

Robustness of Measures of Interaction to  
Unmeasured Confounding

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# Robustness of Measures of Interaction to Unmeasured Confounding

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## Abstract

In this paper, we study the impact of unmeasured confounding on inference about a two-way interaction in a mean regression model with identity, log or logit link function. Necessary and sufficient conditions are established for a two-way interaction to be nonparametrically identified from the observed data, despite unmeasured confounding for the factors defining the interaction. A lung cancer data application illustrates the results.

## 1 Introduction

An important scientific goal of many studies in the health sciences is increasingly to determine whether an interaction between two factors under study is present in the effect that they produce on the mean of the outcome. For instance, genetic epidemiology studies routinely aim to establish the presence of an interaction between a genetic factor and an environmental factor or two genetic factors, in the effect that they produce on the risk of a disease outcome. In such observational stud-

ies, to avoid reporting of a spurious interaction, and to ensure that an estimated interaction has a meaningful causal interpretation, efforts are usually made to minimize bias due to confounding of either factor defining the interaction. Thus, to minimize confounding bias, investigators strive to measure and to account in regression analysis for as many potential confounders of the environmental factors as practically possible, and to control for population stratification for the genetic factors. However, whether unmeasured confounding is absent in a given observational study can rarely be established with certainty, and it is typically recommended that one supplement data analyses with a sensitivity analysis to assess the degree to which inferences are robust to possible unmeasured confounding. A variety of sensitivity analysis techniques for unmeasured confounding when total effects are in view, are now well developed in the causal inference literature (Rosembaum, 1995, Lin et al, 1998, Robins, 1999, VanderWeele and Arah, 2011, Tchetgen Tchetgen and Robins, 2012). Similar techniques have also appeared in recent literature on causal mediation analysis (Imai et al, 2010, VanderWeele, 2010, Tchetgen Tchetgen, 2011). In the context of inference about a two-way interaction, VanderWeele et al (2011) develop a sensitivity analysis technique to assess the extent to which unmeasured confounding in one or both factors involved in an interaction operating on an additive or multiplicative scale, can alter inference. As a corollary to their proposed sensitivity analysis framework, VanderWeele et al (2011) establish sufficient conditions for nonparametric identification of a causal additive or multiplicative interaction in the presence of unmeasured confounding. Their identification result is particularly striking upon noting that identification of causal effects in the presence of unmeasured confounding typically entails fairly strong assumptions, such as say, the availability of an instrumental variable. The results of VanderWeele et al (2011) reveal that the situation is quite different when causal interactions are in view, and that considerable progress can be made under weaker assumptions. For instance, an important implication of their results is that if the two exposures are independent, and a confounder of the

first factor is unobserved, but is known to be independent and not to additively interact with the second factor, then the additive interaction of the two factors is nonparametrically identified.

In the current paper, the authors extend the results of VanderWeele et al (2011) in significant directions. First and foremost, necessary and sufficient conditions are given for nonparametric identification of a two-way interaction on the additive and multiplicative scales, thus generalizing previous sufficient conditions given in VanderWeele et al (2011). Subsequently, related conditions are given for a two-way interaction on the logit scale, a setting not considered in previous literature. Because our results are nonparametric they apply to the entire literature on statistical methods for the estimation of an interaction. Some recent cutting-edge methods stand out in this rich literature, that are primarily concerned with robust adjustment for measured confounding in the context of inference about an interaction, and are given by Vansteelandt et al (2008), Tchetgen Tchetgen and Robins (2010), Tchetgen Tchetgen (2011), Bhattacharjee et al (2010) and Tchetgen Tchetgen (2012). While the aforementioned papers are primarily concerned with robustness to model mis-specification, the current paper concerns robustness to unmeasured confounding and therefore complements the previous literature.

## 2 Notation and definitions

We will let  $X_1$  and  $X_2$  denote our two exposures of interest; these could represent genetic and environmental factors respectively, or both could either be genetic factors, or environmental exposures; the results derived below apply quite broadly and are not restricted to studies of gene-environment interaction. Let  $Y$  denote the outcome of interest. Both exposures and the outcome can be continuous, count or binary. Defining causal interactions is facilitated by counterfactual notation which we introduce next. We let  $Y_{x_1, x_2}$  denote the counterfactual or potential outcome for  $Y$  for each

individual if possibly contrary to fact, the first exposure had been set to  $x_1$  and the second to  $x_2$ . We proceed with the usual consistency assumption that the only observed counterfactual is  $Y_{x_1, x_2} = Y$  which holds almost surely if  $\{X_1 = x_1, X_2 = x_2\}$ . Throughout, we suppose that data arises from an observational study, and therefore, the exposures are not randomized and their causal effects are potentially subject to confounding. However, we hypothesize a set of variables  $\{U, C\}$  suffices to control for confounding, where  $C$  is observed, one or more confounders  $U$  are unobserved, but  $C$  by itself does not suffice to control for confounding. Formally, we assume that  $Y_{x_1, x_2} \perp\!\!\!\perp \{X_1, X_2\} \mid \{U, C\}$  but  $Y_{x_1, x_2} \not\perp\!\!\!\perp \{X_1, X_2\} \mid C$ .

Let  $\mu(x_1, x_2, c, u) = \mathbb{E}(Y_{x_1, x_2} \mid C = c, U = u) = \mathbb{E}(Y \mid X_1 = x_1, X_2 = x_2, C = c, U = u)$  denote the mean of  $Y_{x_1, x_2}$  in the stratum  $\{U = u, C = c\}$ ; and define the interaction function of inferential interest:

$$\begin{aligned} \gamma(x_1, x_2, c, u) &= g^{-1} \{ \mu(x_1, x_2, u, c) \} - g^{-1} \{ \mu(x_1^*, x_2, u, c) \} - g^{-1} \{ \mu(x_1, x_2^*, u, c) \} + g^{-1} \{ \mu(x_1^*, x_2^*, u, c) \} \end{aligned}$$

where  $(x_1^*, x_2^*)$  is a fixed reference value which we suppress in  $\gamma$  to simplify notation,  $g^{-1}$  is either the identity, log or logit link function. Therefore,  $\gamma(x_1, x_2, c, u) = 0$  implies that the controlled direct effect of  $X_1$  on  $Y$  on the  $g^{-1}$  scale, when  $X_2$  is set to  $x_2$  is constant across values of  $x_2$ , and vice-versa for  $x_1$ . Throughout, we make the crucial assumption that the interaction function  $\gamma(x_1, x_2, c, u)$  does not depend on the unmeasured confounder  $U$ , that is

