Asking too much of epidemiologic studies: the problem of collider

bias and the obesity paradox

Stijn Vansteelandt

Department of Applied Mathematics, Computer Sciences and Statistics,

Ghent University, Krijgslaan 281 (S9), 9000 Gent, Belgium

and Centre for Statistical Methodology,

London School of Hygiene and Tropical Medicine, U.K.

stijn.vansteelandt@ugent.be

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ABOUT THE AUTHOR. Stijn Vansteelandt is Professor of Statistics at

Ghent University, Professor of Statistical Methodology at the London

School of Hygiene and Tropical Medicine, and Co-Editor of

Biometrics. He develops statistical methods to address causal questions

originating primarily from epidemiologic studies.

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The question whether obesity leads to an increased risk of mortality among individuals with chronic disease is of interest to many clinicians and epidemiologists[1]. Understanding the answer to that question may help to assess the importance and potential impact of interventions that target weight loss in this disease group. Because such interventions must take place after disease onset, epidemiological studies that aim to address this question should assess the association between *changes in body mass since disease onset* and mortality in such individuals. Collider bias - and the related obesity paradox - is only one of several adverse consequences of not adhering to this important principle.

Asking the wrong question

Whether collider bias can distort the association between obesity and mortality in, say, diabetic patients to a degree that matters, necessarily depends on the interpretation one assigns to that association. Viallon and Dufournet[2] and Sperrin et al.[3], along with a number of other authors (see e.g. [4]) consider interpretation in terms of a controlled direct effect of obesity on mortality in diabetic patients. However, this does not capture how one is likely to interpret that association and, moreover, does not reflect the effect of clinical interest. The reason is that a controlled direct effect expresses the effect obesity would have

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on mortality if one were to induce diabetes, an intervention that clinicians obviously do not envisage.

Of the effect measures considered in Sperrin et al.[5] and Viallon and Dufournet[2], the one which arguably comes closest to clinicians' interest, is that originally considered by Sperrin et al.[5]. In particular, let A denote 1 for obese individuals (and 0 otherwise) and M denote 1 for diabetic individuals (and 0 otherwise). In typical studies reporting on the obesity paradox, including [2,5], the measurement A reflects a cause (rather than an effect) of chronic disease M. This is generally quite plausible when, as is the case in many studies, A and M are measured concurrently or when A is measured prior to the diagnosis of diabetes. Focussing on this setting, Sperrin et al.[5] consider a contrast between $E(Y^1|M{=}1)$ and $E(Y^0|M{=}1)$, with Y^1 (Y^0) the counterfactual mortality status if (not) obese. Further letting M^1 (M^0) be the counterfactual diabetes status if (not) obese, and $p=P(A{=}1|M{=}1)$, we have that

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\begin{aligned}
E\left(Y^1 \middle| M=1\right) &= E\left(Y^{1M^1} \middle| M=1, A=1\right)p + E\left(Y^{1M^1} \middle| M=1, A=0\right)(1-p) \\
&= E\left(Y^{1M^1} \middle| M^1=1, A=1\right)p + E\left(Y^{1M^1} \middle| M^0=1, A=0\right)(1-p) \\
&= E\left(Y^{11} \middle| M^1=1, A=1\right)p + E\left(Y^{1M^1} \middle| M^0=1, A=0\right)(1-p),
\end{aligned}
$$

where we use that Y^1 equals Y^{1M^1}, the counterfactual mortality status if obese with diabetes status M^1. Likewise,

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$$E\left(Y^0 \middle| M = 1\right) = E\left(Y^{0M^0} \middle| M^1 = 1, A = 1\right) p + E\left(Y^{01} \middle| M^0 = 1, A = 0\right)\left(1 - p\right).$$

It follows from the above that the causal effect of obesity in diabetic patients, $\Delta_{CE|M=1} \equiv E\left(Y^1 - Y^0 \middle| M = 1\right)$, equals the controlled direct effect of obesity in diabetic patients, $\Delta_{CDE|M=1} \equiv E\left(Y^{11} - Y^{01} \middle| M = 1\right)$, when for all individuals, obesity does not affect the risk of diabetes (i.e. $M^1 = M^0$), but not generally otherwise; this is precisely the setting where collider bias is not a concern. I conclude that the results of Viallon and Dufournet[2] and Sperrin et al.[3] do not provide immediate insight into the extent to which collider bias can make the association between obesity and mortality in diabetic patients differ from the effect of obesity on mortality in those patients.

