Twin Research and Human Genetics (2019), **22**, 290–296
doi:10.1017/thg.2019.67

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Article

Sibling Comparison Designs: Addressing Confounding Bias with Inclusion of Measured Confounders

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Abstract

Genetically informative research designs are becoming increasingly popular as a way to strengthen causal inference with their ability to control for genetic and shared environmental confounding. Co-twin control (CTC) models, a special case of these designs using twin samples, decompose the overall effect of exposure on outcome into a within- and between-twin-pair term. Ideally, the within-twin-pair term would serve as an estimate of the exposure effect controlling for genetic and shared environmental factors, but it is often confounded by factors not shared within a twin-pair. Previous simulation work has shown that if twins are less similar on an unmeasured confounder than they are on an exposure, the within-twin-pair estimate will be a biased estimate of the exposure effect, even more biased than the individual, unpaired estimate. The current study uses simulation and analytical derivations to show that while incorporating a covariate related to the nonshared confounder in CTC models always reduces bias in the within-pair estimate, it will be less biased than the individual estimate only in a narrow set of circumstances. The best case for bias reduction in the within-pair estimate occurs when the within-twin-pair correlation in exposure is less than the correlation in the confounder and the twin-pair correlation in the covariate is high. Additionally, the form of covariate inclusion is compared between adjustment for only one's own covariate value and adjustment for the deviation of one's own value from the covariate twin-pair mean. Results show that adjusting for the deviation from the twin-pair mean results in equal or reduced bias.

Keywords: Co-twin control; discordant twin; bias; confounding; covariate adjustment; between-within

(Received 2 May 2019; accepted 7 August 2019; First published online 27 September 2019)

Co-twin control (CTC) or discordant twin models are a special case of what are commonly referred to as between-within models (Begg & Parides, 2003; Carlin et al., 2005; McGue et al., 2010). CTC models make use of the genetic and environmental relationships within twin-pairs to estimate an exposure effect controlling for all factors shared within a pair. Monozygotic (MZ) twins share all genetic factors and rearing environment, so any difference in outcome must be due to factors not shared within the twin-pair. If an exposure has a causal effect on an outcome, the outcome levels will differ within exposure discordant twin-pairs. In this way, the unexposed twin acts as the counterfactual to their exposed co-twin; they are an approximation of what the twin would have looked like had they not been exposed. The same logic can be extended to genetic relationships other than twins, as in sibling comparison designs (Lahey & D'Onofrio, 2010).

The power in the CTC design lies in its ability to implicitly control for all factors shared within a twin-pair even when they are unmeasured (McGue et al., 2010). For this reason, CTC designs are widely used as a stronger method of causal inference than using genetically unrelated individuals (Donovan & Susser, 2011). Examples of their use range from the effects of cannabis on intelligence (Jackson et al., 2016) and educational attainment (Meier et al., 2018; Verweij et al., 2013) to alcohol's effect on stroke risk (Kadlecová et al., 2015) or hippocampal volume (Wilson et al., 2018) and to how lifestyle factors influence cancer risk (Hübinette et al., 2001; Milán et al., 2003; Swerdlow et al., 1999). Despite the increasing popularity of the CTC design, it has not been fully explored methodologically. Work by Frisell and colleagues has shown that bias can be introduced in the CTC estimates in the presence of nonshared confounding (Frisell et al., 2012). The magnitude of this bias is a function of the within-twin-pair correlation in the exposure and the confounder. This work also shows that measurement error in the exposure will bias the CTC estimate toward the null.

The current study builds on these findings by testing whether the inclusion of a measured covariate can counteract the nonshared confounding bias. In other words, can the bias induced by a nonshared confounder be reduced when a measured covariate is included in the CTC model? Incorporating potential confounders as covariates in a regression model is a popular way of controlling for confounding bias (Greenland & Morgenstern, 2001). If the covariate is a perfect measure of the confounder, doing so will eliminate all confounding bias. Most often, however, the covariate measures the confounder with some error, resulting in residual confounding bias (Becher, 1992). Using analytic derivations and simulations, we investigate whether covariate inclusion will reduce the bias in the CTC model estimates more than in a model treating the twins as individuals and explore what parameters affect the bias reduction in this scenario. Lastly, the impact of measurement error in not only the exposure, but also the measured covariate, is investigated. The interpretation of CTC model estimates is discussed in light of our findings.

