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Z-scores and the birthweight paradox

Enrique F. Schisterman^a, Brian W. Whitcomb^{a,b}, Sunni L. Mumford^{a,c}, and Robert W. Platt^d

^aEpidemiology Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

^bDivision of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA

^cDepartment of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

^dDepartment of Epidemiology, McGill University, Montreal, QC, Canada

Abstract

Summary—Investigators have long puzzled over the observation that low-birthweight babies of smokers tend to fare better than low-birthweight babies of non-smokers. Similar observations have been made with regard to factors other than smoking status, including socio-economic status, race and parity. Use of standardised birthweights, or birthweight *z*-scores, has been proposed as an approach to resolve the crossing of the curves that is the hallmark of the so-called birthweight paradox. In this paper, we utilise directed acyclic graphs, analytical proofs and an extensive simulation study to consider the use of *z*-scores of birthweight and their effect on statistical analysis. We illustrate the causal questions implied by inclusion of birthweight in statistical models, and illustrate the utility of models that include birthweight or *z*-scores to address those questions.

Both analytically and through a simulation study we show that neither birthweight nor *z*-score adjustment may be used for effect decomposition. The *z*-score approach yields an unbiased estimate of the total effect, even when collider-stratification would adversely impact estimates from birthweight-adjusted models; however, the total effect could have been estimated more directly with an unadjusted model. The use of *z*-scores does not add additional information beyond the use of unadjusted models. Thus, the ability of *z*-scores to successfully resolve the paradoxical crossing of mortality curves is due to an alteration in the causal parameter being estimated (total effect), rather than adjustment for confounding or effect decomposition or other factors.

Keywords

birthweight; birthweight paradox; simulation; directed acyclic graphs; *z*-scores

Introduction

Birthweight is a robust predictor of neonatal and infant mortality.^{1–3} In the United States in 2004, infants born weighing <2500 g were reported to have 25-fold higher mortality rates than those weighing ≥2500 g.^{4,5} As a result, investigators of associations of perinatal mortality with various factors also linked to birthweight often consider birthweight as a confounder and utilise traditional epidemiological approaches to modelling, despite the fact that birthweight often lies on the causal pathway and should not be adjusted for.⁶ Assessments of associations between

Correspondence: Enrique F. Schisterman, PhD, Epidemiology Branch, Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, 6100 Executive Blvd, 7B03, Bethesda, MD 20892, USA. schistee@mail.nih.gov.

maternal smoking,⁷ multiple pregnancies,⁸ placenta praevia,⁹ black race¹⁰⁻¹² and infant mortality, have employed analyses stratified on (or adjusted for) birthweight. In the context of numerous risk factors, stratification on birthweight yields a puzzling result that has long been a source of controversy: in the lower stratum of birthweight, babies born to mothers with the risk factor of interest tend to have better outcomes than babies born to mothers without the risk factor.² The 'birthweight paradox' as described by Wilcox² is shown graphically in Fig. 1¹³ and is characterised by the crossover of the stratum-specific mortality curves.

Various approaches have been suggested for addressing the paradox,¹⁴⁻¹⁶ but no consensus has been reached in the literature.^{3,17,18} Recognising that adjustment for birthweight itself may have inadvertent effects on estimation, some have adopted a strategy dependent upon *z*-scores of birthweight that is more akin to standardisation.^{2,14} *Z*-scores - birthweight in units of standard deviations within strata of the other risk factors of interest - are generated and then used for adjustment, for example as a regression covariate.¹⁴ Proponents of *z*-scores have suggested the paradox to be an artifact of adjustment for unstandardised birthweight, and claim that the substitution of *z*-scores for birthweight eliminates the crossover of the curves and produces unbiased results.¹⁴ Greenland and others have cautioned against the use of standardised regression coefficients on the grounds that standardisation of coefficients may result in confounding and also because there is a loss of interpretability. The issues regarding use of standardised regression coefficients and *z*-scores are very much related because adjusting for *z*-scores influences interpretation of the effect of interest.^{19,20}

We have previously utilised directed acyclic graphs (DAG) to show that adjustment for birthweight in the estimation of total effects of an exposure of interest (e.g. smoking on infant mortality) introduces bias under certain plausible causal assumptions.^{21,22} The paradoxical crossing of curves may be explained as the product of stratification on a common effect in the presence of unmeasured confounders.^{21,23-26} In this paper, we expand this finding to consideration of standardised birthweight - birthweight *z*-scores - and provide estimates for the potential magnitude of bias. We use DAGs to illustrate causal questions in the context of direct, indirect and total effects on an outcome of interest, and to describe how *z*-scores fit into causal systems relating risk factors with birthweight and neonatal mortality. We present analytical results, as well as a simulation study to evaluate the use of *z*-scores as a regression term on estimates under a range of scenarios.

