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Selection Bias

Importance of Identification and Adjustment

Kristie N. Carter, Tony Blakely

Health Inequalities Research Program, Department of Public Health, School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand

In their paper in this issue of *Neuroepidemiology*, Haneuse et al. [1] demonstrate adjusting for selection bias in an observational study by assessing the association of neuropathological factors with dementia, using data from autopsied subjects only. The authors state that there has been little emphasis placed on potential selection bias in neuropathological studies of dementia [2]. Haneuse et al. attempt to provide information on how to identify and adjust for selection bias, using directed acyclic graphs (DAGs) and inverse probability weighting (IPW). In this commentary, we review what selection bias is, and critique the Haneuse et al. [1] paper.

Selection bias is 1 of the 3 main sources of systematic error that may threaten internal validity (the other 2 being information bias and confounding). Selection bias results from procedures influencing selection of subjects available for analysis. It occurs when the association between the exposure and outcome (e.g. relative risk) is different for those included in the final analyses compared to all eligible members of the target population [3]. Hence, it is critical to define the target population, and understand how and why one's final sample differs (or not) from the target population.

DAGs facilitate explication of selection bias. Hernán et al. [4] define selection bias as: 'Conditioning on a common effect of two variables, one of which is either the exposure or a cause of the exposure and the other is either the outcome or a cause of the outcome.' In figure 1, we present a simple DAG for an exposure, an outcome (dementia) and a third variable that is independently caused by both exposure and outcome. Death is a common effect (collider) in this DAG, because 2 arrows are entering it. A common effect is different from a common cause, i.e. confounding, in that conditioning on a common effect (a collider variable) may introduce bias, opening a blocked pathway between the exposure and outcome, where none was found without conditioning on it [5]. What is more, if (as in the Haneuse et al. paper) we can only examine the association of exposure with outcome among those who have died (conditioning the analysis on the collider), our study findings are likely to be biased by selection bias.

In table 1, we have presented hypothetical data that is consistent with this simple DAG, and in some respects similar to the

data in Haneuse et al. [1]. The risk ratio of dementia by exposure in the total target population is 2.0, and is the true association (there is no confounding in our simple DAG; fig. 1). Table 1 shows the expected distribution by exposure and outcome by strata of dead/alive under the following assumptions: half of the population dies; there is a risk ratio of death for the exposed compared to unexposed of 2.0 within both the demented and non-demented; likewise, there is a risk ratio of death for the demented compared to non-demented of 2.0 within both the exposed and unexposed. That is, the independent nature of the 2 arrows colliding into death in figure 1 is fulfilled. The association of exposure with dementia among those subsequently dying is a risk ratio of 1.60. This shows conducting an analysis among only the deceased is biased by selection, as in the paper by Haneuse et al. [1]. Likewise, the risk ratio of 1.25 among those who happen to be alive at the end of follow-up is also biased.

This brings us to a criticism of the paper by Haneuse et al. [1]. Whilst an elegant demonstration of how IPW might be used to adjust for selection bias, they (essentially) choose the people alive at the end of follow-up as their target population. The more relevant target population is the total eligible population; it does not make sense to estimate the association of neuropathological risk factors with dementia among just those who survive, as this is just substituting one selection bias for another. It is interesting to note that Tsuang et al. [6] conducted a similar analysis on a target population of all individuals and found that adjustment had little effect on the relative frequencies.

Haneuse et al. [1] provide a DAG (see fig. 4 of Haneuse et al.) of the extended relationship between the exposure, neuropathological risk factors (X), the outcome dementia (Y) and selection (R). The common effect, i.e. selection ($R = 1$), those who died and consented to undergo autopsy, depends on the selection mechanism, a set of covariates (L) consisting of the outcome (Y), common confounders (C_0) of the exposure-outcome association, as well as additional predictors of selection (Z) not related to X or Y, $L = (Y, C_0, Z)$. We feel their DAG obscures the roles of consent and death as drivers of autopsy (the collider generating selection bias), and we have accordingly presented an alternative DAG in figure

Fig. 1. Simple DAG of exposure, dementia outcome, and death as a collider, and therefore inducing selection bias if used to select sample.

