A Nearly Unavoidable Mechanism for Collider Bias with Index-Event Studies

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Abstract: Factors suspected of causing certain chronic diseases and death are often associated with lower mortality among those with disease. For end-stage renal disease, examples include high cholesterol and homocysteine. Here, we consider obesity, thought to cause both end-stage renal disease and premature mortality, but which is associated with lower mortality among end-stage renal disease patients. Such seeming paradoxes could reflect collider (index event) bias due to selection of a diseased population for study. However, previous descriptions are incomplete, as they posit an uncontrolled factor causing both end-stage renal disease (the index event) and death. Here, we explicitly note that death can precede end-stage renal disease onset. The target population is obese persons with end-stage renal disease, effects of interest are seemingly controlled direct effects, the usual estimator is a conditional risk ratio, and remaining at risk until the onset of end-stage renal disease is a collider. Collider bias is then expected if any mortality risk factor is uncontrolled, even if no factor also affects end-stage renal disease. The bias is similar to, but differs from, that associated with competing risks. Because control of every mortality risk factor is implausible, bias of the standard estimator is practically unavoidable. Better awareness of these issues by clinicians and researchers is needed if observational research is to usefully guide care of this vulnerable patient population.

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S ubstantial evidence suggests that obesity causes both end-stage renal disease and premature mortality in unselected populations[1–3] but is typically associated with lower mortality among those with end-stage renal disease.[4] Such "reversed" associations have led some observers to suggest that the effect of obesity on mortality may differ between populations with and without end-stage renal disease.[4–6]

Similarly, reversed associations are commonly reported for other attributes and diseases.[4,7–13] Most studies in which such a reversal is found share certain basic characteristics. They usually involve selection of exposed and unexposed subjects with disease (the index event),[13] follow-up of those selected to estimate exposure-specific mortality risks for the post-index-event period, and comparison of these risks using a risk or rate ratio. For brevity, we refer to such studies as "index-event" studies.

Collider bias due to selection of a diseased population for study[13–18] can potentially explain the "reversed" associations often found in index-event studies. Collider bias posits that end-stage renal disease is caused by both obesity and an uncontrolled factor U*, as in the causal graph[19–21] of Figure 1. End-stage renal disease is therefore a collider—a factor caused by 2 other factors.[20–22] As further described below, the observed risk ratio (RR) is then expected to be a biased effect estimator due to selecting on a collider.[14,21,22]

However, previous considerations of bias in index-event studies are incomplete. There is also a second collider—survival until occurrence of end-stage renal disease. The importance of this collider is generally recognized[14] but overlooked in considerations of index-event studies. In these studies, bias can exist if any outcome risk factor is uncontrolled. This differs from previous conclusions concerning index-event studies wherein the uncontrolled factor(s) is posited to cause both the index event and death. Collider bias is well recognized[14]; that it is likely present in these studies even after controlling for every factor causing the index event directly is not. Bias is more likely than previously recognized.
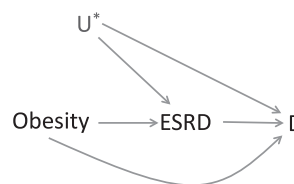
FIGURE 1. Causal graph showing the usually recognized situation for collider bias. ESRD represents end-stage renal disease, the intermediate event; D represents death (presumably after disease onset [at age a_1] and before age a_3); U* represents an uncontrolled risk factor with direct effects on both disease and death—the situation usually described for collider bias in this context.

Our goal is to highlight issues that affect obesity–end-stage renal disease–mortality and other index-event studies. Specifically, we define the causal effect of interest, note the relevance of considering time and temporal sequences, emphasize the importance of the additional collider, and describe bias of standard effect estimators. Despite challenges inherent in studying the effects of obesity on mortality,[23,24] obesity merely illustrates the issues because the described biases are expected even if a well-defined point exposure had been randomized before occurrence of the index event.

BACKGROUND

In studies of obesity, end-stage renal disease, and mortality, the usual effect estimator is the observed hazard ratio or RR. It is calculated by selecting subjects with end-stage renal disease and comparing subsequent mortality among the obese with that among the nonobese.[12] Most estimators are stratified by, or otherwise adjusted for, age at onset of end-stage renal disease to control potential confounding. Usually unspecified, the estimand is seemingly a controlled direct effect of obesity[25] for the target population consisting of the obese with end-stage renal disease (eAppendix 1, http://links.lww.com/EDE/A800 provides additional details). Conceptually, this represents the effect of preexisting obesity on death after disease onset, controlling for age at disease onset. In a causal graph (Figure 1), the arrow from obesity (E) to death (D) represents a direct effect, and the arrows from obesity to ESRD (the "intermediate") and from ESRD to death represent an indirect effect.[26]

