

Risk Factor Reversal in Studies of Infectious Disease: Making Counterintuitive Results Intuitive Again

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Abstract: A previously published study reported the seemingly paradoxical finding that men who have sex with men status was strongly protective and recent sexual abstinence strongly deleterious in relation to mortality prognosis. We explain why these results are entirely logical and that the counterintuitive direction of the effects derives from the comparison group implied by the study design.

The jazz pianist Les McCann had a 1969 hit titled “*Compared to What?*”, which should become an official epidemiology theme song, as it is the central question underlying the interpretation of every effect estimate. We often forget the centrality of this question when the context seems unambiguous. For example, if we read that circumcision decreases risk of HIV acquisition by 56%, the implicit comparison group is obviously the uncircumcised.¹ If the two groups are similar in other ways besides the fact of circumcision, then the contrast may be interpreted as the effect of the exposure on the outcome. However, when study samples are selected or analyzed according to some consequence of an exposure, this simplicity vanishes and results can emerge that initially seem counterintuitive. Some well-known examples of this sort of apparently counterintuitive results include the “birthweight paradox” and the “obesity paradox.”^{2,3}

In the “birthweight paradox,” the covariate affected by an exposure, such as maternal smoking during pregnancy, is birthweight.² Contrasting smokers to nonsmokers implies a differential impact on birthweight, but this variable is instead used to stratify the outcome, infant mortality. The paradoxical result is that infants with low birthweight have lower risk of mortality if they had exposure to smoking than if they had none, even though smoking is harmful. Likewise, in the “obesity paradox,” the covariate affected by

obesity is a clinical diagnosis such as diabetes or heart failure.³ Once again, presence of obesity leads to excess diagnosed disease, but this consequence of exposure is made a condition of study recruitment. The paradoxical result is that patients with a chronic disease diagnosis have lower risk of mortality if they were obese at baseline than if they were normal weight, even though obesity is harmful. To date, however, few such examples have been described in infectious disease epidemiology, despite a large number of studies restricting participation to those with a consequence of exposure, for example, in the recruitment or eligibility requirements.

Adams et al⁴ recently published a article examining the association between cannabis, stimulant, and alcohol use with mortality prognosis in 3099 HIV-infected men participating in the Veterans Aging Cohort Study (VACS). As hypothesized, the authors found an increased mortality risk for stimulant use.⁴ However, they also reported two seemingly counterintuitive findings: (1) a strong protective effect of reported men who have sex with men (MSM) status on mortality prognosis; and (2), a strong negative effect of reported sexual abstinence in the last 12 months on mortality prognosis (Table 2 in the published study).⁴ The authors cautiously avoided any explicit interpretation of these apparently counterintuitive findings. These unexpected findings may simply be the result of a structural bias that is common in the study of clinically defined cohorts, but has still not been widely discussed in substantively focused journals. The purpose of this Research Note is to propose an explanation for these results, using the study by Adams et al as a recent example that is relevant for scientists who study sexually transmitted infections.

The results initially seem surprising because of the natural tendency to think of the comparison being made to the entire population, so that a protective effect of MSM status in the results may be mistaken to imply that any man responding as MSM in the general population would have higher mortality risk if he were counterfactually not MSM. However, if studies are restricted in the design to only those with a certain condition affected by exposure, then the exposed group is not being compared with similar but unexposed people. Rather, the exposed group is being compared with individuals who must have contracted the condition via another cause. Consequently, reversal in associations can occur so that factors that are harmful in the general population may appear protective in the study analysis, or vice versa.

The crucial design issue in this instance is, therefore, restricting study recruitment to HIV-positive men and then estimating the effects of exposures that have previously affected HIV infection status. This study design generates “collider stratification bias,” a form of selection bias.⁵ In causal graphs, such as the one shown below, a “collider” is simply a node on a causal pathway that receives more than one incoming arrow, indicating that it has more than one cause (Fig. 1). Like some other sexually transmitted infections, such as hepatitis B, HIV can be acquired through sex or through other behaviors, such as injection drug use (IDU). Restricting the study recruitment to only HIV-positive men results in collider stratification bias because potentially unrelated factors like MSM status and IDU “collide” by each competing as

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J.S.K. theorized that the paradoxical results would occur. S.D.S. searched for and found the existing study reporting the theoretically anticipated results. J.S.K., S.D.S., and H.R.B. then drafted the article, which was reviewed, edited and improved by J.W.A. and B.D.L.M., the first and senior author of the original publication, respectively. All authors then made final edits before the article was submitted.