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Cite this article: Saunders GRB, McGue M, and Malone SM. (2019) Sibling Comparison Designs: Addressing Confounding Bias with Inclusion of Measured Confounders. *Twin Research and Human Genetics* **22**: 290–296, https://doi.org/10.1017/thg.2019.67

Co-Twin Control Model

A generalized linear regression model, treating twins as individuals (the individual-level model), is given by

$$g\{E(Y_{ij}|X_{ij})\} = \beta_0 + \beta X_{ij}, \quad (1)$$

where X_{ij} is the exposure of person j in twin-pair i, Y_{ij} is their outcome and $g\{\ \}$ is a link function allowing the generalized linear model to be extended to different forms of regression, like linear or logistic regression. For example, in a linear regression model, Y follows a normal distribution with the identity link function ($g\{\mu\} = \mu$).

The CTC model decomposes the exposure effect from the individual-level model (β) into a within-twin-pair and between-twin-pair effect by incorporating the twin-pair mean. The CTC model is given as

$$g\{E(Y_{ij}|X_{ij}, \overline{X}_i)\} = \beta_0 + \beta_W(X_{ij} - \overline{X}_i) + \beta_B\overline{X}_i, \quad (2)$$

where $\overline{X}_i$ is the mean exposure of twin-pair i. The within-twin-pair estimate (β_W) is the estimate of the exposure effect controlling for all genetic and shared environmental factors. The between-twin-pair estimate (β_B) is an estimate of the magnitude of confounding due to shared factors. In general, the within-twin-pair effect is of more interest to researchers than the between-pair effect.

Interpretation of the within-pair effect is commonly made by comparing β_W from the CTC model to β from the individual-level model (McGue et al., 2010). When these estimates are not significantly different from one another, $\beta = \beta_W$, this would suggest that the observed association is not due to confounding factors, consistent with a causal effect of exposure on outcome. When β_W is significantly different from β but is not 0, $\beta \neq \beta_W > 0$, this suggest that the observed association is partially due to confounding factors. And, finally, when the within-pair effect is not significantly different from 0, $\beta_W = 0$, this would suggest that the entire association is due to confounding and is not consistent with a causal interpretation.

Bias Due to Nonshared Confounding

Prior statistical analysis of CTC models by Frisell et al. (2012) has shown that bias is induced in the within-twin-pair estimate in the presence of factors that are not perfectly shared within a twin-pair. Environmental confounding within-twin-pairs will increase bias in the within-twin-pair term as a function of the degree to which such confounding reflects influences that are unshared within a pair. If all confounding variables are perfectly shared within a twin-pair, the estimate of the effect of the exposure (β_W) will be unconfounded. As the correlation between confounding variables decreases within a twin-pair, the estimate of the effect of the exposure (β_W) will be biased upward. In some cases, this bias will exceed that of the individual-level effect (β). To illustrate this, we assume that the confounding variable affects both the exposure and the outcome, but that the exposure does not have a causal effect on the outcome. If we select twin-pairs in which the members of the pair are discordant on the exposure, they will also likely be more discordant on the confounding variable than unselected twin-pairs (the correlation of the confounding variable between members of a pair will be reduced). This will in turn increase the correlation between the confounder and the exposure variables and create a spurious relationship between the exposure and the outcome. The impact of nonshared confounders on the bias of β and β_W depends on the ratio of the within-pair correlation of the confounding variable (ρ_C) to the within-pair correlation of the exposure variable (ρ_X). If the within-pair correlation in the confounder is greater than the within-pair correlation in the exposure, the within-twin-pair term is less biased than the individual-level term (if $\rho_C > \rho_X$ then $bias(\beta_W) < bias(\beta)$). If the correlation between confounders is less than the correlation between exposure, the within-twin-pair term is *more* biased than the individual-level term (if $\rho_C < \rho_X$ then $bias(\beta_W) > bias(\beta)$). If the correlations are equal, both estimates will have the same amount of bias. Unless $\rho_C = 1$, however, bias will always exist in the within-pair estimate (Frisell et al., 2012).

Additionally, random measurement error in the exposure can lead to twin-pairs being incorrectly classified as concordant or discordant, which is important given that only discordant twin-pairs are informative for the within-pair effect in CTC models. As measurement error increases, the within-twin-pair estimate increasingly underestimates the true effect. Both biases due to confounding and measurement error affect the estimates from CTC models as well as more general between-within models (i.e., any models in which an exposure–outcome relationship is decomposed into a within- and between-cluster effect).

Inclusion of a Measured Covariate to Reduce Bias

While nonshared confounding may induce bias in the within-twin-pair effect, most researchers attempt to control for this by including covariates in the CTC regression model. The rationale is that the covariates incorporated into the model are an imperfect measure of unmeasured confounding variables, and by controlling them, bias due to confounding is thereby reduced. Figure 1 shows a causal diagram for one twin-pair where the exposure–outcome relationship is confounded by an unmeasured variable, C, that also affects the measured covariate, Z.

