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# Sensitivity analyses for unmeasured confounding assuming marginal structural models under various standard populations

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## Summary

**Objectives.** Unmeasured confounding commonly poses a problem in observational studies. Although sensitivity analysis based on marginal structural models (MSMs) can now be used, its use is limited to cases in which the standard population is the total group. Herein, we propose methods for sensitivity analysis based on MSMs with the exposed and unexposed groups as the standard population.

**Methods.** We derived the methods for risk differences and risk ratios using the potential outcome model. The methods developed are applied to a classic cohort study.

**Results.** Sensitivity analyses using the exposed and unexposed groups as the standard population are simpler to formulate than those using the total group. Through an application to data from an observational study, this paper demonstrates that our methods of sensitivity analysis can be conducted for both the risk differences and risk ratios in observational studies.

**Conclusions.** The proposed methods will help researchers to provide a realistic picture of the potential impact of unmeasured confounding.

KEY WORDS: *confounding, epidemiologic methods, inverse probability of treatment weighting, observational studies, potential outcomes, propensity score.*

## Introduction

Confounding is widely recognized as one of the principal problems faced by researchers conducting observational studies. When unmeasured confounders are present, causal effects will generally not be estimated in an unbiased manner without making assumptions that cannot be identified from the study data alone. Recently, a new framework for sensitivity analysis based on modeling bias due to confounding was proposed (1-8). This framework includes a method that applies marginal structural models (MSMs) (1, 2, 9).

The MSM is a tool used to estimate the inverse-probability-of-treatment-weighted (IPTW) estimator (1),

which is a natural extension of standardization, using a regression analysis. The parameters are estimated by a weighted regression analysis (10) with the weight defined as the inverse of the propensity score (11, 12) for the exposed individuals and the inverse of 1 minus the propensity score for the unexposed individuals. Here, the propensity score is the probability of exposure, given the measured baseline variables.

While the method of sensitivity analysis assuming MSMs can be applied to effect measures with the total group as the standard population, such methods have not been developed for effect measures with the exposed and unexposed groups as the standard population. Therefore, we propose methods of sensitivity analyses for the latter groups.

## Methods

### Notation

We use  $X$  as an exposure indicator, and assume the now-standard deterministic potential outcome model, in which  $Y_{X=1}$  and  $Y_{X=0}$  are the potential outcome indicators under  $X = 1$  and  $X = 0$ , respectively (13, 14), a model used in several textbooks (15-17). The potential risks  $E(Y_{X=1}) = P(Y_{X=1} = 1)$  and  $E(Y_{X=0}) = P(Y_{X=0} = 1)$  are then the expectations of  $Y$ , if everyone in the study population is exposed or given  $X = 1$ , and if everyone is not exposed or given  $X = 0$ , respectively. Causal effects with the total group as the standard population are contrasts between these two expectations. Those with the exposed group as the standard population are contrasts between  $E(Y_{X=1} | X = 1)$  and  $E(Y_{X=0} | X = 1)$ , and those with the unexposed group as the standard population are contrasts between  $E(Y_{X=1} | X = 0)$  and  $E(Y_{X=0} | X = 0)$ . Note that the observed outcome  $Y$  equals the potential outcome  $Y_{X=x}$  whenever  $X = x$ . Hence,

$$E(Y | X = x) = E(Y_{X=x} | X = x).$$

### Risk Differences

Following Brumback et al. (5), for formulating the bias due to unmeasured confounding for the risk differences (RDs), we define the bias factors  $\alpha_{RD}$  and  $\beta_{RD}$  as

$$\alpha_{RD} \equiv E(Y_{X=1} | X = 1, Z = z) - E(Y_{X=1} | X = 0, Z = z) \quad [1]$$

and

$$\beta_{RD} \equiv E(Y_{X=0} | X = 1, Z = z) - E(Y_{X=0} | X = 0, Z = z) \quad [2]$$

where  $Z$  is the vector of all measured confounders, and  $\alpha_{RD}$  is the difference between the expected outcome of those actually exposed and the expected outcome of those unexposed had they been exposed, among the subgroup of subjects with  $Z = z$ . Similarly,  $\beta_{RD}$  is the difference between the expected outcome of exposure under non-exposure and the expected outcome of those actually unexposed among the subgroup of subjects with  $Z = z$ .