$$\tilde{\gamma}(x_1, x_2, c) = \gamma(x_1, x_2, c, u) \tag{1}$$

When  $g^{-1}$  is the identity link, assumption (1) implies that

$$\begin{aligned}\tilde{\gamma}(x_1, x_2, c) &= \mathbb{E}(Y_{x_1, x_2} - Y_{x_1^*, x_2} - Y_{x_1, x_2^*} + Y_{x_1^*, x_2^*} | C = c) \\ &= \mathbb{E}(Y_{x_1, x_2} - Y_{x_1^*, x_2} - Y_{x_1, x_2^*} + Y_{x_1^*, x_2^*} | C = c, U = u)\end{aligned}$$

is homogeneous in the unmeasured confounder. Although these quantities are not in general identified without data on  $U$ . We note that assumption (1) does not place any restriction on the observed data likelihood, and therefore, the assumption is perfectly compatible with a nonparametric model for the mean of  $[Y|X_1, X_2, C]$ :

$$g^{-1}\{\mathbb{E}(Y | X_1 = x_1, X_2 = x_2, C = c)\} = \alpha_1(x_1, c) + \alpha_2(x_2, c) + \alpha_3(x_1, x_2, c) + \alpha_4(c)$$

where  $\alpha_1, \alpha_2$  and  $\alpha_4$  encode the main effects of  $X_1, X_2$  and  $C$  respectively, and  $\alpha_3$  encodes the statistical interaction

$$\begin{aligned}g^{-1}\{\mathbb{E}(Y | X_1 = x_1, X_2 = x_2, C = c)\} - g^{-1}\{\mathbb{E}(Y | X_1 = x_1^*, X_2 = x_2, C = c)\} \\ - g^{-1}\{\mathbb{E}(Y | X_1 = x_1, X_2 = x_2^*, C = c)\} + g^{-1}\{\mathbb{E}(Y | X_1 = x_1^*, X_2 = x_2^*, C = c)\}\end{aligned}\quad (2)$$

between  $X_1$  and  $X_2$  as a function of  $C$ . Then, irrespective of assumption (1), the only restriction on  $\alpha_1, \alpha_2, \alpha_3$ , and  $\alpha_4$  is the anchoring condition, which states without loss of generality,  $0 = \alpha_1(x_1^*, c) = \alpha_2(x_2^*, c) = \alpha_3(x_1^*, x_2, c) = \alpha_3(x_1, x_2^*, c) = \alpha_4(c^*)$  for a fixed reference value  $c^*$ . Furthermore,  $\alpha_3(x_1, x_2, c) \neq \tilde{\gamma}(x_1, x_2, c)$  without additional assumptions, because without data on  $U$ , the causal interaction of interest  $\tilde{\gamma}$  is generally not identified by the statistical interaction  $\alpha_3$ . A trivial con-

dition that entails  $\alpha_3 = \tilde{\gamma}$  is  $\mu(x_1, x_2, u, c) = \mu(x_1, x_2, u^*, c)$  for all  $u$ , where  $u^*$  is a fixed reference value, i.e.  $U$  does not predict the mean of  $Y$  and therefore does not confound the joint causal effect of  $(X_1, X_2)$  on  $Y$ . Below, we consider necessary and sufficient conditions (which are non-trivial), such that  $\alpha_3 = \tilde{\gamma}$  and yet  $U$  is an unobserved confounder for the joint causal effect of  $(X_1, X_2)$  on  $Y$ .

### 3 Identification of additive interactions

The results presented in this section give simple sufficient and necessary conditions such that  $\alpha_3 = \tilde{\gamma}$  when  $g^{-1}$  is the identity link. Proofs are relegated to the appendix.

**Theorem 1** *Suppose that  $g^{-1}$  is the identity link,  $Y_{x_1, x_2} \perp\!\!\!\perp \{X_1, X_2\} | \{U, C\}$ , and assumption (1) holds; then  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$  if and only if  $\tilde{\theta}(x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  within levels of  $c$ , where  $\tilde{\theta}(x_1, x_2, c) = \mathbb{E}\{\mu(X_1, X_2, u, c) - \mu(X_1, X_2, u^*, c) | X_1 = x_1, X_2 = x_2, C = c\}$ .*

An equivalent formulation of the result states that  $\alpha_3 = \tilde{\gamma}$  if and only if there exist three functions  $\tilde{\theta}_1(x_1, c)$ ,  $\tilde{\theta}_2(x_2, c)$ , and  $\tilde{\theta}_4(c)$  of  $(x_1, c)$ ,  $(x_2, c)$  and  $c$  respectively, such that  $\int \mu(x_1, x_2, u, c) - \mu(x_1, x_2, u^*, c) dF(u|x_1, x_2, c) = \tilde{\theta}_1(x_1, c) + \tilde{\theta}_2(x_2, c) + \tilde{\theta}_4(c)$ ,

where  $F(A|D)$  is the cumulative distribution function of  $[A|D]$ .

Then, it is straightforward to verify that

$$\alpha_4(c) = \tilde{\theta}_4(c) + \mu(x_1^*, x_2^*, u^*, c);$$

and

$$\alpha_1(x_1, c) = \tilde{\theta}_1(x_1, c) + \mu(x_1, x_2^*, u^*, c) - \mu(x_1^*, x_2^*, u^*, c);$$

$$\alpha_2(x_2, c) = \tilde{\theta}_2(x_2, c) + \mu(x_1^*, x_2, u^*, c) - \mu(x_1^*, x_2^*, u^*, c)$$

are biased for the causal main effects of  $X_1$  and  $X_2$  respectively, but according to the theorem, collapsing over  $U$  does not introduce a spurious interaction between  $X_1$  and  $X_2$ , and therefore  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ . To illustrate Theorem 1, it is instructive to relate the result to Corollary 1B of VanderWeele et al (2011). The corollary is reproduced here in the current notation for convenience.