A standard way to include covariates in CTC models is given by

$$g\{E(Y_{ij}|X_{ij}, \overline{X}_i, Z_{ij})\} = \beta_0 + \beta_W(X_{ij} - \overline{X}_i) + \beta_B\overline{X}_i + \beta_Z Z_{ij}, \quad (3)$$

where Z is the measured covariate. Sjölander et al. (2012), however, show that this model specification does not properly adjust for the covariate and causes β_W to lose its causal interpretation. Briefly, by conditioning on $\overline{X}_i$, a spurious association is induced between the exposure of twin 1 (X_{i1}) and the covariate of their co-twin (Z_{i2}) and between the outcome of twin 1 (Y_{i1}) and the covariate of twin 2 (Z_{i2}). Essentially, Z_{i2} becomes a collider variable, a common effect of two or more variables (Greenland, 2003), and an artificial confounder of the exposure–outcome relationship. Given this model specification, even in the absence of a true causal effect $\beta_{YX} = 0$, β_W will not equal 0. The authors show that a simple modification of the model can recapture the causal interpretation of β_W:

$$g\{E(Y_{ij}|X_{ij}, \overline{X}_i, Z_{ij}, \overline{Z}_i)\} = \beta_0 + \beta_W(X_{ij} - \overline{X}_i) + \beta_B\overline{X}_i + \beta_Z(Z_{ij} - \overline{Z}_i), \quad (4)$$

where $\overline{Z}_i$ is the mean covariate value of twin-pair i (Sjölander et al., 2012). The current study explores both forms of covariate inclusion to evaluate whether confounding bias can be reduced, with particular interest in bias reduction in β_W. We focus on whether, or to what extent, bias remains in the within-pair estimate even if the causal interpretation is retained as in equation 4.

https://doi.org/10.1017/thg.2019.67 Published online by Cambridge University Press

Bias Reduction with a Covariate under a Linear Model

Assuming that all effects in the causal diagram (Figure 1) are linear and that all variables are continuous, we are able to derive the exact mathematical formula for the regression coefficients. We further assume, without loss of generality, that all variables other than error terms are standardized (a mean of 0 and a standard deviation of 1). We can then ignore the intercept term so that the true causal model is given by

$$Y_{ij} = \beta_{YX} X_{ij} + \beta_{YC} C_{ij} + \varepsilon_{Y_{ij}}, \tag{5}$$

$$X_{ij} = \beta_{XC} C_{ij} + \varepsilon_{X_{ij}}, \tag{6}$$

$$Z_{ij} = \beta_{ZC} C_{ij} + \varepsilon_{Z_{ij}}. \tag{7}$$

With this data-generating structure, all confounding between X and Y is due to C, with Z being a measure of C that has no direct effect on X or Y. We let $\text{var}(C) = \sigma_C^2 = 1$, $\text{var}(\varepsilon_{Y_{ij}}) = \sigma_{Y_{ij}}^2$, $\text{var}(\varepsilon_{X_{ij}}) = \sigma_{X_{ij}}^2$ and $\text{var}(\varepsilon_{Z_{ij}}) = \sigma_{Z_{ij}}^2$. Because the causal diagram assumes twin-pairs, we have $\text{cov}(C_{i1}, C_{i2}) = \rho_C \sigma_C^2$, $\text{cov}(\varepsilon_{Y_{i1}}, \varepsilon_{Y_{i2}}) = \rho_{\varepsilon_Y} \sigma_{\varepsilon_Y}^2$, $\text{cov}(\varepsilon_{X_{i1}}, \varepsilon_{X_{i2}}) = \rho_{\varepsilon_X} \sigma_{\varepsilon_X}^2$ and $\text{cov}(\varepsilon_{Z_{i1}}, \varepsilon_{Z_{i2}}) = \rho_{\varepsilon_Z} \sigma_{\varepsilon_Z}^2$. Furthermore, we make the assumptions that each twin's error terms (ϵ) are independent of all other variables and there is no correlation between the error terms of different variables within a twin-pair.

We are interested in the true causal effect of X on Y (β_{YX}). Regressing Y on X and C would result in an unbiased estimate of the exposure effect. However, C is unmeasured and leaving it out results in a biased estimate of the exposure effect. We explore the bias when regressing Y on X and Z instead. Because Z is a measure of C, including it in the regression model may reduce the confounding bias induced by the unmeasured confounder C. Furthermore, we are interested in whether the inclusion of Z reduces the bias more for the within-twin-pair effect (β_W) than the individual-level effect (β).