Table 1. Hypothetical example of association of exposure with dementia for total population, and by strata of dead or alive to demonstrate selection bias

	Total population				Dead at end of follow-up				Alive at end of follow-up			
	D	no D	total	risk	D	no D	total	risk	D	no D	total	risk
Exposed	667	333	1,000	0.67	571	143	714	0.80	95	190	286	0.33
Unexposed	333	667	1,000	0.33	143	143	286	0.50	190	524	714	0.27
Total	1,000	1,000	2,000		714	286	1,000		286	714	1,000	
Risk ratio	2.00				1.60				1.25			

D = Dementia. In addition to the (true) risk ratio of 2.0 for the total population, the data is structured such that: (1) within strata of dementia, the risk ratio of death for exposed compared to unexposed is 2.0: i.e. $[571/(571 + 95)]/[143/(143 + 190)] = 2.0$; $[143/(143 + 190)]/[143/(143 + 524)] = 2.0$; (2) within strata of exposure, the risk ratio of death for demented compared to not demented is 2.0: i.e. $[571/(571 + 95)]/[143/(143 + 190)] = 2.0$; $[143/(143 + 190)]/[143/(143 + 524)] = 2.0$.

Fig. 2. Modified DAG for Haneuse et al. [1] .

2. The box in the top right includes the selection mechanism, but identifies both prior consent and death as necessary conditions for an autopsy. Confounders of the exposure-outcome association are also probably determinants of both consent and death independent of dementia as demonstrated by the arrows (although there is insufficient detail in Haneuse et al. to confirm these suppositions). Likewise, one would assume that dementia influences likelihood of consent as well as death. Thus, we not only have the selection mechanism in total as a collider, but also both consent and death – there is a lot of potential colliding going on that may actually generate selection bias. The DAG also suggests that there must be a reasonably strong association between some of the confounders and exposure to ensure substantial selection bias; however, such data is not presented in Haneuse et al.

Our final comment on the Haneuse et al. paper relates to small number of non-demented and demented decedents among those with any of the 4 neuropathological risk factors (see table 3 of Haneuse et al.). They have provided corrected confidence intervals,

but we wonder whether the data may be too sparse. This would be particularly so if 1 or 2 ‘events’ were given a large weighting by the IPW – a not unlikely occurrence, and the reason why stabilized weights are often used during IPW (but not the case in Haneuse et al., as best as we can tell).

In conclusion, we agree with Haneuse et al. that it is important to understand how the target population and the population used in analyses differ, and how the selection of the sampled population may bias the results reported. We want to stress the importance of identifying these potential biases and defining the appropriate target and sampled populations ‘a priori’, in the design stage of a study, and to facilitate adjustment analyses such as IPW. We hope these methods will be more routinely used in the future.

References

- 1 Haneuse S, Schildcrout J, Crane P, Sonnen J, Breitner J, Larson E: Adjustment for selection bias in observational studies with application to the analysis of autopsy data. *Neuroepidemiology* 2009;32:229–239.
- 2 Zaccai J, Ince P, Brayne C: Population-based neuropathological studies of dementia: design, methods and areas of investigation – a systematic review. *BMC Neurol* 2006;6:2.
- 3 Rothman KJ, Greenland S: *Modern Epidemiology*, ed 2. Philadelphia, Lippincott-Raven, 1998.
- 4 Hernán MA, Hernandez-Diaz S, Robins JM: A structural approach to selection bias. *Epidemiology* 2004;15:615–625.
- 5 Greenland S, Pearl J, Robins JM: Causal diagrams for epidemiologic research. *Epidemiology* 1999;10:37–48.
- 6 Tsuang D, Simpson KL, Li G, Barnhart RL, Edland SD, Bowen J, McCormick W, Teri L, Nochlin D, Larson EB, Thompson ML, Leverenz JB: Evaluation of selection bias in an incident-based dementia autopsy case series. *Alzheimer Dis Assoc Disord* 2005;19:67–73.

Kristie Carter
Health Inequalities Research Program
School of Medicine and Health Sciences
University of Otago, Wellington
PO Box 7343, Wellington South, Wellington 6242 (New Zealand)
Tel. +64 4 385 5541, ext. 4617, Fax +64 4 389 5319
E-Mail kristie.carter@otago.ac.nz