PREVIOUSLY RECOGNIZED COLLIDER

Valid estimation of the controlled direct effect requires strong assumptions[26]—essentially no uncontrolled confounding of both the obesity–mortality and end-stage renal disease–mortality associations. Bias of controlled-direct-effect estimators like the conditional RR is expected if 2 conditions hold. First, obesity and another factor U^* both affect end-stage renal disease, so that end-stage renal disease is a collider (Figure 1). Second, subjects are selected for study based on the collider. Such selection is normally built into index-event studies. Thus, if U^* is uncontrolled and affects both end-stage renal disease and death, observed conditional RRs are expected to be biased (inconsistent) effect estimators.[13,14,26]

ANOTHER COLLIDER

Because death can precede the onset of end-stage renal disease, we now consider temporality and the possible sequences of events. Thus, we specifically consider preexisting obesity measured at age a_0 and the age stratum a_1 of subjects with disease onset at age a_1, where $a_1 > a_0$. Define $S = 1$ if selected for study, and 0 otherwise. We use subscripts to indicate age-specific death and reflect the sequence of events: D_1 and D_2 are dichotomous indicators of death before age a_1, and between a_1 and a_2, respectively. For age stratum a_1, selection is conditional on being at risk ($D_1 = 0$) and having end-stage renal disease occur at age a_1. We assume death is caused by obesity (the nonnull) and an additional factor U (Figure 2).

Under these assumptions, D_1 is a collider and obesity tends to be associated with U among those selected.[20–22] Therefore, we expect standard effect estimators such as the conditional RR to be biased if U is uncontrolled,[14] reflecting well-known limitations of conditional risks.[14,27] In contrast to previous descriptions, bias can exist even if end-stage renal disease is not a collider (eg, U^* of Figure 1 is absent in Figure 2)—a deviation from the situation usually posited for collider bias in this context[13] and in associated causal graphs.[25]

DISCUSSION

We emphasize here several conditions that have rarely been considered in discussions of studies of the relationships among obesity and end-stage renal disease, and mortality: a target consisting of exposed, at-risk, diseased subjects, the temporal sequence of events, particularly the possibility that the outcome can precede the index event; and the implications for bias. Careful consideration of temporal sequences in connection with causal relationships has been useful in other contexts, such as development of methods to address time-varying confounding[28–30] and in the birth-outcomes literature[31,32]; further evaluation might yield additional insights or solutions here.

Collider bias in index-event studies reflects general limitations of conditional risks.[14,27] Although resembling potential biases associated with competing risks, this bias can exist for nonfatal outcomes and so can differ technically ("censoring" can occur through target selection alone, as discussed in eAppendix 1, http://links.lww.com/EDE/A800).

Although some clearly suspect controlled direct effect and related effect estimators will often be biased,[33,34] recognition of this additional collider is important. It underscores the importance of considering temporal issues and implies that, to avoid bias in index-event studies, one must control or account for every mortality risk factor, not just the subset that
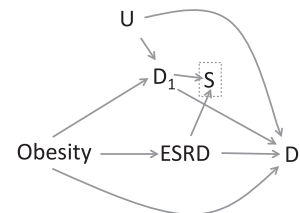

FIGURE 2. Causal graph for age stratum a_1 reflecting temporality of events, and another collider (S). ESRD represents end-stage renal disease with onset at age a_1, the intermediate event; D_1 represents death before age a_1 and D_2 represents death between ages a_1 and a_3; S represents selection into the study for age stratum a_1; U represents an uncontrolled risk factor with direct effects only on D_1 and D_2. The arrow from U to ESRD is omitted because U has no direct effect on ESRD. The arrow from D_1 to ESRD is omitted because the bias described here can be present for nonfatal outcomes with no effect on the intermediate.

causes both end-stage renal disease and death. This reinforces the suspicion that most studies of obesity–end-stage renal disease–mortality associations likely suffer from collider bias.