The causal question and causal diagrams

Causal diagrams are useful tools for displaying the causal structure underlying relations in epidemiological studies.^{27,28} DAGs may be used to show how standard adjustment (stratification or regression) for variables affected by exposure may create bias by introducing a spurious (non-causal) association between the exposure and the outcome.^{24,28} A simple DAG representing the factors under consideration is shown in Fig. 2a.

Direct and indirect effects

The DAGs may be used to illustrate the notion of effect decomposition from total into direct and indirect effects.²⁹⁻³³ This circumstance arises when a causal network resembles that shown in Fig. 2a, in which there are two paths from the exposure to neonatal mortality: one direct effect of exposure and one indirect effect that passes through birthweight. Effect decomposition is of particular relevance if interventions are possible that act on one of the separate effects. In the context of birthweight and neonatal mortality, those interested in assessing risk factors such as smoking have often been concerned about the effects on mortality which are separate from those mediated through birthweight.^{21,22} It should be noted that decomposition is only valid under certain very strong assumptions. Specifically, validity requires absence of confounding, monotonicity, no unit-level interaction, use of linear contrasts as measures of effects and

homogeneity of causal effects across strata of birthweight.^{25,30,31} It is doubtful that these assumptions would be met in most real world applications, putting into question the utility of effect decomposition under most circumstances. However, for illustration we assume that these assumptions are met, and assume the causal structure displayed in Fig. 2a. Therefore, regression models for mortality may be considered as follows: Total effects model:

$$\log(p(NM=1)) = \alpha_1 + (\beta_{RF_1} \times RF); \quad (1)$$

Effect decomposition model:

$$\log(p(NM=1)) = \alpha_2 + (\beta_{RF_2} \times RF) + (\beta_{BWT} \times BWT); \quad (2)$$

where p is the probability of neonatal mortality (NM), RF represents the risk factor of interest and BWT represents birthweight. According to the causal structure represented in Fig. 2a, we assume that the risk factor is the only cause of differences in birthweight. If we then assume that the association between the risk factor and birthweight follows a linear function such that:

$$BWT = \gamma + (\bar{\omega}_{RF} \times RF), \quad (3)$$

then the effect decomposition model is equal to:

$$\begin{aligned} \log(p(NM=1)) &= \alpha_2 + (\beta_{RF_2} \times RF) + (\beta_{BWT} \times BWT) \\ &= \alpha_2 + (\beta_{RF_2} \times RF) + \beta_{BWT} \left(\gamma + (\bar{\omega}_{RF} \times RF) \right) \\ &= \alpha_2 + \beta_{BWT} \times \gamma + (\beta_{RF_2} \times RF) + \\ &\quad (\beta_{BWT} \times \bar{\omega}_{RF} \times RF). \end{aligned} \quad (4)$$

It then follows that

$$\beta_{RF_1} = \beta_{RF_2} + \beta_{BWT} \times \bar{\omega}_{RF}. \quad (5)$$

The direct effect is represented by β_{RF_2} , and the indirect effect as $\beta_{BWT} \times \bar{\omega}_{RF}$. The sum of these effects is the total effect of exposure on the log rate ratio of neonatal mortality.

Unmeasured factors - confounders and colliders

The presence of additional factors in causal networks when one is interested in total effect decomposition is potentially problematic. As shown in Fig. 2b, adjustment for birthweight, in the presence of an unmeasured variable that affects both birthweight and mortality, introduces collider-stratification bias by creating a spurious association between the unmeasured variable $\mathcal{U}$ and exposure (the back door pathway is shown as a dotted line). Additionally, the indirect effect estimate is confounded by the unmeasured factor, $\mathcal{U}$. The direct effect is also biased and cannot be estimated without bias using the available data. Collider-stratification bias is a result of adjusting for birthweight whenever the relation between birthweight and mortality is confounded by an unmeasured factor and there is a link between the exposure of interest and birthweight (Fig. 2b). This is true even when there is no direct effect of the exposure on mortality or between birthweight and neonatal mortality (as represented in Fig. 2c).