Confounding Bias with Covariate Inclusion

The derived estimate of the exposure effect from the individual-level model without adjusting for a covariate (equation 1) is

$$\beta = \beta_{YX} + \beta_{YC}\beta_{XC}\,. \tag{8}$$

The derived estimate of the exposure effect from the CTC model without adjusting for a covariate (equation 2) is

$$\beta_W = \beta_{YX} + \frac{\beta_{YC}\beta_{XC}}{\left(\frac{1-\rho_{\varepsilon_X}}{1-\rho_C}\right)}. \tag{9}$$

The full derivation steps can be found in Frisell et al. (2012). It is clear that both estimates are a function of the true causal effect (β_{YX}) plus a bias term. Because the within-twin-pair correlation in the exposure, ρ_X, is a linear combination of ρ_{ε_X} and ρ_C (i.e., $\rho_X = \rho_{\varepsilon_X}\sigma_{\varepsilon_X}^2 + \beta_{XC}^2\rho_C$), the difference in bias between the β and β_W is a function of the relative magnitudes of ρ_X and ρ_C. When $\rho_X = \rho_C$, then by definition resulting in $\beta = \beta_W$. Following similar reasoning, when $\rho_X > \rho_C$, ρ_{ε_X} will be greater than ρ_C resulting in $\left(\frac{1-\rho_{\varepsilon_X}}{1-\rho_C}\right) > 1$. This illustrates how bias in β_W will be larger than bias in β when the within-pair correlation in the exposure is greater than the within-pair correlation in the confounder.

After inclusion of a covariate Z, the derived exposure estimate from the individual-level model becomes (see supplementary material for full derivation)

$$\beta_{\text{cov}} = \beta_{YX} + \frac{\beta_{YC}\beta_{XC}\left(1-\beta_{ZC}^2\right)}{1-\beta_{ZC}^2\beta_{XC}^2}. \tag{10}$$

The bias term now additionally depends on how well Z measures C (the magnitude of β_{ZC}), which confirms our intuition. The estimate for the within-pair effect when adjusting for a covariate in the standard way (equation 3) is given by

$$\beta_{W_{\text{covstd}}} = \frac{\beta_{YX}\left(1-\beta_{XC}^2\rho_C-\sigma_{\varepsilon_X}^2\rho_{\varepsilon_X}\right)+\beta_{YC}\beta_{XC}(1-\rho_C)-\beta_{ZC}\beta_{XC}(1-\rho_C)(\beta_{YX}\beta_{XC}\beta_{ZC}+\beta_{YC}\beta_{ZC})}{2\left(1-\beta_{XC}^2\rho_C-\rho_{\varepsilon_X}\sigma_{\varepsilon_X}^2\right)-[\beta_{ZC}\beta_{XC}(1-\rho_C)]^2}. \tag{11}$$

The estimate for the within-pair effect when adjusting for a covariate in a way that retains the correct causal interpretation (equation 4) becomes

$$\beta_{W_{\text{cov}}} = \frac{\left[2\left(1-\beta_{ZC}^2\rho_C-\rho_{\epsilon_Z}\sigma_{\epsilon_Z}^2\right)\right]\left[\beta_{YX}\left(1-\beta_{XC}^2\rho_C-\rho_{\epsilon_X}\sigma_{\epsilon_X}^2\right)+\beta_{YC}\beta_{XC}(1-\rho_C)\right]-\left[2\beta_{ZC}\beta_{XC}(\beta_{YX}\beta_{XC}\beta_{ZC}+\beta_{YC}\beta_{ZC})(1-\rho_C)^2\right]}{\left[2\left(1-\beta_{ZC}^2\rho_C-\rho_{\epsilon_Z}\sigma_{\epsilon_Z}^2\right)\left(1-\beta_{XC}^2\rho_C-\rho_{\epsilon_X}\sigma_{\epsilon_X}^2\right)\right]-\left[2\beta_{ZC}\beta_{XC}(1-\rho_C)\right]^2}. \tag{12}$$

The interpretation of this estimate is not intuitively clear, though it must depend on the within-twin-pair correlation in exposure (ρ_X), the confounder (ρ_C) and the covariate (ρ_Z). Like the individual-level estimate, it also depends on the magnitude of β_{ZC}, that is, how well the covariate measures the confounder.

Results

To help interpret how covariate inclusion affects bias in CTC models, we simulated paired data according to the data-generating structure in Figure 1. Details of the simulation setup are included in the supplementary material. While the simulation is not strictly necessary after deriving exact estimates of β and β_W, we include it here as a visual depiction of the patterns of bias to show the consistency with results from the derivations (Supplemental Figure 1). The simulation code can also be adapted to show that the patterns of results hold for other forms of regression (i.e., logistic regression), though not shown here. The values chosen for each parameter were mostly arbitrary, though we attempted to choose practical values (R code is included in the Appendix if readers wish to test other parameter combinations). The general pattern of results holds for all values chosen, though in some cases a particular combination of parameters is not possible (e.g., low ρ_Z, high ρ_C and high β_{ZC}). For this reason, some lines in the figures illustrating the results may abruptly cut off when an inadmissible situation occurs. Figure 2 essentially recapitulates the work of Frisell et al. (2012), whereas Figure 3 extends this to a variety of situations. In both figures, only derivation results are shown for ease of clarity (Supplemental Figure 1 displays simulation results overlaid on the derivation results to show their concordance). In Figure 3, solid lines denote the exposure effect estimate with covariate inclusion, while dashed lines denote the same estimate without covariate inclusion to better show the change in bias between these models. The true causal exposure effect was 0 for all simulations ($\beta_{YX} = 0$).