When  $\alpha_{RD} > 0$  and  $\beta_{RD} > 0$ ,

$$E(Y_{X=x} | X = 1, Z = z) > E(Y_{X=x} | X = 0, Z = z),$$

which means that the subjects in the exposed group tend

to be sicker than those in the unexposed group. Conversely, when  $\alpha_{RD} < 0$  and  $\beta_{RD} < 0$ ,

$$E(Y_{X=x} | X = 1, Z = z) < E(Y_{X=x} | X = 0, Z = z),$$

which means that the subjects in the unexposed group tend to be sicker than those in the exposed group. No confounding occurs when  $\alpha_{RD} = \beta_{RD} = 0$ .

First, we discuss a sensitivity analysis for the causal RD with the exposed group as the standard population,  $RD_{X=1}$ . To conduct the sensitivity analysis,  $Y^{\beta_{RD}}$  is introduced as bias-corrected versions of  $Y$ :

$$Y^{\beta_{RD}} = Y + \beta_{RD}$$

Substituting equation [2] into this equation gives

$$\begin{aligned} E(Y^{\beta_{RD}} | X = 0, Z = z) &= E(Y | X = 0, Z = z) + \{E(Y_{X=0} | X = 1, Z = z) - E(Y_{X=0} | X = 0, Z = z)\} \\ &= E(Y_{X=0} | X = 1, Z = z). \end{aligned}$$

Therefore,  $RD_{X=1}$  is transformed as

$$\begin{aligned} RD_{X=1} &= E(Y_{X=1} | X = 1) - E(Y_{X=0} | X = 1) \\ &= E(Y | X = 1) - \sum_{i=1}^N E(Y_{X=0} | X = 1, Z = z_i) P(Z = z_i | X = 1) \\ &= \frac{P(Y = 1, X = 1)}{P(X = 1)} - \sum_{i=1}^N E(Y^{\beta_{RD}} | X = 0, Z = z_i) P(X = 1 | Z = z_i) \frac{P(Z = z_i)}{P(X = 1)}, \end{aligned}$$

where  $i = 1, \dots, N$  denotes a subject. Then, once  $P(X = x | Z = z_i)$  has been calculated, a sensitivity analysis for  $RD_{X=1}$  is conducted using the IPTW method,

$$RD_{X=1} = \frac{1}{N_1} \sum_{i=1}^N y_i x_i - \frac{1}{N_1} \sum_{i=1}^N \frac{P(X = 1 | Z = z_i)}{P(X = 0 | Z = z_i)} y_i^{\beta_{RD}} (1 - x_i), \quad [3]$$

with  $Y^{\beta_{RD}}$  for some fixed values of  $\beta_{RD}$ , where  $N_1 = N \times P(X = 1)$  denotes the number of subjects in the exposed group.

The  $RD_{X=1}$  can be estimated using a linear MSM, i.e., the weighted linear regression analysis (10) with 1 for the subjects taking  $X = 1$  and  $P(X = 1 | Z = z_i) / P(X = 0 | Z = z_i)$  for the subjects taking  $X = 0$  as the weight, where  $Y$  is the dependent variable and  $X$  is the independent variable. The details are found elsewhere (18). For a sensitivity analysis,  $Y^{\beta_{RD}}$  is used for the subjects

with  $X = 0$  for some fixed values of  $\beta_{RD}$ , and  $Y$  itself is used for those with  $X = 1$ .