Application of z-scores for adjustment

Use of z-scores within strata of the other risk factors of interest has been suggested as an approach to remove the crossover of the curves and produce unbiased results.^{10,11,14,26} This approach requires calculation of the z-score for each individual birthweight (bw_{ij}) within strata such that:

$$Z_i = \frac{bw_{ij} - \bar{bw}_j}{SD(bw_j)}, \quad (6)$$

where i represents individuals 1 through n ; j represents strata of another risk factor 1 through k , bw_{ij} is the birthweight of the i th individual in the j th stratum, $\bar{bw}_j$ is the estimated mean birthweight for the j th stratum, and $SD(bw_j)$ is the standard deviation of birthweight in the j th stratum. These methods have been applied extensively in the analysis of various risk factors on neonatal mortality when birthweight is considered as a covariate. A modified approach has also been proposed, where instead of the z-score, the within-stratum percentile is utilised to ensure the curves do not cross. These claims have not been evaluated either analytically or numerically. Nevertheless, the effect of use of z-scores in regression models has not been explicitly stated; it is unclear if the estimators for the main exposure effect adjusted by z-scores that yield the ‘uncrossing’ of the curves yield unbiased estimators for the direct effect, indirect effect, both or neither.

Smoking, birthweight z-scores and neonatal mortality

When the interest is estimation of the total effect of an exposure, both that acting through its effect on birthweight and directly on neonatal mortality, the question of whether to use birthweight or z-scores is an academic one, as neither will be in the model. Thus, we limit our focus to whether the inclusion of a regression term for birthweight z-scores in models of neonatal mortality allows for decomposition of total effects into direct and indirect effects.

Z-scores may be seen as a variable transformation approach. Although it is clear that both birthweight and exposure have a deterministic relation with individual z-scores (Fig. 2d), the effect of the transformation is to create a birthweight variable that is independent of exposure status. It may be demonstrated in datasets with information on smoking (yes/no), birthweight and neonatal mortality, and in which a relationship between birthweight and neonatal mortality is observed, that z-scores retain an association with birthweight and neonatal mortality but are independent of smoking status. One way to think about the independence of z-scores and smoking is to consider the simple case where smoking shifts the birthweight distribution. In this manner, the counterfactual smoking birthweight for non-smokers could be calculated by subtracting a given value and the counterfactual non-smoking birthweight for smokers could be calculated by adding the same value. A given birth would then be the same distance from the mean smoking birthweight as it would be from the mean non-smoking birthweight if all smokers had been non-smokers. Thus, because the z-score is a measure of distance from the mean, it remains independent of the smoking stratum the birth is in. The DAG in Fig. 2e shows the resultant relationships among variables in the system. This DAG suggests that the z-score, because of its retained relationship with birthweight, will be related to outcome whenever birthweight is related to outcome. Effect estimates for z-scores will differ from those of birthweight because of the different scale due to transformation. The exact relationship between regression coefficients of the relationship between z-score and outcome and regression coefficients of birthweight and outcome is demonstrated in an analytical proof (see Appendix 1).

Note that Fig. 2e represents a situation that has been described as ‘unfaithfulness’.³⁴ Unfaithfulness is the situation where the DAG does not represent reality and the true causal structure. In this case, the smoking variable was used to perform the transformation thereby implying the presence of an arrow between smoking and z -score, as shown in Fig. 2d; however, the transformed variable, z -score, is independent of smoking, thereby implying no arrow between the two nodes as shown in Fig. 2e. There are important implications of the fact that smoking is uncorrelated with birthweight z -scores. First, the independence of smoking and birthweight z -scores suggests that estimates from smoking-only models and those adjusted for z -score should be equal. That is:

$$\begin{aligned} \text{smoking} \perp\!\!\!\perp z - \text{score} &\Rightarrow \\ E(Y|\text{smoking}) &= E(Y|\text{smoking}, z - \text{score}) \end{aligned}$$

Accordingly, the DAG suggests that the use of z -scores should be effective for avoiding collider-stratification bias; the backdoor pathway opened with stratification on birthweight is no longer so with the z -score. This result also is demonstrated in an analytic proof (see Appendix 2).

Simulation study

An extensive simulation study was conducted to compare estimates of exposure effects from the unadjusted (crude) model, the birthweight-adjusted model and the adjusted model utilising birthweight z -scores based on the causal relationships illustrated in Fig. 2e. These simulations were run in the absence (Table 1) and presence (Table 2) of unmeasured factors that confound the relationship between birthweight and neonatal mortality. Birthweight was simulated as:

$$BWT = 3500 + (e \times \text{smoking}) + (a \times \mathcal{U}_{BWT}), \quad (7)$$

where e is the effect of smoking on birthweight with values (-100, -150, -200, -500),³⁵ $\mathcal{U}_{BWT}$ represents the unmeasured variable affecting birthweight with values (0, 1), and a is the effect of the unmeasured factor with values (-100, -200, -400, -500, -1000).