Figure 2 shows how nonshared confounding induces bias in both the individual-level and within-pair exposure effect, and

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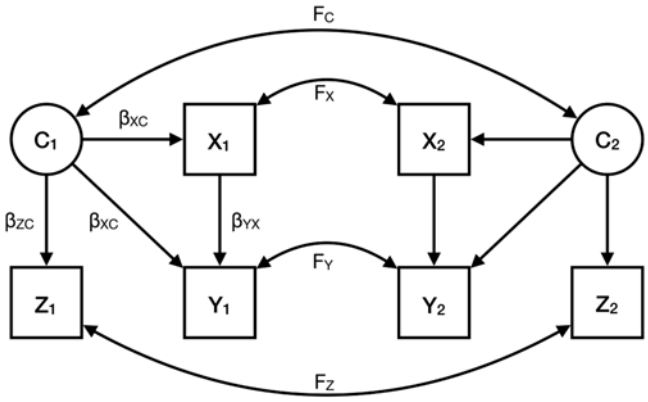

Fig. 1. Causal diagram shown for one twin-pair (subscripts of 1 and 2 represent each twin). Variables *X*, *Y* and *C* represent the exposure, outcome and unmeasured confounder, respectively. *Z* represents the measured covariate. β_{YX} is the true causal effect of exposure on outcome. β_{ZC} is the effect of the confounder on the covariate. Double-headed arrows represent familial factors that cause aggregation of phenotypes within families.

how the bias is affected by the relationship between the within-pair correlation in the exposure and the confounder in the absence of covariates (Frisell et al., 2012). The blue line indicates the estimated exposure effect from the individual-level model, while the red line indicates the within-pair effect from the CTC model. Because no covariates are included in either model, bias does not depend on the magnitude of β_{ZC}. Each panel shows the bias under the possible relationships between ρ_X and ρ_C: $\rho_X < \rho_C$, $\rho_X = \rho_C$ and $\rho_X > \rho_C$. As was found in the previous work, when $\rho_X > \rho_C$, the β_W estimate from CTC models is a more biased estimate of the exposure effect than the individual-level β.

We now consider each relationship between ρ_X and ρ_C separately. Figure 3(A) illustrates the bias when the twin correlation is greater for the covariate than the exposure $(\rho_C > \rho_X)$ with the inclusion of a covariate. In this case, based on findings from Frisell et al. (2012), we expect that β_W will be less biased than β. We do indeed see that for most values of ρ_Z and β_{ZC}. As β_{ZC} increases, meaning the covariate is an increasingly accurate measure of the confounder, the bias decreases in both β_W and β, as would be expected. The magnitude of ρ_Z, the within-pair correlation in the covariate, affects the rate at which the bias decreases in the β_W coefficients only. When ρ_Z is high, the rate of decrease in bias of the β_W estimate is the highest. Comparing both forms of covariate inclusion, when β_{ZC} is low, $\beta_{W_{cov}}$ and $\beta_{W_{covstd}}$ perform similarly. As the value of β_{ZC} increases, $\beta_{W_{covstd}}$ shows less bias at low values of ρ_Z, while $\beta_{W_{cov}}$ shows less bias at high values of ρ_Z.

Figure 3(B) illustrates the bias with the inclusion of a covariate when $\rho_X = \rho_C$. In this case, we expect that β_W will have the same amount of bias as β. This occurs only when ρ_Z is also the same (i.e., $\rho_X = \rho_C = \rho_Z$). When ρ_Z is low, the within-pair effect is more biased than the individual-level effect. The reverse is true when ρ_Z is high. As in the previous scenario, as ρ_Z increases in magnitude, the rate of bias reduction also increases but only for the within-pair effect. Comparing both forms of covariate inclusion in this scenario, $\beta_{W_{covstd}}$ shows similar bias to β across all values of β_{ZC} and ρ_Z. As the value of β_{ZC} increases, $\beta_{W_{cov}}$ shows increased bias at low values of ρ_Z but reduced bias at high values of ρ_Z.