Preliminary work using accelerated life models with plausible parameters suggests that the bias is potentially large even if all factors directly affecting both end-stage renal disease and death are controlled.[35] Furthermore, the bias can make a harmful effect appear beneficial, even if both the exposure and the index event were randomized (eAppendix 2, http://links.lww.com/EDE/A800). These biases could be avoided if exposure were randomized after end-stage renal disease onset or, in observational studies, if conditioning on survival could be avoided. Potential bias in these types of studies must be more widely recognized if results are to usefully guide care.[36]

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REFERENCES

1. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363:2211–2219.
2. Kalaitzidis RG, Siamopoulos KC. The role of obesity in kidney disease: recent findings and potential mechanisms. *Int Urol Nephrol*. 2011;43:771–784.
3. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. *J Chronic Dis*. 1979;32:563–576.
4. Kopple JD. The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. *Am J Clin Nutr*. 2005;81:1257–1266.
5. Levin NW, Handelman GJ, Coresh J, Port FK, Kaysen GA. Reverse epidemiology: a confusing, confounding, and inaccurate term. *Semin Dial*. 2007;20:586–592.
6. Kalantar-Zadeh K. What is so bad about reverse epidemiology anyway? *Semin Dial*. 2007;20:593–601.
7. Bucholz EM, Rathore SS, Reid KJ, et al. Body mass index and mortality in acute myocardial infarction patients. *Am J Med*. 2012;125:796–803.
8. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol*. 2009;53:1925–1932.
9. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J*. 2008;156:13–22.
10. Kokkinos P, Myers J, Faselis C, Doumas M, Kheirbek R, Nylen E. BMI-mortality paradox and fitness in African American and Caucasian men with type 2 diabetes. *Diabetes Care*. 2012;35:1021–1027.
11. Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. *JAMA*. 2012;308:581–590.
12. Kovesdy CP, Anderson JE. Reverse epidemiology in patients with chronic kidney disease who are not yet on dialysis. *Semin Dial*. 2007;20:566–569.
13. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. *JAMA*. 2011;305:822–823.
14. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15:615–625.
15. Hernández-Díaz S, Schisterman EF, Hernán MA. The birth weight "paradox" uncovered? *Am J Epidemiol*. 2006;164:1115–1120.
16. Cole SR, Hernán MA. Fallibility in estimating direct effects. *Int J Epidemiol*. 2002;31:163–165.
17. Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider. *Int J Epidemiol*. 2010;39:417–420.
18. Smits LJ, van Kuijk SM, Leffers P, Peeters LL, Prins MH, Sep SJ. Index event bias-a numerical example. *J Clin Epidemiol*. 2013;66:192–196.
19. Greenland S, Pearl J. Causal diagrams. In: Boslaugh S, ed. *Encyclopedia of Epidemiology*. Thousand Oaks, CA: Sage Publications; 2007:149–156.
20. Pearl J. *Causality*. 2nd ed. Cambridge: Cambridge University Press; 2009.
21. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10:37–48.
22. Glymour MM, Greenland S. Causal diagrams. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2008:183–209.
23. Hernán MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes (Lond)*. 2008;32(suppl 3):S8–S14.
24. Flanders WD, Augestad LB. Methodologic issues in observational studies of obesity and mortality. *Norsk Epidemiologi* 2011;20:143–148.
25. Banack HR, Kaufman JS. Perhaps the correct answer is: (D) all of the above. *Epidemiology*. 2014;25:7–9.
26. Petersen ML, Sinisi SE, van der Laan MJ. Estimation of direct causal effects. *Epidemiology*. 2006;17:276–284.
27. Flanders WD, Klein M. Properties of 2 counterfactual effect definitions of a point exposure. *Epidemiology*. 2007;18:453–460.
28. Robins J. A new approach to causal inference in mortality studies with sustained exposure periods- application to control of the health worker survivor effect. *Mathematical Modeling* 1986;7:1393–1515.
29. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550–560.
30. Robins JM. Causal models for estimating the effects of weight gain on mortality. *Int J Obes (Lond)*. 2008;32(suppl 3):S15–S41.
31. Kramer MS, Zhang X, Platt RW. Analyzing risks of adverse pregnancy outcomes. *Am J Epidemiol*. 2014;179:361–367.
32. Hernán MA, Schisterman EF, Hernández-Díaz S. Invited commentary: composite outcomes as an attempt to escape from selection bias and related paradoxes. *Am J Epidemiol*. 2014;179:368–370.
33. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3:143–155.
34. Kaufman JS. Invited commentary: decomposing with a lot of supposing. *Am J Epidemiol*. 2010;172:1349–1351.
35. Flanders WD, Eldridge RC, McClellan W. Abstact: potentially large collider bias in direct effect estimators among the diseased target – without any uncontrolled disease risk factors. Presented and accepted at SER 47th Annual Meeting. Seattle, Washington. June 24–27, 2014.
36. McClellan WM, Plantinga LC. A public health perspective on CKD and obesity. *Nephrol Dial Transplant*. 2013;28(suppl 4):iv37–iv42.