Next, we discuss a sensitivity analysis for the causal RD with the unexposed group as the standard population,  $RD_{X=0}$ . We introduce

$$Y^{\alpha RD} = Y - \alpha_{RD}$$

as a bias-corrected version of  $Y$ . Similar to the case with the exposed group as the standard population, substitution of equation [1] into this equation gives

$$\begin{aligned} & E(Y^{\alpha RD} | X = 1, Z = z) \\ &= E(Y | X = 1, Z = z) - \{E(Y_{X=1} | X = 1, Z = z) - E(Y_{X=1} | X = 0, Z = z)\} \\ &= E(Y_{X=1} | X = 0, Z = z). \end{aligned}$$

Then,  $RD_{X=0}$  is transformed as

$$\begin{aligned} RD_{X=0} &= E(Y_{X=1} | X = 0) - E(Y_{X=0} | X = 0) \\ &= \sum_{i=1}^N E(Y_{X=1} | X = 0, Z = z_i) P(Z = z_i | X = 0) - E(Y | X = 0) \\ &= \sum_{i=1}^N E(Y^{\alpha RD} | X = 1, Z = z_i) P(X = 0 | Z = z_i) \frac{P(Z = z_i)}{P(X = 0)} - \frac{P(Y = 1, X = 0)}{P(X = 0)}. \end{aligned}$$

Once  $P(X = x | Z = z_i)$  has been calculated, a sensitivity analysis for  $RD_{X=0}$  is conducted by the IPTW method,

$$RD_{X=0} = \frac{1}{N_0} \sum_{i=1}^N \frac{P(X = 0 | Z = z_i)}{P(X = 1 | Z = z_i)} y_i^{\alpha RD} x_i - \frac{1}{N_0} \sum_{i=1}^N y_i (1 - x_i), \quad [4]$$

with  $Y^{\alpha RD}$  for some fixed values of  $\alpha_{RD}$ , where  $N_0 = N \times P(X = 0)$  denotes the number of subjects in the unexposed group. In the context of a linear MSM, for the subjects with  $X = 1$ ,  $P(X = 0 | Z = z_i) / P(X = 1 | Z = z_i)$  is used as the weight and  $Y^{\alpha RD}$  is used for some fixed values of  $\alpha_{RD}$ . For the subjects with  $X = 0$ , the weight is 1 and  $Y$  itself is used.

Note that

$$Y^{\alpha RD} = Y - \alpha_{RD} P(X = 0 | Z = z)$$

is used for the subjects with  $X = 1$  and

$$Y^{\beta RD} = Y + \beta_{RD} P(X = 1 | Z = z)$$

is used for subjects with  $X = 0$  when the standard population is the total group. In the context of a linear MSM, the weights are  $1 / P(X = 1 | Z = z_i)$  for  $X = 1$  and  $1 / P(X = 0 | Z = z_i)$  for  $X = 0$ .

### Risk Ratios

We can use  $Y^{\alpha RD}$  and  $Y^{\beta RD}$  for sensitivity analyses of the risk ratios (RRs). However, their use is troublesome in the context of MSMs, because they give negative values for some subjects. For example, under  $\alpha_{RD} = 0.05$ , the values of  $Y^{\alpha RD}$  for subjects with  $X = 1$  and  $Y = 0$  are

$$Y^{\alpha RD} = 0 - 0.05 < 0.$$

Poisson MSMs, i.e., the weighted Poisson regression analyses, are used to yield the adjusted RRs. However, when the outcome variables include negative values, some commercial programs such as the SAS procedure PROC GENMOD (19) do not yield the estimates of parameters. Therefore, we introduce bias factors to formulate the bias due to unmeasured confounding for RRs.

Following Chiba (8), we define the bias factors  $\alpha_{RR}$  and  $\beta_{RR}$  as

$$\alpha_{RR} \equiv E(Y_{X=1} | X = 1, Z = z) / E(Y_{X=1} | X = 0, Z = z)$$

and

$$\beta_{RR} \equiv E(Y_{X=0} | X = 1, Z = z) / E(Y_{X=0} | X = 0, Z = z)$$

instead of equations [1] and [2]. They can be interpreted in a manner similar to  $\alpha_{RD}$  and  $\beta_{RD}$ , and the direction of bias is determined by whether  $\alpha_{RR}$  and  $\beta_{RR}$  are greater or less than 1.