Finally, Figure 3(C) illustrates the bias with the inclusion of a covariate when $\rho_X > \rho_C$. This is the 'worst case' scenario where we expect that β_W will have more bias than β. As β_{ZC} increases, the bias in both estimates decreases. Additionally, as ρ_Z increases, there comes a point at which β_W is less biased than β. It is clear, however, that this only occurs when ρ_Z is high and for narrow ranges of β_{ZC}. Finally, comparing both forms of covariate inclusion, we see a similar relationship between $\beta_{W_{cov}}$ and $\beta_{W_{covstd}}$ as in Figure 3(A). When β_{ZC} is low, $\beta_{W_{cov}}$ and $\beta_{W_{covstd}}$ perform similarly. As the value of β_{ZC} increases, $\beta_{W_{covstd}}$ shows less bias at low values of ρ_Z, while $\beta_{W_{cov}}$ shows less bias at high values of ρ_Z. Interestingly, $\beta_{W_{covstd}}$ never results in less bias than β even at very high values of β_{ZC} and ρ_Z.

Discussion

The current study extends work by Frisell et al. (2012) by showing that the inclusion of a covariate as a proxy measure of a confounder always reduces bias in individual-level and CTC exposure effect estimates. However, in situations in which we expect the within-pair estimate (β_W) to me more biased than the individual-level estimate (β), the inclusion of a covariate results in less bias in β_W, compared with β, in only a limited set of circumstances. It remains that in most situations likely encountered in practice, β_W will be a biased estimate of the true causal exposure effect. This result has important implications for the use and interpretation of CTC, and more broadly between-within, models.

As previously shown in CTC models, when the within-twin-pair correlation in the exposure is greater than the within-pair

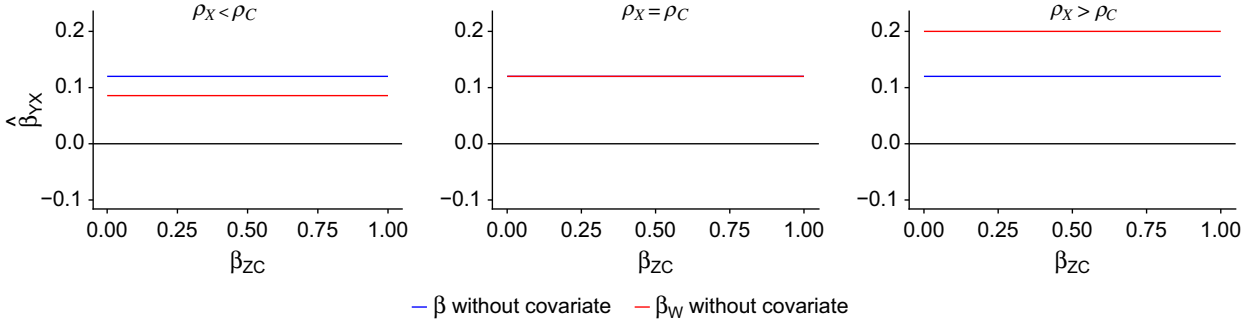

Fig. 2. (Colour online) Results recreated from Frisell et al. (2012). Blue lines denote the exposure estimate from individual-level models, while red lines denote the exposure estimate from CTC models. The true causal effect is 0 ($\beta_{YX} = 0$). The within-twin-pair correlations in the exposure and the confounder are ρ_X and ρ_C, respectively. For each scenario $\rho_C = 0.5$, while ρ_X varies between 0.3, 0.5 and 0.7. The bias in the individual-level effect and the within-twin-pair effect does not depend on β_{ZC}, the effect of the confounder on the covariate, because the covariate is not included in these models.