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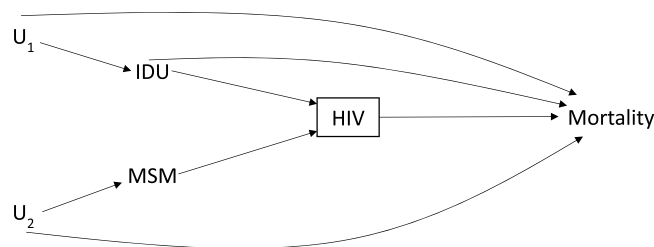


Figure 1. Simplified schematic diagram representing the relevant associations between IDU, MSM, HIV status, and mortality. Note: U_1 and U_2 represent unmeasured confounders of the risk factor-mortality relationship. The box around HIV indicates conditioning on HIV status (ie, only including HIV-positive men in the study). The arrow from IDU to HIV is mediated by sharing of contaminated needles. The arrow directly from IDU to mortality reflects other pathways that do not require HIV infection, such as overdose. Conditioning on HIV in the study design creates a non-causal association between IDU and MSM in the study data set, because getting into the study via one pathway makes one less likely to have the other characteristic. Adjustment for IDU status in the multivariable model should, in principle, remove this bias. However, since nearly all men in the study acquired infections through sex with other men or through injection, adjustment for IDU in the model reported by Adams et al. may induce a positivity violation or near violation and therefore not validly estimate independent effects of the two variables.

mechanisms for the HIV infection that qualifies participants for inclusion into the study.⁵ Meeting the criteria for recruitment via one mechanism makes it statistically less likely to have acquired HIV through the other mechanism. Any true correlation between these two risk factors will therefore be distorted in the study sample, and if they were actually independent of one another in the source population, they would appear negatively correlated in the study data set.⁵ Because the Adams et al. study includes only men who are HIV-positive, there is stratification on a common consequence of the risk factors in the recruitment.⁴

Within the population of men studied by Adams, et al.,⁴ restricting recruitment to only those with HIV infection implies that participants must have engaged in a behavior that led to HIV acquisition, primarily either IDU or unprotected sexual activities.^{6,7} Behaviors tend to persist over time and to be associated with other lifestyle factors. Given that there is more than one type of behavior that leads to HIV infection, there must be some behaviors that are less likely to lead to death than others. The initially surprising findings in the study by Adams et al. simply suggest that if one acquires HIV infection, being an MSM is the relatively lower risk lifestyle by which to do so, simply because these participants have lower mortality than those who became HIV-positive via IDU. This relative benefit of MSM status is entirely plausible, because people who inject drugs (PWID) tend to have other physical and mental health comorbidities, as well as a greater social and structural vulnerabilities that may contribute independently to mortality risk.⁸ The MSM status therefore appears comparatively protective in the analysis because it is associated with lower mortality risk than IDU. Likewise, reported sexual abstinence in this selected cohort is a marker for 1 of 2 things: being more likely to be a PWID, or being a person too ill to be sexually active. The latter concern is essentially confounding by a strong prognostic indicator or causal precursor of the outcome, often termed, “reverse causation.”⁹

The figure depicts our hypothesized structural relationships between MSM, IDU, HIV status, and mortality. The diagram is simplified, as there are more than just 2 ways to acquire HIV, but the figure serves to explain the basic structure of the bias responsible for the seemingly counterintuitive results. If PWID have unmeasured physical or mental health comorbidities or other psychological, social, or structural vulnerabilities (U_1), these variables become confounders of the relationship between MSM status and mortality by virtue of the negative correlation that arises from the collider stratification. This confounding process is represented in the diagram by the unblocked pathways to mortality

through either U_1 or IDU via MSM, and U_2 , where it is the conditioning on HIV in the design that opens these paths.¹⁰

Selection bias like that described here would be potentially relevant in any context in which there is a stratification variable with more than one cause, which could be common in research on other sexually transmitted diseases. For example, chlamydia and gonorrhea are both important causes of pelvic inflammatory disease and resultant infertility.¹¹ Therefore, in a study restricted to women with pelvic inflammatory disease, chlamydia would appear protective for infertility, simply because it is not as aggressive a cause of infertility as gonorrhea. This apparently protective effect would not imply, however, that intentionally exposing a woman to chlamydia would lower her risk of infertility. In fact, the opposite would be true. This stratified association is therefore not causally valid, even for women within the selected stratum of pelvic inflammatory disease.

In light of the restricted study design such as that in Adams et al.,⁴ there is nothing really surprising or counterintuitive about the reported associations. Readers focused on HIV or other sexually transmitted diseases should recognize that because infections may result from more than one route, studies that restrict participants to one stratum of a variable affected by other variables under study may obtain surprising associations. These would be misleading if they were thought to have a causal interpretation or to represent associations that one might observe in the general population. To avoid being misled, we recommend heeding the advice handed down by Les McCann so many years ago, to always ask of each reported effect estimate: compared to what?

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