**Corollary 2** (VanderWeele et al, 2011): *Suppose that the effects of  $X_1$  and  $X_2$  on  $Y$  are unconfounded conditional on  $(C, U)$  and we have  $X_1 \perp\!\!\!\perp (X_2, U) | C$  then if  $U$  does not interact with  $X_1$  on the additive scale in the sense that  $\mu(x_1, x_2, u, c) - \mu(x_1, x_2, u^*, c)$  is constant across  $x_1$  then  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ .*

One can show that Corollary 1 implies that  $\tilde{\theta}(x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  within levels of  $c$  and therefore the condition of Theorem 1 is satisfied. However, Theorem 1 states that the condition for Corollary 1 may be relaxed without altering the conclusion. Furthermore, we note that the conditions of the corollary imply condition (1), but the latter condition is less restrictive and thus more general, than required by the corollary. To illustrate, suppose that instead  $X_1 \perp\!\!\!\perp U | X_2, C$  but  $X_1$  and  $X_2$  are conditionally dependent given  $C$  whether one conditions on  $U$  or not. Then, Theorem 1 states that  $\alpha_3 = \tilde{\gamma}$  while Corollary 1 does not lead to this conclusion. Theorem 1 also indicates alternative conditions such that the interaction parameter  $\tilde{\gamma}$  is identified. For instance, suppose that  $\mu(x_1, x_2, u, c) - \mu(x_1, x_2, u^*, c)$  is constant across  $(x_1, x_2)$  but  $X_1, X_2$  and  $U$  are dependent within levels of  $C$ . Then, Theorem 1 implies that  $\alpha_3 = \tilde{\gamma}$  provided  $\int \{\mu(x_1^*, x_2^*, u, c) - \mu(x_1^*, x_2^*, u^*, c)\} dF_{U|X_1, X_2, C}(u|x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$ . In the special case of a binary  $U$ , the above condition reduces to  $\Pr(U = 1|x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  within levels of  $c$ .



VanderWeele et al (2011) also consider in their Corollary 1C, a result similar to Corollary 1 under the assumption that  $X_1$  and  $X_2$  are independent, and that there is an unmeasured confounder  $U_1$  of  $X_1$  and similarly, that there is another unmeasured confounder  $U_2$  of  $X_2$ , such that  $U_1$  and  $U_2$  are both binary. They establish that if in addition,  $X_1$  and  $U_2$  do not interact,  $X_2$  and  $U_1$  do not interact, and  $U_1$  and  $U_2$  do not interact, then  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ . This result is particularly relevant if we imagine  $X_1$  to be a genetic factor and  $X_2$  to be an environmental factor, so that unmeasured confounders of the environmental exposure neither interact nor confound the genetic variant, and similarly, the unmeasured confounders of the genetic factor neither interact nor confound the environmental exposure, and the unmeasured confounders do not interact. Theorem 1 indicates that one could still identify a gene-environment interaction under an alternative set of assumptions that would allow for  $(U_1, U_2, X_1, X_2)$  to be dependent. In fact, it is straightforward to verify that the condition for Theorem 1 would hold if both  $U_1$  and  $U_2$  did not interact with either  $X_1$  or  $X_2$ , provided that  $\int \{\mu(x_1^*, x_2^*, u_1, u_2, c) - \mu(x_1^*, x_2^*, u_1^*, u_2^*, c)\} dF_{U|X_1, X_2, C}(u|x_1, x_2, c)$  were additive in  $x_1$  and  $x_2$  within levels of  $c$ .

## 4 Identification of multiplicative interactions

On the multiplicative scale, (1) implies that when  $g^{-1}$  is the log-link,  $\tilde{\gamma}(x_1, x_2, c)$  is

$$\begin{aligned} & \log \frac{\mathbb{E}(Y_{x_1, x_2} | U = u, C = c)}{\mathbb{E}(Y_{x_1^*, x_2} | U = u, C = c)} / \frac{\mathbb{E}(Y_{x_1, x_2^*} | U = u, C = c)}{\mathbb{E}(Y_{x_1^*, x_2^*} | U = u, C = c)} \\ &= \log \frac{\mathbb{E}(Y_{x_1, x_2} | C = c)}{\mathbb{E}(Y_{x_1^*, x_2} | C = c)} / \frac{\mathbb{E}(Y_{x_1, x_2^*} | C = c)}{\mathbb{E}(Y_{x_1^*, x_2^*} | C = c)} \end{aligned}$$

neither of which are in general identified without data on  $U$ . The following theorem presents simple sufficient and necessary conditions for  $\alpha_3 = \tilde{\gamma}$

**Theorem 3** Suppose that  $g^{-1}$  is the log link,  $Y_{x_1, x_2} \perp\!\!\!\perp \{X_1, X_2\} | \{U, C\}$ , and assumption (1) holds; then  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$  if and only if  $\tilde{\theta}^\dagger(x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  within levels of  $c$ , where  $\theta^\dagger(x_1, x_2, c) = \log E \{ \mu(X_1, X_2, u, c) / \mu(X_1, X_2, u^*, c) | X_1 = x_1, X_2 = x_2, C = c \}$ .

Similar to the additive scale, an equivalent formulation of the above theorem states that  $\alpha_3 = \tilde{\gamma}$  if and only if there exist three functions  $\theta_1^\dagger(x_1, c)$ ,  $\theta_2^\dagger(x_2, c)$ , and  $\theta_4^\dagger(c)$  of  $(x_1, c)$ ,  $(x_2, c)$  and  $c$  respectively, such that  $\log \int \mu(x_1, x_2, u, c) / \mu(x_1, x_2, u^*, c) dF_{U|X_1, X_2, C}(u|x_1, x_2, c) = \theta_1^\dagger(x_1, c) + \theta_2^\dagger(x_2, c) + \theta_4^\dagger(c)$ .

