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COMMENTARY

Effects of time-varying exposures adjusting for time-varying confounders: the case of alcohol consumption and risk of incident human immunodeficiency virus infection

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Abstract

Objective Discuss issues related to time-varying exposures using as an example the recently meta-analyzed literature (Baliunas et al. in Int J Public Health, 2009) on alcohol consumption and risk of HIV infection.

Methods Cataloged sources of bias and imprecision in the context of time-varying exposures.

Results Confounding, selection, or measurement bias may occur when standard regression approaches are used to estimate effects of time-varying exposures. The reviewed literature on alcohol consumption and HIV infection suffer from one or more of these biases.

Conclusions Detailed prospective data and thoughtful implementation of appropriate statistical methods are needed to obtain unbiased estimates of time-varying exposures, such as alcohol consumption.

Keywords HIV/AIDS · Alcohol · Confounding · Bias

We commend Baliunas et al. (2009) for their summary of the literature on alcohol consumption and risk of incident human immunodeficiency virus infection. However, the ten articles selected for their meta-analysis, and more generally the extant literature, do not adequately assess the relationship between alcohol consumption and HIV acquisition. We first digress to describe bias, precision, and their sources.

Bias is a systematic error where the true population value of a measure [e.g., relative risk (RR)] differs from the value obtained in a study. Bias is distinct from precision which is a measure of random error. Meta-analysis, an approach which pools estimates across studies, typically produces gains in precision and a consequent reduction in random error. However, pooling does not necessarily reduce bias and in fact can increase the relative contribution of systematic error.

In observational studies, when standard regression approaches are used to estimate effects of time-varying exposures in the presence of time-varying confounders several sources of bias exist (Robins et al. 2000). First and well known, regardless of whether the exposure is measured only at baseline or updated at intervals over study follow-up, failure to adjust for confounders may result in confounding bias. Second, even in the presence of an exposure measured without error, use of the baseline exposure value may result in measurement bias. This bias is due to misclassification of the actual (time-varying) exposure by use of the static baseline exposure as follow-up proceeds (Hu et al. 1999). Third, when the values of confounders may change over time in the study population, they too should be measured and updated over follow-up in the analysis to avoid a similar residual confounding bias (Greenland and Robins 1985). Finally and least well known, stratification or regression for time-updated confounders may block indirect effects through these confounders and induce a selection bias when confounders are affected by prior levels of the main exposure (Robins et al. 2000; Hernan et al. 2004).

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We now return to the meta-analysis of alcohol consumption and HIV acquisition. Many of the estimates used in this work are unadjusted or do not account for expected confounding by sexual activity and drug use. Among the studies examining binge consumption, one (Plankey et al. 2007) did attempt to account for potential confounding by sexual activity and drug use through adjustment for concurrent time-updated reports. The reported measure of association was nearly null [i.e., RR of 1.13, 95% confidence interval (CI) 0.81, 1.56], whereas estimates obtained from unadjusted (Chesney et al. 1998; Read et al. 2007) and inadequately adjusted analyses (Nopkesorn et al. 1998; Koblin et al. 2006) were substantially further from the null (i.e., range of RRs 1.97–3.60) and drove the meta-analysis summary finding for binge drinking (i.e., RR of 2.20, 95% CI 1.29, 3.74) away from the null.

The attenuation observed between the unadjusted or inadequately adjusted studies, and the adjusted analysis may be due in part to reduction in confounding bias after adjustment. However, alcohol consumption may also affect subsequent sexual activity and drug use (Stein et al. 2002; Zule et al. 2002). Therefore, as stated above, standard adjustment for time-updated sexual activity and drug use may remove the indirect effect of alcohol consumption on HIV acquisition mediated through these behaviors.

Methods such as marginal structural models (Robins et al. 2000; Hernan et al. 2000; Cole et al. 2003) are needed to obtain unbiased estimates of the effect of alcohol consumption on HIV acquisition. Similar to standard regression methods, marginal structural models assume exchangeability, positivity, consistency, and correct model specification (Cole and Hernan 2008). However, given that these necessary assumptions hold, marginal structural models will remove confounding bias without introducing selection bias and preserve the full effect of alcohol consumption. Use of such models also requires close attention to the temporal ordering of covariates as well as the main exposure and outcome which further facilitates proper causal inference. Therefore, we call for the use of such modern methods to decipher whether alcohol consumption increases the risk of HIV acquisition.

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