Neonatal mortality risk was simulated as:

$$\log(p(NM=1)) = -3.5 + (c \times \text{smoking}) + (d \times BWT) + (b \times \mathcal{U}_{NM}), \quad (8)$$

where c is the direct effect of smoking with effects (0.2, 0.3, 0.4), and $\mathcal{U}_{NM}$ is an unmeasured factor affecting neonatal mortality with values (0, 1), b is the effect of the unmeasured factor with values (0.2, 0.4, 1.0, 1.6), and d is the effect of birthweight on neonatal mortality (-0.0005). The coefficients a , b , c , d and e represent direct effects of one variable on another and are displayed in Fig. 2e. The choice of parameters was based on realistic scenarios; where there is no effect of the unmeasured factors $\mathcal{U}_{BWT}$ and $\mathcal{U}_{NM}$ the values of $\mathcal{U}$ are set to 0. Using these equations, the true direct effect of smoking is equal to $\Theta_D = c$, the true indirect effect is $\Theta_I = d^*e$, and therefore the true total effect of smoking on neonatal mortality is $\Theta_T = c + d^*e$.

We utilised three regression models of neonatal mortality for estimation of direct, indirect and total effects of the binomial factor smoking (S), accounting for birthweight in grams (BWT), or birthweight z -scores (Z) as follows: Unadjusted Model:

$$\log(p(NM=1)) = \alpha_1 + \beta_S S, \quad (9)$$

Adjusted model by birthweight:

$$\log(p(NM=1)) = \alpha_2 + \beta_{S|BWT} S + \beta_{BWT} BWT, \quad (10)$$

Adjusted model by birthweight z-score:

$$\log(p(NM=1)) = \alpha_3 + \beta_{S|Z} S + \beta_Z Z, \quad (11)$$

where β_S is the total effect, $\beta_{S|BWT}$ is the direct effect, and $\beta_{S|Z}$ is the standardised effect. For each scenario, 5000 datasets were generated with 10 000 observations each and the mean and variance of the estimates, β_S , $\beta_{S|BWT}$ and $\beta_{S|Z}$ were calculated.

Simulation study results

No unmeasured confounding factors of the birthweight-neonatal mortality relation

—The results of simulations where smoking, birthweight and neonatal mortality are sufficient to describe the causal system (Fig. 2a) can be found in Table 1. Examining these results, we find that the unadjusted and the z-score-adjusted model calculate the same point estimates and variances for the total effect of smoking on neonatal mortality. In other words, inclusion of birthweight z-scores does not alter the estimate of the total effect from the basic unadjusted model. Conversely, we observe that the birthweight-adjusted model correctly estimates the direct effect of smoking on neonatal mortality. When smoking and birthweight are sufficient to predict neonatal mortality and there are no unmeasured confounders or other causes of mortality, the effect estimate for birthweight itself is equivalent to the indirect effect of smoking on neonatal mortality. However, sufficiency of the DAG, and the absence of unmeasured confounding are strong assumptions. Violation of these assumptions can substantially impair the effect decomposition approach.^{25,30}

Unmeasured confounding factors of the birthweight-neonatal mortality relation

—Table 2 displays the results of simulations run under the addition of a factor $\mathcal{U}$ that confounds the relationship between birthweight and neonatal mortality, reflecting a potential for collider-stratification (Fig. 2b). The factor $\mathcal{U}$ was used to create the birthweight variable as described above, but these models did not include $\mathcal{U}$ in order to simulate the effects of an unmeasured confounder. The unadjusted model yielded unbiased estimates of the total effect, under various assumptions regarding the strength of the associations between $\mathcal{U}$ and birthweight and neonatal mortality. Adjustment for birthweight resulted in unbiased estimates of the direct effect when the effect of $\mathcal{U}$ on birthweight was small. As the effect of $\mathcal{U}$ on birthweight and the effect of $\mathcal{U}$ on neonatal mortality increased, estimation of the direct effect was negatively biased, and the relative bias was also a function of the strength of these effects (Fig. 3). Z-score-adjusted models yielded nearly identical estimates as unadjusted models. Z-score-specific mortality curves for smokers and nonsmokers, as shown in Fig. 4, further demonstrate that while adjusting for z-scores removes the paradoxical crossing of the curves, this adjustment is not an issue of confounding. Rather, at issue is the effect being estimated, as the distance between the curves for smokers and nonsmokers is equal to the total effect.