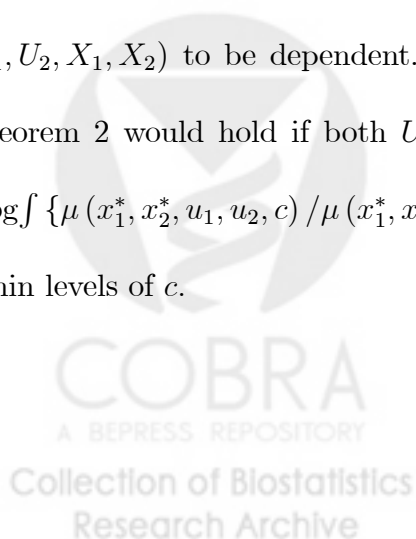
Then, it is straightforward to verify that  $\alpha_4(c) = \theta_4^\dagger(c) + \log \mu(x_1^*, x_2^*, u^*, c)$ ; and  $\alpha_1(x_1, c) = \theta_1^\dagger(x_1, c) + \log \{ \mu(x_1, x_2^*, u^*, c) / \mu(x_1^*, x_2^*, u^*, c) \}$ ,  $\alpha_2(x_2, c) = \theta_2^\dagger(x_2, c) + \log \{ \mu(x_1^*, x_2, u^*, c) / \mu(x_1^*, x_2^*, u^*, c) \}$  are biased for the causal main effects of  $X_1$  and  $X_2$  respectively, but according to the theorem, collapsing over  $U$  does not introduce a spurious interaction between  $X_1$  and  $X_2$ , and therefore  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ . To illustrate Theorem 2, it is instructive to relate the result to Corollary 2B of VanderWeele et al (2011). The corollary is reproduced here in the current notation for convenience.

**Corollary 4** (VanderWeele et al, 2011): Suppose that the effects of  $X_1$  and  $X_2$  on  $Y$  are unconfounded conditional on  $(C, U)$  and we have  $X_1 \perp\!\!\!\perp (X_2, U) | C$  then if  $U$  does not interact with  $X_1$  on the multiplicative scale in the sense that  $\mu(x_1, x_2, u, c) / \mu(x_1, x_2, u^*, c)$  is constant across  $x_1$  then  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ .

One can show that Corollary 2 implies that  $\tilde{\theta}^\dagger(x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  within levels of  $c$  and therefore the condition of Theorem 1 is satisfied. However, Theorem 2 states that the condition for Corollary 2 may be relaxed without altering the conclusion. To illustrate, suppose that instead  $X_1 \perp\!\!\!\perp U | X_2, C$  but  $X_1$  and  $X_2$  are conditionally dependent given  $C$  whether one conditions on  $U$  or not. Then, Theorem 2 states that  $\alpha_3 = \tilde{\gamma}$  while Corollary 2 does not

lead to this conclusion. Theorem 2 also indicates alternative conditions such that  $\tilde{\gamma}$  is identified. For instance, suppose that  $\mu(x_1, x_2, u, c) / \mu(x_1, x_2, u^*, c)$  is constant across  $(x_1, x_2)$  but  $X_1, X_2$  and  $U$  are dependent within levels of  $C$ . Then, theorem 2 implies that  $\alpha_3 = \tilde{\gamma}$  provided  $\log \int E \{ \mu(x_1^*, x_2^*, u, c) / \mu(x_1^*, x_2^*, u^*, c) | X_1 = x_1, X_2 = x_2, C = c \} dF_{U|X_1, X_2, C}(u | x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$ .

VanderWeele et al (2011) also consider in their Corollary 2C, a result similar to Corollary 2 under the assumption that  $X_1$  and  $X_2$  are independent, and that there is an unmeasured confounder  $U_1$  of  $X_1$  and similarly, that there is another unmeasured confounder  $U_2$  of  $X_2$ , such that  $U_1$  and  $U_2$  are both binary and independent of each other. They establish that if  $X_1$  and  $U_2$  do not interact,  $X_2$  and  $U_1$  do not interact, and  $U_1$  and  $U_2$  do not interact, then  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ . Their Corollary 2C requires  $U_1$  and  $U_2$  be binary, but it can be verified that the condition of Theorem 2 would hold under their assumption even if  $U_1$  and  $U_2$  were not binary, and therefore that the gene-environment interaction would still be identified for  $(U_1, U_2)$  of more general support, as long as the unmeasured confounders satisfied the other conditions of their Corollary 2C described above. Moreover, Theorem 2 also indicates that one could still identify a gene-environment interaction under an alternative set of assumptions that would allow for  $(U_1, U_2, X_1, X_2)$  to be dependent. In fact, it is straightforward to verify that the condition for Theorem 2 would hold if both  $U_1$  and  $U_2$  did not interact with either  $X_1$  or  $X_2$ , provided that  $\log \int \{ \mu(x_1^*, x_2^*, u_1, u_2, c) / \mu(x_1^*, x_2^*, u_1^*, u_2^*, c) \} dF_{U|X_1, X_2, C}(u | x_1, x_2, c)$  were additive in  $x_1$  and  $x_2$  within levels of  $c$ .



## 5 Identification of odds ratio interactions

In this section, we consider odds ratio interactions and take  $g^{-1}$  to be the logit link. We present general results that allow for a polytomous  $Y$ . In this vein, we consider the odds ratio interaction given by  $\tilde{\gamma}^g(y, x_1, x_2, c) =$

$$\begin{aligned} & \log \left\{ \frac{\text{ODDS}(Y_{x_1, x_2} = y | u, c)}{\text{ODDS}(Y_{x_1^*, x_2} = y | u, c)} / \frac{\text{ODDS}(Y_{x_1, x_2^*} = y | u, c)}{\text{ODDS}(Y_{x_1^*, x_2^*} = y | u, c)} \right\} \\ & = \log \left\{ \frac{\text{ODDS}(Y = y | x_1, x_2, u, c)}{\text{ODDS}(Y = y | x_1^*, x_2, u, c)} / \frac{\text{ODDS}(Y = y | x_1, x_2^*, u, c)}{\text{ODDS}(Y = y | x_1^*, x_2^*, u, c)} \right\} \end{aligned} \quad (3)$$

where  $\text{ODDS}(A = a | d) = \Pr(A = a | D = d) / \Pr(A = a^* | D = d)$ , with  $a^*$  a reference value. Note that the equation above reduces to (1) when  $Y$  is binary and  $y = 1$ , and thus  $\tilde{\gamma}^g(1, x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ . The following theorem presents simple sufficient and necessary conditions such that  $\alpha_3^g(y, x_1, x_2, c) = \tilde{\gamma}(y, x_1, x_2, c)$ , where we define  $\alpha_3^g(y, x_1, x_2, c) =$

$$\log \left\{ \frac{\text{ODDS}(Y = y | x_1, x_2, c)}{\text{ODDS}(Y = y | x_1^*, x_2, c)} / \frac{\text{ODDS}(Y = y | x_1, x_2^*, c)}{\text{ODDS}(Y = y | x_1^*, x_2^*, c)} \right\}$$

which reduces to  $\alpha_3(x_1, x_2, c)$  when  $Y$  is binary and  $y = 1$ .