First, we discuss a sensitivity analysis of

$$RR_{X=1} = E(Y_{X=1} | X = 1) / E(Y_{X=0} | X = 1),$$

which is the causal RR using the exposed group as the standard population. We present the following formula for the bias-corrected version of  $Y$ :

$$Y^{\beta RR} = \beta_{RR} Y.$$

Then, it is easily verified that

$$E(Y^{\beta RR} | X = 0, Z = z) = E(Y_{X=0} | X = 1, Z = z).$$

By the similar transformation as  $RD_{X=1}$ , a sensitivity analysis of  $RR_{X=1}$  is conducted using the ratio version of equation [3],

$$RR_{X=1} = \frac{\sum_{i=1}^N y_i x_i}{\sum_{i=1}^N \frac{P(X = 1 | Z = z_i)}{P(X = 0 | Z = z_i)} y_i^{\beta RR} (1 - x_i)},$$

with  $Y^{\beta_{RR}}$  for some fixed values of  $\beta_{RR}$ , once  $P(X = x | Z = z_i)$  has been calculated. In the context of MSMs, the  $RR_{X=1}$  can be estimated using a Poisson MSM (cf. 18), where the weights are the same as those used to estimate  $RD_{X=1}$ . For a sensitivity analysis,  $Y^{\beta_{RR}}$  is used for the subjects with  $X = 0$  for some fixed values of  $\beta_{RR}$ , and  $Y$  itself is used for those with  $X = 1$ . Next, for a sensitivity analysis of

$$RR_{X=0} = E(Y_{X=1} | X = 0) / E(Y_{X=0} | X = 0),$$

which is the causal RR with the unexposed group as the standard population, we introduce

$$Y^{\alpha_{RR}} = Y / \alpha_{RR}$$

as the bias-corrected version of  $Y$ . Then,

$$E(Y^{\alpha_{RR}} | X = 1, Z = z) = E(Y_{X=1} | X = 0, Z = z),$$

and a sensitivity analysis of  $RR_{X=0}$  is conducted using the ratio version of equation [4],

$$RR_{X=0} = \frac{\sum_{i=1}^N \frac{P(X = 0 | Z = z_i)}{P(X = 1 | Z = z_i)} y_i^{\alpha_{RR}} x_i}{\sum_{i=1}^N y_i (1 - x_i)}$$

with  $Y^{\alpha_{RR}}$  for some fixed values of  $\alpha_{RR}$ , once  $P(X = x | Z = z_i)$  has been calculated. In the context of MSMs, a sensitivity analysis of  $RR_{X=0}$  can be conducted using a Poisson MSM, where  $Y^{\alpha_{RR}}$  is used for the subjects with  $X = 1$  for some fixed values of  $\alpha_{RR}$ , and  $Y$  itself is used for those with  $X = 0$ .

Note that

$$Y^{\alpha_{RR}} = \{P(X = 0 | Z = z_i) / \alpha_{RR} + P(X = 1 | Z = z_i)\} Y$$

is used for the subjects with  $X = 1$  and

$$Y^{\beta_{RR}} = \{P(X = 0 | Z = z_i) + \beta_{RR} P(X = 1 | Z = z_i)\} Y$$

is used for those with  $X = 0$  when the standard population is the total group. In the context of a Poisson MSM, the weights are  $1 / P(X = 1 | Z = z_i)$  for  $X = 1$  and  $1 / P(X = 0 | Z = z_i)$  for  $X = 0$ .

## Results

Table 1 presents data from an 8.5-year follow up in a

Table 1. Data from the Western Collaborative Group Study (20): Coronary heart disease (CHD) incidence by behavior pattern.

Behavior	CHD	No CHD	Total
Type-A	178	1411	1589
Type-B	79	1486	1565

classic observational cohort study, the Western Collaborative Group Study (20), which examined the effect of behavior patterns on coronary heart disease (CHD). Type-A behavior was characterized by enhanced aggressiveness, ambitiousness, competitive drive, and a chronic sense of time urgency; type-B behavior was the absence of these behavioral characteristics. We used data from this study as they were presented in a textbook (21).

