and  $cov_{AB}$  the covariance between these confounders. Similarly, the variance of the combination of more than two confounders can be calculated taking each pairwise covariance into account. Because the confounding effect of a continuous confounder depends on the variance of that confounder, the joint effect of multiple confounders depends on the variance of each of the confounders as well as their covariance. For example, the total confounding effect by two confounders that are positively correlated will be larger than the confounding effect by the two confounders if they were independent. Conversely, if two confounders are inversely correlated (i.e., negative covariance), the biases they introduce may (partly) cancel out.

When there are several confounders, all with the same direction of effect with exposure, and all with the same direction of effect on the outcome, the effect estimate that is adjusted for a subset of these confounders ("partially adjusted") will be closer to the true exposure–outcome association than the unadjusted estimate [21]. However, if the effects of some of the confounders on either exposure or outcome are in different directions, the partially adjusted estimate can actually be further away from the true

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