As previously discussed, z-score-adjusted models estimated the total effects of smoking, with bias equivalent to the unadjusted model. When simulations do not include an unmeasured factor affecting birthweight and neonatal mortality, z-score parameter estimates can be transformed

to recapture the unstandardised birthweight-neonatal mortality relationship, as described in Appendix 1. When $\mathcal{U}$ was included in the causal system, neither the birthweight-adjusted nor the z -score adjusted model were effective for effect decomposition, with estimates of the direct smoking effect being biased (birthweight adjustment), or unbiased estimates of the total effect (z -score adjustment).

Discussion

Attempts to resolve the birthweight paradox have led investigators to a variety of practices regarding the handling of birthweight, in models of outcomes and risk factors of interest, such as inclusion of birthweight in regression models.¹⁴ Others have proposed various approaches to the use of z -scores towards this end, leading to questions about the effect of modelling standardised birthweight.^{2,3,18} In this paper, we have evaluated the effect of inclusion of the z -score as a regression term both in the absence and presence of unmeasured factors using a simulation study and analytical proofs. We have demonstrated that adjustment of z -scores in regression models yields unbiased estimates for the total effect of the primary factor of interest when birthweight *does* and *does not* represent a collider. It should be pointed out that these results match results from the unadjusted model, and that z -score adjustment offers no advantage over unadjusted models. However, in the presence of confounding of the risk factor-outcome relationship, graphical representation of the z -scores (which removes the crossing of the curves, and gives an estimate of the total effect) does not allow for multivariable confounding adjustment. Only a model-based approach using the unadjusted model as the base model can be used to find unconfounded estimates of the total effect.

It is not uncommon practice to adjust for an intermediate variable (results of birthweight) when estimating the effect of a risk factor on an outcome (e.g. smoking on neonatal mortality). However, birthweight adjustment is not recommended for effect decomposition. The potential pitfalls of effect decomposition have been described in the literature and require several strong assumptions, which are generally not met in practice.^{23,25,30} The results presented here show that models that use adjustment for z -scores are not effective for separating direct and indirect effects, adding to the concerns regarding effect decomposition. Models adjusting for z -scores can be used to estimate total effects, but not direct effects. We have demonstrated that a scaled version of the indirect effects can be evaluated through consideration of the estimate for birthweight z -scores, which may be rescaled to reflect unstandardised birthweight. However, this approach is not recommended because it also requires strong assumptions, including equal variances, and is contingent upon additional computation to address potential differences in birthweight distributions between strata of the standardising factor (e.g. smoking) (see Appendix 1). Regardless, the interpretation of unadjusted, birthweight-adjusted and z -score-adjusted estimates is important to understand for models to reflect investigator hypotheses correctly.

In this paper, we have used causal diagrams to illustrate the causal relationships among risk factors, birthweight, z -scores of birthweight and neonatal mortality both in the absence and presence of unmeasured common causes of birthweight and neonatal mortality. Importantly, many such factors have been postulated in the literature, including genetic, environmental and behavioural factors. Both analytically and through an extensive simulation study, we have shown that neither birthweight nor z -scores may be used for effect decomposition, and that the true utility of z -scores is in estimating unbiased total effects of exposures, even when collider-stratification would adversely influence estimates from birthweight-adjusted models. However, the use of z -scores does not add any additional information beyond the use of unadjusted models.

While the work presented here has only focused on the relationship between smoking, birthweight and neonatal mortality, the implications are more farreaching. The issue of the birthweight paradox and intersecting mortality curves is a more general phenomenon and applies to other outcomes, such as stillbirth,¹⁶ other exposures, such as race, parity, altitude and infant sex,⁷ and other standardised variables, such as gestational age.¹⁷ It should be acknowledged that the ability of z -scores to successfully resolve the paradoxical crossing of the curves (in any of these situations), is due to an alteration in the causal parameter being estimated (total effect), rather than adjustment for confounding or effect decomposition.

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Appendix

Appendix 1

In the case where there are no unmeasured factors affecting birthweight and neonatal mortality, z -score parameter estimates can be transformed to recapture the unstandardised birthweight-neonatal mortality relation. To this end, we define:

S : Binomial factor indicating smoking status (1 = Yes, 0 = No),

BWT : Birthweight in grams,

Z : Standardised birthweight (z -score),

NM : Neonatal mortality rate.

We consider the following three models where α_1 , α_2 , and α_3 correspond to the intercept in models 1 through 3, respectively:

1. $\log(p(NM = 1)) = \alpha_1 + \beta_S S + \varepsilon_1$;
2. $\log(p(NM = 1)) = \alpha_2 + \beta_S |_{BWT} S + \beta_2 BWT + \varepsilon_2$;
3. $\log(p(NM = 1)) = \alpha_3 + \beta_S |_Z S + \beta_3 Z + \varepsilon_3$.