The crude RD and RR were 6.15% (95% confidence interval [CI]: 4.26%, 8.05%) and 2.22 (95% CI: 1.72, 2.87), respectively. To estimate the adjusted RD and RR under the assumption of no unmeasured confounder, we chose three variables as confounders: age, body mass index (weight(kg) / height(m)<sup>2</sup>) (these two are continuous variables), and smoking (this is a dichotomous variable: smoker or nonsmoker). The propensity score for each subject was estimated using the logistic model, giving the estimated weights. Linear MSMs yielded  $RD_{X=1} = 5.50\%$  (95% CI: 3.51%, 7.49%) and  $RD_{X=0} = 4.97\%$  (95% CI: 3.17%, 6.77%), and Poisson MSMs yielded  $RR_{X=1} = 1.96$  (95% CI: 1.52, 2.55) and  $RR_{X=0} = 1.98$  (95% CI: 1.53, 2.57), where the robust variance was applied. Calculations were performed using the SAS procedure PROC GENMOD (19).

In addition to the above measured confounders, homocysteine, diabetes, stress, and family history are known risk factors for CHD. Since these factors may be related to behavior patterns, they should be considered as confounders. However, we cannot perform the analysis adjusting for these factors because they are unmeasured confounders. Therefore, we need to conduct a sensitivity analysis for unmeasured confounding.

Before conducting a sensitivity analysis, we decided on reasonable ranges of  $\alpha_{RD}$ ,  $\beta_{RD}$ ,  $\alpha_{RR}$  and  $\beta_{RR}$ . To establish the ranges, we utilized the effects of a strong risk factor,  $C$ , on the outcome as in Chiba (8). In many cases, the values of the bias factors may be smaller than those of the effect measures of a strong risk factor. Then,

if  $C$  is dichotomous, ranges of  $\alpha_{RD}$  and  $\beta_{RD}$  are  $-RD_{C0} \leq \alpha_{RD} \leq RD_{C0}$ , where  $RD_{C0} = E(Y|X=0, C=1) - E(Y|X=0, C=0) > 0$ , and  $-RD_{C1} \leq \beta_{RD} \leq RD_{C1}$ , where  $RD_{C1} = E(Y|X=1, C=1) - E(Y|X=1, C=0) > 0$ . Likewise, ranges of  $\alpha_{RR}$  and  $\beta_{RR}$  are  $1/RR_{C0} \leq \alpha_{RR} \leq RR_{C0}$ , where  $RR_{C0} = E(Y|X=0, C=1) / E(Y|X=0, C=0) > 1$ , and  $1/RR_{C1} \leq \beta_{RR} \leq RR_{C1}$ , where  $RR_{C1} = E(Y|X=1, C=1) / E(Y|X=1, C=0) > 1$ . When we chose smoking as a strong risk factor,  $RD_{C0}$ ,  $RD_{C1}$ ,  $RR_{C0}$  and  $RR_{C1}$  were calculated to be 4.09%, 4.49%, 2.27, and 1.50, respectively.

The results of sensitivity analyses of RDs are shown in Figure 1, and those of RRs are shown in Figure 2. These figures provide realistic pictures of the potential impact of unmeasured confounding, and show that the effect measures, except for  $RR_{X=0}$ , are greater than 1, i.e., the risk of CHD increases with type-A behavior, in the defined ranges.