Suppose that  $Y_{x_1, x_2} \perp\!\!\!\perp \{X_1, X_2\} | \{U, C\}$ , and  $\tilde{\gamma}^g(y, x_1, x_2, c)$  is given by equation (3), then  $\alpha_3^g(y, x_1, x_2, c) = \tilde{\gamma}^g(y, x_1, x_2, c)$  if and only if  $\theta^\ddagger(y, x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  within levels of  $c$  and  $y$ , where  $\theta^\ddagger(y, x_1, x_2, c) =$

$$\log \int \left\{ \frac{\text{ODDS}(Y = y | x_1, x_2, u, c)}{\text{ODDS}(Y = y | x_1, x_2, u^*, c)} \right\} dF(u | x_1, x_2, c, y^*)$$

To illustrate the theorem, consider the case of  $Y$  binary, so that  $y^* = 0$ . Then, if either the conditional odds ratio relating  $X_1$  to  $Y$ ,  $\text{OR}_{Y, X_1}(x_1 | x_2^*, u, c) = \text{ODDS}(Y = 1 | x_1, x_2^*, u, c) /$

ODDS( $Y = 1|x_1^*, x_2^*, u, c$ ) is constant across levels of  $u$ , or the conditional odds ratio relating  $X_2$  to  $Y$ ,  $OR_{Y,X_2}(x_2|x_1^*, u, c) = \text{ODDS}(Y = 1|x_1^*, x_2, u, c) / \text{ODDS}(Y = 1|x_1^*, x_2^*, u, c)$  is constant across levels of  $u$ , the following corollary uses Theorem 3 to obtain additional conditions such that  $\tilde{\gamma}^g(y, x_1, x_2, c) = \alpha_3^g(y, x_1, x_2, c)$ .

**Corollary 5** *Suppose that  $Y_{x_1, x_2} \perp\!\!\!\perp \{X_1, X_2\} | \{U, C\}$ , and  $\tilde{\gamma}^g(y, x_1, x_2, c)$  is given by equation (3), then  $\alpha_3^g(y, x_1, x_2, c) = \tilde{\gamma}^g(y, x_1, x_2, c)$  if at least one of the following conditions holds:*

1.  $OR_{Y,X_1}(x_1|x_2^*, u, c)$  is constant across levels of  $u$  and  $U \perp\!\!\!\perp X_1 | X_2, Y = 0, C$ .
2.  $OR_{Y,X_1}(x_1|x_2^*, u, c)$  and  $OR_{Y,X_2}(x_2|x_1^*, u, c)$  are both constant across levels of  $u$ , and

$$\log \mathbb{E} \{ OR_{Y,U}(U|x_1^*, x_2^*, c) | x_1, x_2, c, Y = 0 \} = \log \int OR_{Y,U}(u|x_1^*, x_2^*, c) dF(u|x_1, x_2, c, Y = 0)$$

*is additive in  $x_1$  and  $x_2$ .*

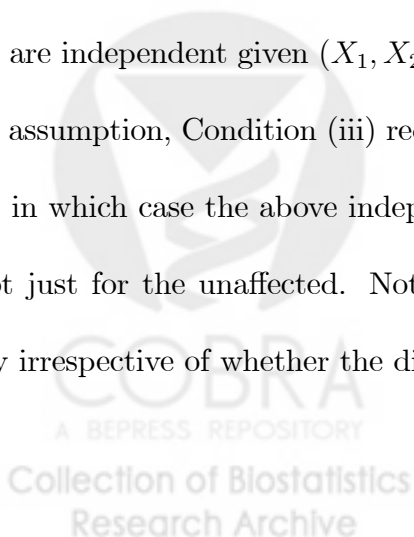
3.  $U = (U_1, U_2)$  such that  $OR_{Y,X_1}(x_1|x_2^*, u, c)$  is constant across levels of  $u_2$ ,  $OR_{Y,X_2}(x_2|x_1^*, u, c)$  is constant across levels of  $u_1$ ,  $OR_{Y,U_1}(u_1|x_1^*, x_2^*, u_2, c)$  is constant across levels of  $u_2$ ,  $U_1 \perp\!\!\!\perp U_2 | (X_1, X_2, Y = 0, C)$ ,  $U_2 \perp\!\!\!\perp X_1 | (X_2, Y = 0, C)$ ,  $U_1 \perp\!\!\!\perp X_2 | (X_1 = x_1^*, Y = 0, C)$ .

Condition (i) of the Corollary is similar to the conditions of Corollaries 1B and 2B of VanderWeele for the identity and log links. The first condition states that the main effect of  $X_1$  on  $Y$  is constant across levels of  $U$ , in other words, there is no  $X_1 \times U$  interaction on the logit scale. The second condition is akin to the independence assumption involved in our extension of Corollaries 1B and 2B given in the previous sections, but the assumption is distinct in that it requires the independence  $U$  and  $X_1$  conditional on  $X_2$  and  $C$ , among the unaffected, i.e. among individuals with  $Y = 0$ . In a case-control study, the second assumption entails the conditional independence

of  $U$  and  $X_1$  in the controls; if as often the case in case-control studies, the outcome is rare in the underlying target population across levels of  $(X_1, X_2, U, C)$ , then, the independence assumption is approximately correct conditional on  $(X_1, X_2, U, C)$  only. Intuitively, when the outcome is rare, the logit link is well approximated by the log link and thus the results for identification of multiplicative interactions apply.

Condition (ii) states that if  $U$  interacts with neither  $X_1$  nor  $X_2$  on the logit scale, then the independence assumption of condition (i) can be replaced with an assumption about the functional form of a certain conditional expectation. Specifically, the result states that the  $X_1 \times X_2$  interaction function is nonparametrically identified if there exist functions  $\theta^\ddagger(x_1, c)$ ,  $\theta^\ddagger(x_2, c)$  and  $\theta^\ddagger(c)$ , such that the conditional mean of the odds ratio relating  $U$  to  $Y$  given  $(X_1, X_2, C)$  amongst individuals with  $Y = 0$ , i.e.  $\mathbb{E}\{\text{OR}_{Y,U}(U|x_1^*, x_2^*, c) | x_1, x_2, c, Y = 0\}$  can be expressed  $\exp\{\theta^\ddagger(x_1, c) + \theta^\ddagger(x_2, c) + \theta^\ddagger(c)\}$ .