Z_S and Z_{NS} are the z -scores or standardised birthweight for smokers and nonsmokers, respectively.

$$\text{For smokers, } Z_S = \frac{BWT - \left(\bar{BWT} | (S=1) \right)}{sd \left(\bar{BWT} | (S=1) \right)}.$$

$$\text{For nonsmokers, } Z_{NS} = \frac{BWT - \left(\bar{BWT} | (S=0) \right)}{sd \left(\bar{BWT} | (S=0) \right)}.$$

For smokers the models become:

$$\begin{aligned}
\log(p(NM=1)) &= \alpha_1 + \beta_s + \varepsilon_1, \\
\log(p(NM=1)) &= \alpha_2 + \beta_{s|BWT} + \beta_2(BWT|(S=1)) + \varepsilon_2, \\
\log(p(NM=1)) &= \alpha_3 + \beta_{s|Z} + \beta_3 Z + \varepsilon_3, \\
&= \alpha_3 + \beta_{s|Z} + \beta_3 \frac{BWT - (\bar{BWT}|(S=1))}{sd(BWT|(S=1))} + \varepsilon_3 \\
&= \left(\alpha_3 - \frac{\beta_3 (\bar{BWT}|(S=1))}{sd(BWT|(S=1))} \right) + \beta_{s|Z} + \\
&\quad \frac{\beta_3}{sd(BWT|(S=1))} BWT + \varepsilon_3.
\end{aligned}$$

For nonsmokers the models become:

$$\begin{aligned}
\log(p(NM=1)) &= \alpha_1 + \varepsilon_1, \\
\log(p(NM=1)) &= \alpha_2 + \beta_2(BWT|(S=0)) + \varepsilon_2, \\
\log(p(NM=1)) &= \alpha_3 + \beta_3 Z + \varepsilon_3 \\
&= \alpha_3 + \beta_3 \frac{BWT - (\bar{BWT}|(S=0))}{sd(BWT|(S=0))} + \varepsilon_3 \\
&= \left(\alpha_3 - \frac{\beta_3 (\bar{BWT}|(S=0))}{sd(BWT|(S=0))} \right) + \\
&\quad \frac{\beta_3}{sd(BWT|(S=0))} BWT + \varepsilon_3.
\end{aligned}$$

Consider the expectation of $\log(p(NM=1))$ in Model 2 for smokers and nonsmokers, respectively:

$$\alpha_1 + \beta_s = \alpha_2 + \beta_{s|BWT} + \beta_2(\bar{BWT}|(S=1)),$$

$$\alpha_1 = \alpha_2 + \beta_2(\bar{BWT}|(S=0)).$$

Therefore, we have

$$\beta_s = \beta_{s|BWT} + \beta_2 \left\{ (\bar{BWT}|(S=1)) - (\bar{BWT}|(S=0)) \right\}.$$

If $sd(BWT|(S=1)) = sd(BWT|(S=0))$, we have

$$\beta_2 = \frac{\beta_3}{sd(BWT|(S=0))}.$$

Appendix 2

In order to show that conditioning on z -scores removes the association between smoking status and an unmeasured variable associated with birthweight and infant mortality which is created by conditioning on the collider birthweight (Fig. 2e), we define:

W : Birthweight,

S : Indicator of smoking status (1 = Yes, 0 = No),

$\mathcal{U}$: An unmeasured Bernoulli random variable with $P(\mathcal{U}=1)=p$, and $P(\mathcal{U}=0)=1-p=q$.

The linear model is: $W=W_0+a\mathcal{U}+bS$. For smokers, $S=1$, the birthweight can be written as:

$$W_s=W_0+a\mathcal{U}+b,$$

For nonsmokers, $S=0$, the birthweight can be written

$$\text{as: } W_{NS}=W_0+a\mathcal{U}.$$

It follows that:

$$E(W_s)=W_0+b+ap, \text{Var}(W_s)=a^2p(1-p)$$

$$E(W_{NS})=W_0+ap, \text{Var}(W_{NS})=a^2p(1-p)$$

Application of the standardisation procedure $Z=(X-\mu_W)/\sigma_W$ on smokers and nonsmokers separately, yields the z -scores:

$$\begin{aligned} Z_s &= \frac{W_0+a\mathcal{U}+b-(W_0+ap+b)}{\sqrt{a^2p(1-p)}} = \frac{a(\mathcal{U}-p)}{\sqrt{a^2p(1-p)}} \\ &= \frac{\text{sign}(a)}{\sqrt{p(1-p)}} \times (\mathcal{U}-p), \end{aligned}$$