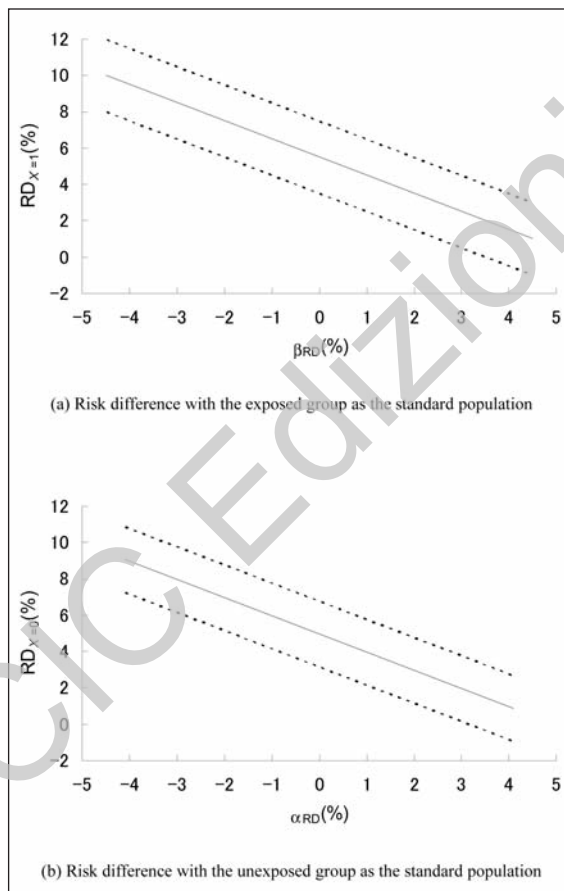


Figure 1. Sensitivity analyses of the risk differences in the Western Collaborative Group Study (20); the solid line indicates the estimated risk difference and the broken lines represent the 95% confidence interval: (a)  $RD_{X=1}$  and (b)  $RD_{X=0}$ .

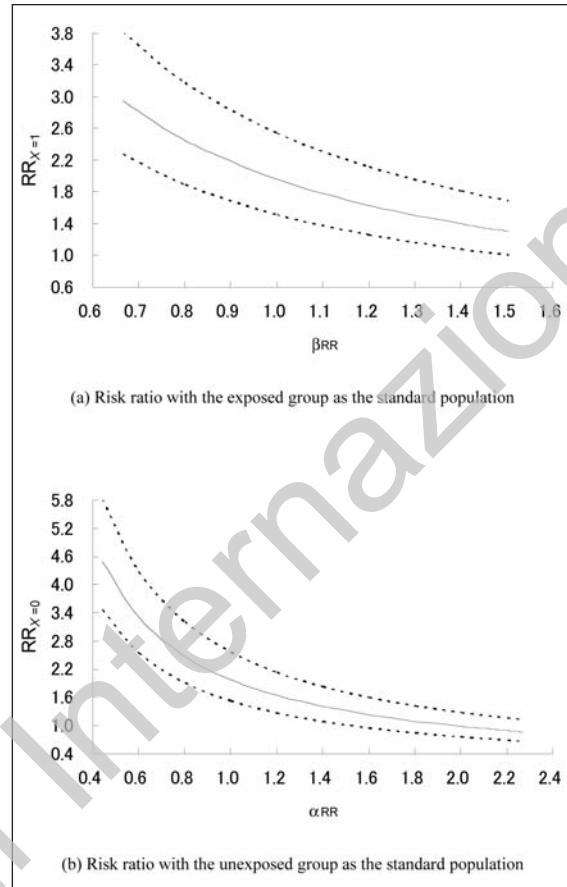


Figure 2. Sensitivity analyses of the risk ratios in the Western Collaborative Group Study (20); the solid line indicates the estimated risk ratio and the broken lines represent the 95% confidence interval: (a)  $RR_{X=1}$  and (b)  $RR_{X=0}$ .

## Discussion

We have proposed methods of sensitivity analysis for unmeasured confounding assuming MSMs when the standard population is the exposed or unexposed group. In some situations, the causal effects with the exposed or unexposed group as the standard population may be more important than the causal effects with the total group as the standard population. For example, the exposed group may be employed as the standard population when we evaluate the effect of occupational exposure, and the unexposed group may be employed for evaluation of new health promotion programs. The proposed methods are useful in such situations.

The proposed methods parameterize the bias due to unmeasured confounding rather than unmeasured confounders themselves. Therefore, an advantage of our



methods is that we can treat multiple confounders, which may include several types of variable, and unknown unmeasured confounders, in a simple and straightforward manner. In parameterizing unmeasured confounders themselves, it may be difficult to conduct a sensitivity analysis using several parameters. However, if one or a few unmeasured confounders exist and we know their distributions, such methods as the Monte-Carlo sensitivity analysis (MCSA; 3, 6, 7), may be more helpful. The bias parameter used in the MCSA is the same as the bias factors used here. Therefore, we can conduct the MCSA by applying MSMs, in which the measured confounders are adjusted by the MSMs.

Performing a sensitivity analysis using the methods proposed here can help researchers explore the potential impact of unmeasured confounding. We recommend performing a sensitivity analysis to evaluate the influence of unmeasured confounders on study results.

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