Condition (iii) extends Corollaries 1C and 2C of VanderWeele et al (2011) for the additive and log scale, to the logit scale. It states that  $\tilde{\gamma}(x_1, x_2, c)$  is identified if  $X_1$  and  $X_2$  do not interact with  $U$  in their effects on  $Y$ ;  $U_1$  and  $U_2$  do not interact in their effects on  $Y$ ,  $U_2$  and  $X_1$  are independent given  $(X_2, C)$  in the unaffected,  $U_1$  and  $X_2$  are independent given  $(X_1, C)$  in the unaffected, and  $U_1$  and  $U_2$  are independent given  $(X_1, X_2, C)$  in the unaffected. Similar to condition (i), under a rare disease assumption, Condition (iii) reduces to the conditions of Corollary 2C of VanderWeele et al (2011), in which case the above independence statements also hold in the underlying population, and not just for the unaffected. Note however that Condition (iii) of Corollary 4 applies more broadly irrespective of whether the disease is rare or not.



## 6 A data illustration

In an investigation of the joint effects of exposure to asbestos and smoking habits on lung cancer risk, Hilt et al. (1986) considered data from the Norwegian Cancer Registry, on men aged 40 years and above in Telemark, Norway. Let  $X_1$  denote an indicator for whether an individual ever smoked,  $X_2$  is an indicator for whether an individual had any previous asbestos exposure and  $Y$  is an indicator for the occurrence of lung cancer within 10 years. Hilt et al. (1986) estimated the following risk of lung cancer for the different of the exposures:

$$p_{11} = \frac{141}{3130}; p_{10} = \frac{118}{12303}; p_{01} = \frac{5}{749}; p_{00} = \frac{6}{5057};$$

where  $p_{x_1x_2} = \Pr(Y = 1|x_1, x_2)$ . Assuming that there are no variables that confound the effects of smoking and asbestos exposure on lung cancer, the following point estimates of interaction are obtained on the additive scale:

$$\text{Additive interaction: } \frac{141}{3130} - \frac{118}{12303} - \frac{5}{749} + \frac{6}{5057} = 0.03 \text{ (} s.e. = 4.85 \times 10^{-3} \text{)}$$

The analysis indicates a significant additive statistical interaction, however this analysis would in general not be given a causal interpretation, because the assumption of no unmeasured confounding is likely inappropriate in this context. The results of VanderWeele et al (2011) required that the two exposures be independent for the interaction measure to be unbiased. Our results here do not require that assumption. Theorem 1 states that the estimated additive interaction can be interpreted causally as long as the mean (wrt to the unmeasured confounders) of the association between unmeasured confounders and lung cancer risk is an additive function of smoking behavior and asbestos exposure. Similarly, Theorem 2 and 3 provide necessary and sufficient conditions for

valid inference of a causal interaction on the multiplicative and odds ratio interaction.

## Appendix

**Proof of Theorem 1:** We note that  $E(Y | X_1 = x_1, X_2 = x_2, C = c) =$

$$\begin{aligned} & \int \mu(x_1, x_2, u, c) dF(u|x_1, x_2, c) \\ &= \int \{\mu(x_1, x_2, u, c) - \mu(x_1, x_2, u^*, c)\} dF(u|x_1, x_2, c) + \mu(x_1, x_2, u^*, c) - \tilde{\gamma}(x_1, x_2, c) \\ &+ \tilde{\gamma}(x_1, x_2, c) \end{aligned}$$

Next, recall that  $\mu(x_1, x_2, u, c)$  can be written

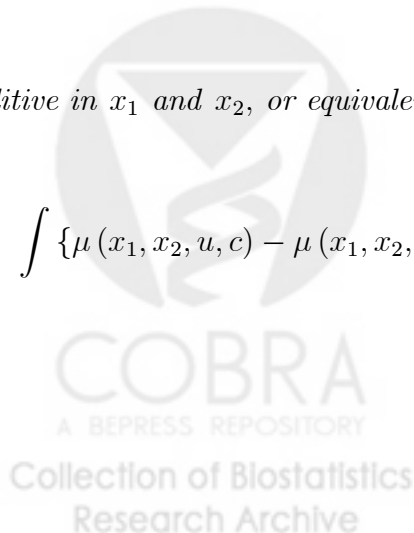
$$\mathbb{E}(Y | X_1 = x_1, X_2 = x_2, C = c) = \alpha_1(x_1, c) + \alpha_2(x_2, c) + \alpha_3(x_1, x_2, c) + \alpha_4(c)$$

therefore,  $\tilde{\gamma}(x_1, x_2, c)$  is identified if and only if  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ , that is, if and only if

$$\mathbb{E}(Y | X_1 = x_1, X_2 = x_2, C = c) - \tilde{\gamma}(x_1, x_2, c) = \alpha_1(x_1, c) + \alpha_2(x_2, c) + \alpha_4(c)$$

is additive in  $x_1$  and  $x_2$ , or equivalently, if and only if

$$\int \{\mu(x_1, x_2, u, c) - \mu(x_1, x_2, u^*, c)\} dF(u|x_1, x_2, c) + \mu(x_1, x_2, u^*, c) - \tilde{\gamma}(x_1, x_2, c)$$





is additive in  $x_1$  and  $x_2$ . We finally note that

$$\begin{aligned}
& \mu(x_1, x_2, u^*, c) - \tilde{\gamma}(x_1, x_2, c) \\
&= \mu(x_1, x_2^*, u^*, c) - \mu(x_1^*, x_2^*, u^*, c) \\
&+ \mu(x_1^*, x_2, u^*, c) - \mu(x_1^*, x_2^*, u^*, c) \\
&+ \underbrace{\mu(x_1, x_2, u^*, c) - \mu(x_1, x_2^*, u^*, c) - \mu(x_1^*, x_2, u^*, c) + \mu(x_1^*, x_2^*, u^*, c)}_{=\tilde{\gamma}(x_1, x_2, c)} \\
&+ \mu(x_1^*, x_2^*, u^*, c) - \tilde{\gamma}(x_1, x_2, c)
\end{aligned}$$