Giving the wrong answer

The simulation results in [5] (as well as those in [2] for $\Delta_{CDE|M=1}$) moreover ignore *important subtleties by relying on strong cross-world assumptions: assumptions about* the dependence between counterfactuals existing in 'different worlds' ('with' versus 'without' obesity). In particular, the displays in the previous section shows that the calculation of $\Delta_{CE|M=1}$ requires assumptions about the dependence between Y^{aM^1} and M^0, and thus in particular about the dependence between M^1 and M^0; [5] implicitly assume that M^1 and M^0 are perfectly

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correlated. Such knowledge about the joint distribution of the counterfactuals M^1 and M^0 is unavailable in practice and not obtainable from - even experimental - data[6]. In view of this, Viallon and Dufournet[2] and Sperrin et al.[3] redirect attention to the controlled direct effect $\Delta_{\text{CDE}|M=1}$. However, to calculate it, they assume that Y^{0m} is independent of M^1, given $A=1$ and U (with U representing a variable that - along with A - is sufficient to adjust for confounding of the effect of M on Y). Also this cross-world assumption is often biologically implausible[7]. Although similar assumptions are routinely employed in mediation analysis, they are arguably more innocent in that context, where the key direct and indirect effect measures remain interpretable even when those assumptions fail[8-10]; such rescue interpretation is less obvious for $\Delta_{\text{CDE}|M=1}$.

Realistic projections of the extent of collider bias should consider the above subtleties and, moreover, recognise that the extent of collider bias is model dependent (e.g., it does not arise in certain classes of multiplicative models[11] and logistic models[12]. To the best of my knowledge, most studies that quantify the role of collider bias in the obesity paradox, have focussed on a single dichotomous confounder U (which is not affected by obesity) (see e.g. [4,13,14]). This is a

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serious oversimplification of reality, which is likely to minimise the role of collider bias. In the next section, I aim to provide more general insight.

A broader perspective on collider bias

In essence, the problem of collider bias is not less important than that of confounding bias. Consider for instance the causal diagram of Figure 1 (left). When all variables are dichotomous, taking values 0 and 1, then it readily follows from Bayes' rule that the conditional *U-A* odds ratio, given *M*=1, can be rewritten as

$$\frac{P\left(M=1|A=1,U=1\right)P\left(M=1|A=0,U=0\right)}{P\left(M=1|A=0,U=1\right)P\left(M=1|A=1,U=0\right)}; \qquad (1)$$

the extent to which it differs from 1 expresses the degree of collider bias. When the data are instead generated as in Figure 1 (right), then it further follows from Bayes' rule that for *a,u*=0,1,

$$P\left(M=1|A=a,U=u\right)=\frac{P\left(A=a|M=1\right)P\left(U=u|M=1\right)P\left(M=1\right)}{P\left(A=a,U=u\right)}.$$

At such data-generating mechanisms, Equation 1 reduces to

$$\frac{P\left(U=1|A=1\right)P\left(U=0|A=1\right)}{P\left(U=1|A=1\right)P\left(U=0|A=0\right)}.$$

Interestingly, this is the reciprocal of the marginal *U-A* odds ratio, which expresses the degree of confounding bias in Figure 1 (right). It

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follows that confounding and collider-stratification both bias the *A-U* association to the same extent in this case.

