



# HHS Public Access

Author manuscript

*Epidemiology*. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

*Epidemiology*. 2017 May ; 28(3): e30–e31. doi:10.1097/EDE.0000000000000630.

## Negative Control Outcomes and the Analysis of Standardized Mortality Ratios

DB Richardson<sup>1</sup>, A Keil<sup>1</sup>, E Tchetgen Tchetgen<sup>2</sup>, and GS Cooper<sup>3</sup>

<sup>1</sup>Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA 27599

<sup>2</sup>Department of Biostatistics, Harvard University, Boston, MA USA 02115

<sup>3</sup>National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA 20460

### To the Editor

We are grateful for the interest in our paper.<sup>1</sup> We proposed an adjusted mortality statistic based on information for an outcome of primary interest and a negative control. In the appendix of our paper<sup>1</sup> 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<sup>2</sup> 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 to the outcome of interest, so that its contribution to the variance of the adjusted SMR is not large.

### Acknowledgments

There is no funding to declare for this response.

### References

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Corresponding author: David Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA, PHONE: 919-966-2675 FAX: 919-966-2089 david.richardson@unc.edu.

The authors declare no conflicts of interest.

2. Hengelbrock J, Becher H. Re. Negative control outcomes and the analysis of standardized mortality ratios. *Epidemiology*. 2016; 28:xxx.

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