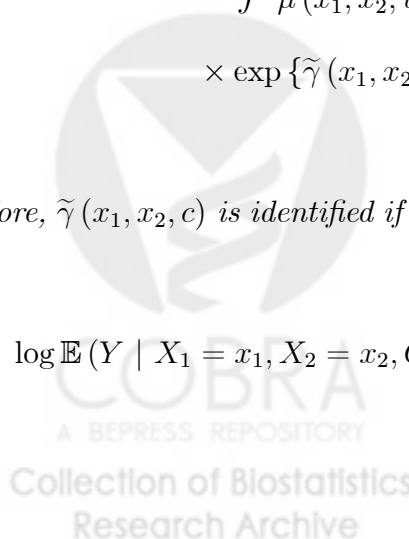
is additive in  $x_1$  and  $x_2$  by assumption, thus  $\tilde{\gamma}(x_1, x_2, c)$  is identified if and only if  $\int \{\mu(x_1, x_2, u, c) - \mu(x_1, x_2^*, u, c) + \mu(x_1^*, x_2, u, c) - \mu(x_1^*, x_2^*, u, c)\} dF(u|x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  proving the result.

**Proof of Theorem 2:** We note that  $E(Y | X_1 = x_1, X_2 = x_2, C = c) =$

$$\begin{aligned}
& \int \mu(x_1, x_2, u, c) dF(u|x_1, x_2, c) \\
&= \int \frac{\mu(x_1, x_2, u, c)}{\mu(x_1, x_2, u^*, c)} dF(u|x_1, x_2, c) \times \frac{\mu(x_1, x_2, u^*, c)}{\exp\{\tilde{\gamma}(x_1, x_2, c)\}} \\
&\quad \times \exp\{\tilde{\gamma}(x_1, x_2, c)\}
\end{aligned}$$

Therefore,  $\tilde{\gamma}(x_1, x_2, c)$  is identified if and only if  $\alpha_3(x_1, x_2, c) = \tilde{\gamma}(x_1, x_2, c)$ , that is, if and only if

$$\log \mathbb{E}(Y | X_1 = x_1, X_2 = x_2, C = c) - \tilde{\gamma}(x_1, x_2, c) = \alpha_1(x_1, c) + \alpha_2(x_2, c) + \alpha_4(c)$$



is additive in  $x_1$  and  $x_2$ , or equivalently, if and only if

$$\log \int \{ \mu(x_1, x_2, u, c) / \mu(x_1, x_2, u^*, c) \} dF(u|x_1, x_2, c) + \log \mu(x_1, x_2, u^*, c) - \tilde{\gamma}(x_1, x_2, c)$$

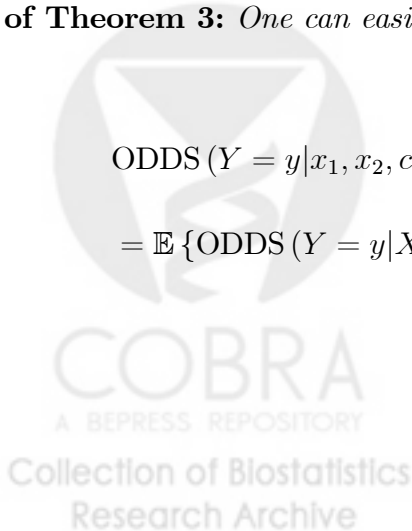
is additive in  $x_1$  and  $x_2$ . We finally note that

$$\begin{aligned} & \log \mu(x_1, x_2, u^*, c) - \tilde{\gamma}(x_1, x_2, c) \\ &= \log \mu(x_1, x_2^*, u^*, c) - \log \mu(x_1^*, x_2^*, u^*, c) \\ &+ \log \mu(x_1^*, x_2, u^*, c) - \log \mu(x_1^*, x_2^*, u^*, c) \\ &+ \left\{ \underbrace{\log \mu(x_1, x_2, u^*, c) - \log \mu(x_1, x_2^*, u^*, c) - \log \mu(x_1^*, x_2, u^*, c) + \log \mu(x_1^*, x_2^*, u^*, c)}_{=\tilde{\gamma}(x_1, x_2, c)} \right\} \\ &+ \log \mu(x_1^*, x_2^*, u^*, c) - \tilde{\gamma}(x_1, x_2, c) \end{aligned}$$

Thus,  $\log E(Y | X_1 = x_1, X_2 = x_2, C = c) - \tilde{\gamma}(x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  by assumption, and  $\tilde{\gamma}(x_1, x_2, c)$  is identified if and only if  $\log \int \{ \mu(x_1, x_2, u, c) / \mu(x_1, x_2, u^*, c) \} dF(u|x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$ , proving the result.

**Proof of Theorem 3:** One can easily verify that

$$\begin{aligned} & \text{ODDS}(Y = y|x_1, x_2, c) \\ &= \mathbb{E} \{ \text{ODDS}(Y = y|X_1, X_2, U, C) | Y = y^*, X_1 = x_1, X_2 = x, C = c \} \end{aligned}$$



Hence,

$$\begin{aligned} & \text{ODDS}(Y = y|x_1, x_2, c) \\ &= \mathbb{E} \left\{ \frac{\text{ODDS}(Y = y|X_1, X_2, U, C)}{\text{ODDS}(Y = y|x_1, x_2, u^*, c)} \middle| Y = y^*, X_1 = x_1, X_2 = x, C = c \right\} \\ & \times \frac{\text{ODDS}(Y = y|x_1, x_2, u^*, c)}{\exp\{\tilde{\gamma}^g(y, x_1, x_2, c)\}} \times \exp\{\tilde{\gamma}^g(y, x_1, x_2, c)\} \end{aligned}$$

Therefore,  $\tilde{\gamma}^g(y, x_1, x_2, c)$  is identified if and only if  $\alpha_3(y, x_1, x_2, c) = \tilde{\gamma}(y, x_1, x_2, c)$ , where