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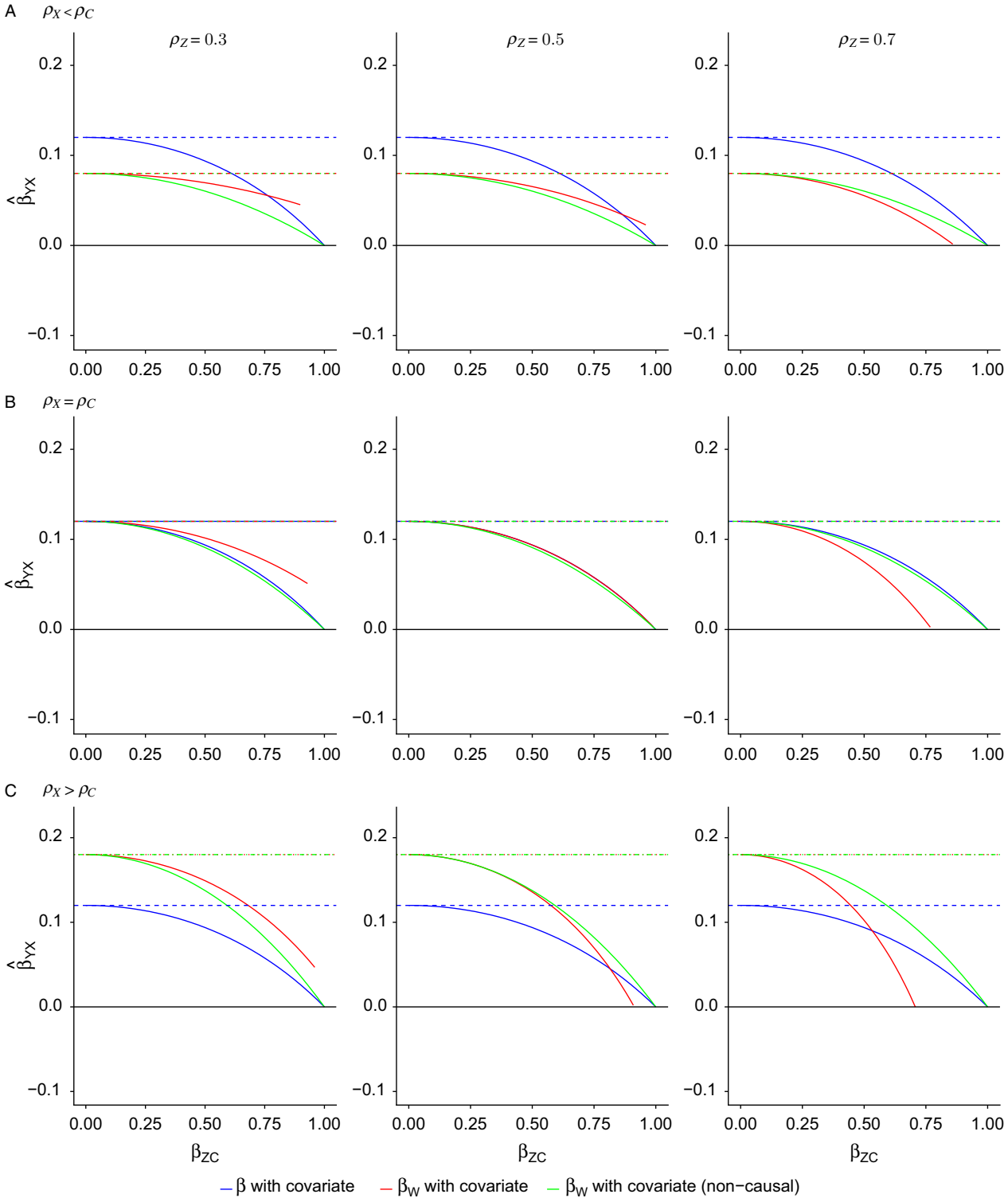

Fig. 3. (Colour online) Exposure effect estimates with the inclusion of a covariate from individual-level and within-pair models when (A) the within-pair correlation in the exposure is less than the within-pair correlation in the confounder; (B) the within-pair correlation in the exposure equals the within-pair correlation in the confounder; (C) the within-pair correlation in the exposure is more than the within-pair correlation in the confounder. For each scenario $\rho_C = 0.5$, while ρ_X varies between 0.3, 0.5 and 0.7 (consistent with Figure 2). Additionally, each column represents a different value of ρ_Z, the within-pair correlation in the covariate. β_{ZC} is the effect of the confounder on the covariate. Blue lines denote the exposure estimate from individual-level models, red lines denote the exposure estimate from CTC models as specified in equation 4 and green lines denote the exposure estimate from CTC models as specified in equation 3. Solid lines denote the exposure effect estimate with covariate inclusion, while dashed lines denote the same estimate without covariate inclusion. The true causal exposure effect is 0 ($\beta_{YX} = 0$).

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correlation in the confounder (i.e., $\rho_X > \rho_C$), β_W will be more biased than the individual-level β. In this 'worst case scenario', one may choose to include a covariate measure as a proxy of the confounder in order to reduce this bias. While covariate inclusion reduces bias in β_W more than in β as illustrated in Figure 3, the current work shows that β_W will be less biased than β only when the within-pair correlation in the covariate (ρ_Z) is high and the covariate is an accurate measure of the confounder (β_{ZC} is large). In comparing forms of covariate inclusion, $\beta_{W_{\text{covstd}}}$ generally shows less bias than $\beta_{W_{\text{cov}}}$ when ρ_Z is low but shows greater bias at high values of ρ_Z. While it may be the case that using $\beta_{W_{\text{covstd}}}$ results in the greatest bias reduction in the exposure effect estimate, this form of covariate inclusion does not retain its assumed causal interpretation (Sjölander et al., 2012). The increased bias reduction in select scenarios is not sufficient to justify its use over $\beta_{W_{\text{cov}}}$, which does retain the correct causal interpretation.