Similar findings are obtained when all variables are multivariate normal. Then it can be shown along similar lines as in[15] that under the causal diagram of Figure 1 (left), the standardised path coefficient on *A* in a linear regression of *U* on *A* and *M* is given by

$$-\frac{\rho_{mu}\rho_{ma}}{1-\rho_{ma}^2},$$

where ρ_{mu} is the correlation between *M* and *U* and ρ_{ma} is the correlation between *M* and *A*. This dependence of *U* on *A* is again the result of collider bias. Its magnitude is determined by the extent to which *M* is associated with both *A* and *U*, and can be especially sizeable when *A* strongly affects *M*. Incidentally, the term $\rho_{mu}\rho_{ma}$ in the numerator is also equal to the standardised path coefficient on *A* in a linear regression of *U* on *A* under the causal diagram of Figure 1 (right), which reflects the extent of confounding bias in that diagram.

Figure 1: Left: Causal diagram expressing collider bias; Right: Causal diagram expressing confounding bias.

We conclude from the above that the problem of collider bias is, in essence, not less important than that of confounding bias. This is in line with Greenland[16], who concludes that 'bias from stratifying on

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variables affected by exposure and disease may often be comparable in size with bias from classical confounding'; it moreover confirms the extreme selection biases found in [17]. However, when considering collider bias of the association between *A* and *Y* (instead of *U*), then the extent of bias is obviously weakened due to the imperfect dependence between *U* and *Y*, just like the degree of confounding bias of the association between *A* and *Y* in Figure 1 (right) diminishes. Depending on the setting, collider bias (and likewise confounding bias) thus need not propagate to deliver sizeable bias in the exposure-outcome association[16].

Getting the wrong answer to the wrong question

Regardless of whether or not collider bias forms the principal explanation for the obesity paradox, perhaps the biggest problems in all studies reporting on the obesity paradox are the following two. First, they attempt to evaluate the effect of an ill-defined intervention on obesity[18]. Second, even if a well-defined intervention were considered, they attempt to evaluate the effect of an intervention on obesity *prior to disease onset* in chronically ill patients. While interventions on obesity might be particularly useful for that subgroup, a good understanding of their effect would be of limited use for making public health decisions

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as it would be unknown, at the time of decision making, who belongs

to that group. An assessment of their effect would moreover be of

limited use to gauge the potential impact of interventions on obesity

that take place after disease onset. The nature of body mass prior to

disease onset (which may be related to genetics, socioeconomic status,

familial eating patterns, ...) and post disease onset (which may

additionally be disease related, or related to the prescription of specific

diets or physical exercise following disease onset) may be very

different, making it unrealistic to believe that interventions on body

mass have the same effect pre versus post disease onset.

To evaluate the possible impact of obesity-related interventions on

mortality in individuals with chronic disease based on observational

studies, one must assess how changes in body mass after disease onset

(ideally brought about by well-defined interventions) relate to

mortality. When the data are deficient (in the sense that they provide no

information on the change in body mass after disease onset), one is

likely to find the wrong answer to the wrong question. The wrong

answer, because deficient data demand dominant assumptions (cfr. the

aforementioned need for cross-world assumptions). The wrong

question, because the effect of obesity prior to disease onset is not

directly informative about the effect which interventions on body mass

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after disease onset might have.

Epidemiologic studies that aim to guide decision-making should focus on the comparison of exposure groups that correspond to the intervention one wishes to evaluate. Only by adhering to this principle, one can avoid the above problem of collider bias and related issues of left truncation[19]. Such bias need not be less severe than bias as a result of ignoring confounders. I am grateful to Viallon and Dufournet for identifying subtleties in the calculation of $\Delta_{CE|M=1}$, and clarifying that sensible degrees of bias may be plausible and may form an explanation for the obesity paradox, to Sperrin and collaborators for recognising these subtleties, and to the Editor for the opportunity to contribute to this discussion.

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Figure