$$\begin{aligned} Z_{NS} &= \frac{W_0+a\mathcal{U}-(W_0+ap)}{\sqrt{a^2p(1-p)}} = \frac{a(\mathcal{U}-p)}{\sqrt{a^2p(1-p)}} \\ &= \frac{\text{sign}(a)}{\sqrt{p(1-p)}} \times (\mathcal{U}-p), \end{aligned}$$

thus $Z_S = Z_{NS} = Z$. It then follows that,

$$\begin{aligned} P(Z=z|S=s) &= P(Z=z), \\ P(\mathcal{U}=u|S=s) &= P(\mathcal{U}=u), \\ \text{and } P(\mathcal{U}=u|S=1, Z_s=z) &= P(\mathcal{U}=u|S=0, Z_{NS}=z). \end{aligned}$$

Consequently, $P(\mathcal{U}=u|S=1, Z_s=z) = P(\mathcal{U}=u|S=0, Z_{NS}=z) = P(\mathcal{U}=u|Z=z)$, by

$$\begin{aligned}
 P(U=u|S=s, Z=z) &= \frac{P(U=u, S=s, Z=z)}{P(Z=z, S=s)} \\
 &= \frac{P(U=u, S=s, Z=z)}{P(Z=z|S=s) \cdot P(S=s)} \\
 &= \frac{P(U=u, S=s, Z=z)}{P(Z=z) \cdot P(S=s)} \\
 &= \frac{P(U=u, Z=z)}{P(Z=z)} \\
 &= P(U=u|Z=z)
 \end{aligned}$$

This is equivalent to: $U \perp\!\!\!\perp S|Z$.

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Figure 1. Birthweight-specific infant mortality curves for smokers and non-smokers.¹³

Figure 2.

Directed acyclic graphs (DAG) representing causal relationships between a risk factor, birthweight, unmeasured variables (U) and neonatal mortality. (a) DAG representing both direct and indirect effects of birthweight on neonatal mortality. (b) DAG representing collider-stratification bias introduced by adjusting for birthweight in the presence of an unmeasured confounder, U . (c) DAG representing collider-stratification bias introduced by adjusting for birthweight in the presence of an unmeasured confounder, U , under alternative causal assumptions. (d) DAG depicting deterministic relationship between birthweight, smoking and individual z-scores. (e) DAG representing relationships among variables under z-score adjustment.

Figure 3.

Relative bias of the direct effect of smoking in a model adjusted for birthweight in the presence of an unmeasured confounder. The effect of smoking on birthweight is $e = -200$, the direct effect is $\Theta_D = c = 0.2$, the total effect is $\Theta_T = c + d \cdot e = 0.3$, $d = -0.0005$, and b corresponds to the effect of the unmeasured confounder on neonatal mortality.

Figure 4.

Z-score-specific mortality curves for smokers and nonsmokers. Effect of smoking on birthweight represented by e , direct effect $\Theta_D = c$, total effect $\Theta_T = c + d^*e$, $d = -0.0005$. (a) $e = -100, c = 0.2$; (b) $e = -100, c = 0.4$; (c) $e = -500, c = 0.2$; (d) $e = -500, c = 0.4$.

Table 1

Simulation study results: true total and direct effects of smoking (S) on neonatal mortality (NM) and parameter estimates under the unadjusted (β_S), birthweight (BWT) adjusted ($\beta_{S|BWT}$) and z -score (Z) adjusted ($\beta_{S|Z}$) regression models^a

True effects			Effect estimated in regression models								
Smoking on BWT (<i>e</i>)	Direct effect $\Theta_D = c$	Total effect $\Theta_T = c$ + d^*e	Smoking			Smoking BWT			Smoking z-score		
			β_S	Bias	MSE	$\beta_{S BWT}$	Bias	MSE	$\beta_{S Z}$	Bias	MSE
-100	0.2	0.250	0.24057	-0.00943	0.07955	0.19065	-0.00935	0.08051	0.24060	-0.00940	0.07954
	0.3	0.350	0.34278	-0.00722	0.07631	0.29266	-0.00734	0.07734	0.34279	-0.00721	0.07632
	0.4	0.450	0.44356	-0.00644	0.06938	0.39306	-0.00694	0.07049	0.44355	-0.00645	0.06938
-150	0.2	0.275	0.26422	-0.01078	0.07724	0.18798	-0.01202	0.07942	0.26424	-0.01076	0.07724
	0.3	0.375	0.36341	-0.01159	0.07372	0.28901	-0.01099	0.07611	0.36341	-0.01159	0.07371
	0.4	0.475	0.47021	-0.00479	0.06767	0.39538	-0.00462	0.06988	0.47020	-0.00480	0.06767
-200	0.2	0.300	0.28665	-0.01335	0.07690	0.18608	-0.01392	0.08098	0.28666	-0.01334	0.07689
	0.3	0.400	0.39026	-0.00974	0.07307	0.29001	-0.00999	0.07771	0.39028	-0.00972	0.07307
	0.4	0.500	0.49566	-0.00434	0.06788	0.39602	-0.00398	0.07125	0.49567	-0.00433	0.06788
-500	0.2	0.450	0.43903	-0.01097	0.06884	0.19157	-0.00843	0.09362	0.43903	-0.01097	0.06884
	0.3	0.550	0.54691	-0.00309	0.06478	0.29914	-0.00086	0.08890	0.54691	-0.00309	0.06478
	0.4	0.650	0.64553	-0.00447	0.06083	0.39743	-0.00257	0.08451	0.64554	-0.00446	0.06083