The effect of β_{ZC} on these results is intuitive. If the covariate is an accurate measure of the confounder, including it in the model will clearly reduce confounding bias. The effect of ρ_Z on bias reduction is less intuitive. Across all relationships between ρ_X and ρ_C, increasing values of ρ_Z decrease the bias in the within-pair estimate, as illustrated in Figure 3. In other words, holding ρ_X and ρ_C constant, increasing ρ_Z will reduce bias in β_W (the individual-level estimate, β is not affected by the value of ρ_Z). This occurs for the same reason that increasing ρ_C, holding ρ_X constant, results in lower levels of bias in β_W as discussed in Frisell et al. (2012). When twins are less discordant on the confounder, meaning that ρ_C is larger, they are also likely to be less discordant on the covariate (ρ_Z is larger). This decreases the correlation between the covariate and the exposure variables resulting in less bias. Importantly, the within-pair estimate is only unbiased when all confounders are perfectly shared within a twin-pair.

The current results have important implications for the interpretation of CTC results. As described above, interpretation of the within-pair effect is commonly made by comparing β_W from the CTC model to β from the individual-level model. We show that in the presence of nonshared confounding, CTC results can support a causal effect of exposure on outcome even when the true causal effect is 0 ($\beta_W = \beta \neq 0$). This will occur even if a covariate is included in the CTC model as a proxy measure of the confounder.

Additionally, the within-pair estimate between the monozygotic $(\beta_{W_{\text{MZ}}})$ and dizygotic $(\beta_{W_{\text{DZ}}})$ twin-pairs is usually compared to identify whether genetic or shared environmental factors confound the exposure–outcome relationship. For instance, when $\beta_{W_{\text{MZ}}} < \beta_{W_{\text{DZ}}} < \beta$, this suggests that the observed relationship is confounded by genetic factors (McGue et al., 2010). This is because MZ twin-pairs share all genetic factors, while DZ twin-pairs shared approximately 50% of these factors. Both types of twin-pairs share all common (rearing) environmental factors. Given heritable phenotypes, the within-pair correlation in exposure, confounder and covariate will be greater for MZ compared with DZ twins influencing the comparison of $\beta_{W_{\text{MZ}}}$ and $\beta_{W_{\text{DZ}}}$. Even in the case of a true, nonzero effect of exposure on outcome, it would be possible to conclude that genetic factors confound the causal relationship $(\beta_{W_{\text{MZ}}} < \beta_{W_{\text{DZ}}} < \beta)$ when, in reality, they do not. This point has been made previously (Frisell et al., 2012), but we highlight that it continues to hold in the context of the current results.

Of additional note, it is likely that the exposure and covariate are measured with some amount of error. It is well documented that measurement error in an exposure will attenuate the exposure effect estimate in a simple linear regression (Hutcheon et al., 2010; Liu, 1988; Spearman, 1904). Furthermore, it has been shown that the estimate from CTC models will be attenuated more than individual-level models (Frisell et al., 2012; McGue et al., 2010). In the case of multiple regression, where covariates are also subject to measurement error, the estimated exposure effect may under or overestimate the true causal effect (Liu, 1988; Rosner et al., 1990). While we do not include derivations for β and β_W in the presence of measurement, the reliability of the covariate Z would function as a measure of β_{ZC}. The effects of measurement error would thus mirror the impact of β_{ZC} as shown in Figure 3.

While we show that exposure effect estimates from CTC designs are likely to be biased, we maintain that the CTC design can provide useful information when used appropriately. Results from CTC studies can often be used to argue that an observed relationship is not consistent with a causal exposure effect. For instance, when $\beta_W = 0$ and the expected level of measurement error does not likely account for this magnitude of attenuation, it would suggest that shared confounders explain at least part of the exposure–outcome relationship. Results may also suggest that an observed association cannot be entirely due to shared confounders within a twin-pair. When $\beta_W \neq 0$, this suggests that some influence beyond shared confounders is contributing to the observed relationship.

The best case for bias reduction in CTC model estimates occurs when the within-twin-pair correlation in the exposure is less than the within-twin-pair correlation in the confounder, when the within-twin-pair correlation in the covariate is high, and the covariate is an accurate measure of the confounder. Of these pieces of information, only ρ_X and ρ_Z are known in practice. These values should always be reported and a case should be made about the likely relationships to the possible confounders to determine whether CTC models are appropriate for a given situation. Lastly, there are additional limitations of the CTC design that the current study does not address, like reverse causality and the potential causal influence of nonshared environmental factors not included in the models (McGue et al., 2010). Future methodological work should be focused on the extent to which these factors affect exposure effect estimates from CTC models.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2019.67

Financial support. This work was supported by grants from the US National Institute on Alcohol Abuse and Alcoholism (R37-AA009367) and the National Institute on Drug Abuse (R01-DA036216).

Conflict of interest. None.

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https://doi.org/10.1017/thg.2019.67 Published online by Cambridge University Press