standardized mortality ratios (SMR) for potential confounding bias. SMRs between a cohort and a reference population can be biased if the cohort and population differ not only with respect to the measured exposure(s) of interest but also with respect to other (unmeasured) factors that influence the outcome of interest. The authors suggest using an alternative negative control outcome that is assumed not to be affected by the exposure of interest but by (ideally) all other unmeasured confounders. This negative control outcome is used to adjust the SMR for potential confounding in a Poisson model:

$$\log(Y) = \beta_0 + \log\left(\frac{I}{J} * Z\right), \qquad (1)$$

with Y as the observed number of deaths from a disease D_1 potentially related to the exposure of interest and Z as the number of deaths from a disease D_2, denoted negative control outcome in Richardson et al.,[1] in the cohort. I and J are the mortality rates for D_1 and D_2 in the reference population, respectively. In this model, $\log\left(\frac{I}{J} * Z\right)$ is used as an offset to adjust for potential confounding and $\exp(\beta_0)$ is the adjusted SMR. Richardson and colleagues[1] suggest using the simple maximum likelihood estimator of β_0, which is asymptotically normally distributed, that is, $\hat{\beta}_0 \sim N\left(\beta_0, V_{\hat{\beta}_0}\right)$, with $V_{\hat{\beta}_0} = Y^{-1}$. This estimate, however, does not account for the variability in Z, which can be estimated from the cohort data as

$$\log(Z) = \beta_1, \qquad (2)$$

with $\hat{\beta}_1 \sim N\left(\beta_1, V_{\hat{\beta}_1}\right)$ and $V_{\hat{\beta}_1} = Z^{-1}$. (1) and (2) is a classical error-in-variables model,[2] with the correct estimate of β_0, denoted as $\hat{\beta}_0^*$, as $\hat{\beta}_0^* \sim N(\beta_0, V_{\hat{\beta}_0^*})$ with $V_{\hat{\beta}_0^*} = Y^{-1} + Z^{-1}$, assuming that $\mathrm{Cov}(\beta_0, \beta_1) = 0$.

The difference between the variances of $\hat{\beta}_0$ and $\hat{\beta}_0^*$ can be substantial: in the appendix of their article, the authors calculate the confidence interval for an adjusted SMR based on hypothetical data, $y = 174$ and $z = 193$, with an adjusted SMR for the outcome of interest of 2.0. Based on $\hat{\beta}_0$, the authors report a nominal 95% confidence interval for the SMR ranging from 1.72 to 2.32. The correct 95% confidence interval based on $\hat{\beta}_0^*$, however, ranges from 1.63 to 2.45. In general, the ratio of the variances of $\hat{\beta}_0^*$ and $\hat{\beta}_0$ solely depends on the ratio of y and z, as illustrated in the Figure. Thus, depending on y and z, ignoring the variability in z can lead to a severe underestimation of the variance of the adjusted SMR.

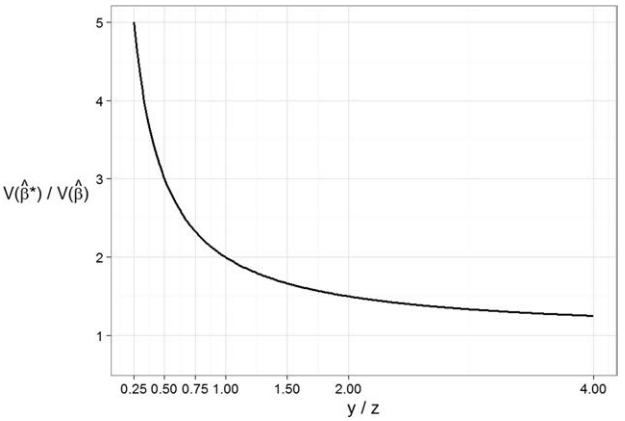

FIGURE. Ratio of the variances unadjusted versus adjusted estimate for log(SMR) for varying ratios of y to z in the cohort.