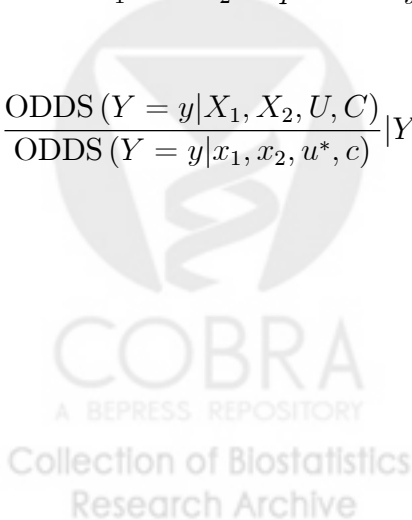
$$\log \text{ODDS}(Y = y|x_1, x_2, c) - \tilde{\gamma}(y, x_1, x_2, c) = \alpha_1(y, x_1, c) + \alpha_2(y, x_2, c) + \alpha_3(y, x_1, x_2, c) + \alpha_4(y, c)$$

such that  $0 = \alpha_1(y, 0, c) = \alpha_2(y, 0, c) = \alpha_3(y, 0, x_2, c) = \alpha_3(y, x_1, 0, c)$ , and thus,  $\tilde{\gamma}^g(y, x_1, x_2, c)$  is identified if and only

$$\begin{aligned} & \log \text{ODDS}(Y = y|x_1, x_2, c) - \tilde{\gamma}^g(y, x_1, x_2, c) \\ &= \alpha_1(y, x_1, c) + \alpha_2(y, x_2, c) + \alpha_4(y, c) \end{aligned}$$

is additive in  $x_1$  and  $x_2$ . Equivalently,  $\tilde{\gamma}^g(y, x_1, x_2, c)$  is identified if and only if

$$\log \mathbb{E} \left\{ \frac{\text{ODDS}(Y = y|X_1, X_2, U, C)}{\text{ODDS}(Y = y|x_1, x_2, u^*, c)} \middle| Y = y^*, X_1 = x_1, X_2 = x, C = c \right\} + \log \frac{\text{ODDS}(Y = y|x_1, x_2, u^*, c)}{\exp\{\tilde{\gamma}^g(y, x_1, x_2, c)\}}$$



is additive in  $x_1$  and  $x_2$ . We finally note that

$$\begin{aligned}
& \log \text{ODDS}(Y = y|x_1, x_2, u^*, c) - \tilde{\gamma}(x_1, x_2, c) \\
&= \log \text{ODDS}(Y = y|x_1, x_2^*, u^*, c) - \log \text{ODDS}(Y = y|x_1^*, x_2^*, u^*, c) \\
&+ \log \text{ODDS}(Y = y|x_1^*, x_2, u^*, c) - \log \text{ODDS}(Y = y|x_1^*, x_2^*, u^*, c) \\
&+ \underbrace{\left\{ \begin{array}{l} \log \text{ODDS}(Y = y|x_1, x_2, u^*, c) - \log \text{ODDS}(Y = y|x_1, x_2^*, u^*, c) \\ - \log \text{ODDS}(Y = y|x_1^*, x_2, u^*, c) + \log \text{ODDS}(Y = y|x_1^*, x_2^*, u^*, c) \end{array} \right\}}_{=\tilde{\gamma}(y, x_1, x_2, c)} \\
&+ \log \text{ODDS}(Y = y|x_1^*, x_2^*, u^*, c) - \tilde{\gamma}^g(y, x_1, x_2, c)
\end{aligned}$$

therefore  $\log \text{ODDS}(Y = y|x_1, x_2, u^*, c) - \tilde{\gamma}(x_1, x_2, c)$  is additive in  $x_1$  and  $x_2$  by assumption, thus

$$\tilde{\gamma}^g(y, x_1, x_2, c) \text{ is identified if and only if } \log E \left\{ \frac{\text{ODDS}(Y=y|X_1, X_2, U, C)}{\text{ODDS}(Y=y|x_1, x_2, u^*, c)} \mid Y = y^*, X_1 = x_1, X_2 = x, C = c \right\}$$

is additive in  $x_1$  and  $x_2$ , proving the result.

**Proof of Corollary 4:** To prove the result, it suffices to note that under

(i)

$$\begin{aligned}
& \log \mathbb{E} \left\{ \frac{\text{ODDS}(Y = y|X_1, X_2, U, C)}{\text{ODDS}(Y = y|x_1, x_2, u^*, c)} \mid Y = 0, X_1 = x_1, X_2 = x, C = c \right\} \\
&= \log \mathbb{E} \left\{ \frac{OR_{Y, X_2}(X_2|x_1^*, U, C)}{OR_{Y, X_2}(X_2|x_1^*, u^*, C)} OR_{Y, U}(U|x_1^*, x_2^*, C) \mid Y = 0, X_2 = x, C = c \right\}
\end{aligned}$$

is additive in  $x_1$  and  $x_2$ , proving the first part of the result.

Next, under

(ii)

$$\begin{aligned} & \log \mathbb{E} \left\{ \frac{\text{ODDS}(Y = y | X_1, X_2, U, C)}{\text{ODDS}(Y = y | x_1, x_2, u^*, c)} \mid Y = 0, X_1 = x_1, X_2 = x, C = c \right\} \\ &= \log \mathbb{E} \{ \text{OR}_{Y,U}(U | x_1^*, x_2^*, C) \mid Y = 0, X_1 = x_1, X_2 = x, C = c \} \end{aligned}$$

proving the second part of the result. And finally under

(iii)

$$\begin{aligned} & \log \mathbb{E} \left\{ \frac{\text{ODDS}(Y = y | X_1, X_2, U, C)}{\text{ODDS}(Y = y | x_1, x_2, u^*, c)} \mid Y = 0, X_1 = x_1, X_2 = x, C = c \right\} \\ &= \log \mathbb{E} \left\{ \frac{\text{OR}_{Y,X_1}(X_1 | x_2^*, U_1, C)}{\text{OR}_{Y,X_1}(X_1 | x_2^*, u_1^*, C)} \text{OR}_{Y,U_1}(U_1 | x_1^*, x_2^*, C) \mid Y = 0, X_1 = x_1, C = c \right\} \\ &+ \log \mathbb{E} \left\{ \frac{\text{OR}_{Y,X_2}(X_2 | x_1^*, U_2, C)}{\text{OR}_{Y,X_2}(X_2 | x_1^*, u_2^*, C)} \text{OR}_{Y,U_2}(U_2 | x_1^*, x_2^*, C) \mid Y = 0, X_2 = x, C = c \right\} \end{aligned}$$

proving the result.



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