MSE, Mean squared error.

^a $BWT = 3500 + (e \times smoking) + (a \times \mathcal{U}_{BWT})$, $\mathcal{U}_{BWT} = 0$; $\log(p(NM = 1)) = -3.5 + (c \times smoking) + (d \times BWT) + (b \times \mathcal{U}_{NM})$, $\mathcal{U}_{NM} = 0$, $d = -0.0005$.

Table 2

Simulation study results: true total and direct effects of smoking (S) on neonatal mortality (NM) and parameter estimates in the presence of an unmeasured confounder $\mathcal{U}$ of the birthweight-mortality relation under the unadjusted (β_S), birthweight (BWT) adjusted ($\beta_{S|BWT}$) and z-score (Z) adjusted (β_{SZ}) regression models^a

True effects		Effect estimated in regression models								
		Smoking			Smoking BWT			Smoking z-score		
$U_{BWT}^{on}(a)$	$U_{NM}^{on}(b)$	β_S	Bias	MSE	$\beta_{S BWT}$	Bias	MSE	$\beta_{S Z}$	Bias	MSE
-100	0.2	0.28653	-0.01347	0.07311	0.18396	-0.01604	0.07717	0.28654	-0.01346	0.07311
	0.4	0.28688	-0.01312	0.07157	0.18146	-0.01854	0.07591	0.28688	-0.01312	0.07157
	1.0	0.28871	-0.01129	0.06411	0.17204	-0.02796	0.06858	0.28872	-0.01128	0.06411
	1.6	0.29167	-0.00833	0.05383	0.15925	-0.04075	0.05891	0.29167	-0.00833	0.05383
-200	0.2	0.28634	-0.01366	0.07282	0.18121	-0.01879	0.07687	0.28635	-0.01365	0.07282
	0.4	0.28708	-0.01292	0.07128	0.17596	-0.02404	0.07570	0.28709	-0.01291	0.07128
	1.0	0.28912	-0.01088	0.06298	0.15490	-0.04510	0.06870	0.28914	-0.01086	0.06298
	1.6	0.29176	-0.00824	0.05263	0.12618	-0.07382	0.06135	0.29177	-0.00823	0.05264
-400	0.2	0.28669	-0.01331	0.07184	0.17648	-0.02352	0.07583	0.28670	-0.01330	0.07184
	0.4	0.28718	-0.01282	0.06993	0.16492	-0.03508	0.07459	0.28720	-0.01280	0.06993
	1.0	0.28951	-0.01049	0.06172	0.12224	-0.07776	0.07127	0.28955	-0.01045	0.06173
	1.6	0.29108	-0.00892	0.05024	0.06430	-0.13570	0.07165	0.29115	-0.00885	0.05026
-1000	0.2	0.28642	-0.01358	0.06883	0.16859	-0.03141	0.07175	0.28645	-0.01355	0.06884
	0.4	0.28790	-0.01210	0.06617	0.14923	-0.05077	0.07071	0.28795	-0.01205	0.06618
	1.0	0.28986	-0.01014	0.05695	0.07869	-0.12131	0.07331	0.29000	-0.01000	0.05699
	1.6	0.29097	-0.00903	0.04367	0.00086	-0.19914	0.08418	0.29095	-0.00905	0.04368

MSE, Mean squared error.

^a $BWT = 3500 + (e \times smoking) + (a \times \mathcal{U}_{BWT}) + (c \times \mathcal{U}_{NM}) + (b \times \mathcal{U}_{NM}) + (d \times BWT) + (e \times \mathcal{U}_{NM})$, $\mathcal{U}_{NM} = 1$, $c=0.2$, $d=-0.0005$. Direct effect $\Theta_D=c=0.2$; Total effect $\Theta_T=c+d^*e=0.3$.