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The Authors Respond

To the Editor:

We are grateful for the interest in our article.[1] We proposed an adjusted mortality statistic based on information for an outcome of primary interest and a negative control. In the appendix of our article,[1] we provided a simple method to estimate this adjusted standardized mortality ratio (SMR) as a modest extension of the classical SMR. The approach involved using the negative control outcome and reference rates as an offset in a Poisson regression model for the outcome of primary interest. Hengelbrock and Becher[2] correctly point out that the variance obtained from using offsets does not account for variability in the observed number of deaths due to the negative control, a component of the offset. They propose a variance estimate for the adjusted SMR which they note may be obtained under the assumption of no covariance between the outcome of interest and the negative control. As in many other settings, with negative control outcomes, there is a cost when addressing bias by calculating our proposed adjusted SMR that is expressed in terms of an increase in variance of the adjusted SMR relative to the standard SMR. Good general advice seems to be to choose a negative control outcome that is not rare compared with the outcome of interest, so that its contribution to the variance of the adjusted SMR is not large.

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Re: Some Thoughts on Consequential Epidemiology and Causal Architecture

To the Editor:

We would like to thank Professor Charles Poole for his views[1] on our commentary[2]; we are always glad to see interest in our study. We would, however, like to take the opportunity to reply to some of Poole's comments. Our read is that Poole's commentary suggests some misunderstanding about the positions we outlined in our own comment. We highlight here our five main concerns.

First, we are not asking anyone to "abandon [their] interests in internal validity." We agree that internal validity is vitally important to scientific inference, and emphasize this view here and in our original commentary. We refer readers who are skeptical of our position on internal validity to Chapter 12 of our textbook "Epidemiology Matters,"[3] which outlines the stages of validity that have formed a foundation of modern scientific inquiry for many decades. Rather than suggesting that we abandon internal validity, instead we argue that too often the goal of estimating an internally valid effect becomes the research agenda itself, rather than the process through which we engage in important public health research.

Second, Poole suggests that we "hail" the ratio measure over the difference measure; we do not do so. We are in agreement with Poole that difference measures provide much more informative evidence regarding the magnitude of public health impact of exposures than ratio measures. Although this may be the epidemiologic and public health "mainstream," most of the papers published in medical and epidemiologic journals continue to use ratio measures. Our comment was on the field as it is, not on as it should be. Furthermore, our argument about the limitations of risk-factor epidemiology is not germane to the merits of differences versus ratios; the same issues apply regardless of the measure. More specifically, in our commentary, we focus on the limitations of studying exposure–outcome relations agnostic to the underlying distributions of causes that vary within and across populations. Difference measures often highlight these underlying distributions as they are, rightfully so, more sensitive to base rates and co-occurring causes. Yet our contention remains that more expansive theorizing and interrogation about the ways in which these measures vary across populations would benefit the field of epidemiology.

Third, Poole asks "What's wrong with restricting first and studying interaction later?" We respond with the question "What's wrong with laying out a series of hypotheses about causal interactions first, and testing all of them simultaneously to build a series of testable, high-stakes hypotheses?" It is the latter question, and its difference with the question that Poole posed, that forms the foundation of what we mean by causal architecture. To answer Poole's question more directly, nothing is wrong with restricting first and studying interaction later. However, we argue that the inherent questions that lead to methods that involve restriction are often not the pertinent questions to engage. Poole's question on restriction leads to his comments that complex systems models rely on parameter estimates from the literature, and therefore internally valid risk ratios and risk differences from single exposures form the bedrock of the validity of the complex systems model. That is true, but experience from agent-based modeling approaches has taught us that what can be parameterized is based on summary ratio measures of single exposures because those are what is available in the literature, rather than a broad array of interactions, which would be much more informative for our models. If the causal architecture approach were adopted, rather than making our complex systems models untenable, as Poole suggests, our models would be more rigorous and flexible.

Fourth, Poole finds our claim that representative sampling enhances the assessment of interaction "dubious." We agree that the representative sampling is not necessary to assess interaction; our point was that we can better understand how the estimates that we obtain translate into actionable public health impact when we inquire about the distributions of other causes of the outcomes we are interested in within the populations for which we would like to intervene. Recent debates about the importance of representativeness have been presented recently in the pages of other journals, and we refer readers to these commentaries.[4–14] We agree with Poole that our studies are always set in the past so it is impossible to know how applicable they will be to populations of the future, and yet, we argue that some thought and consideration to how causes will distribute in populations can aid in our endeavor to use our data to improve public health. Representative sampling is one method (among others) that requires us to engage in that thought process, which is why we recommend it.

Fifth, Poole provocatively asks whether causal architecture is "antithetical to much of social epidemiology." Poole claims that there is no place in causal architecture, or more broadly in the systems sciences within which many causal pathways are parameterized, for researchers aiming to estimate net, total,

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