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Response to letter to the editor: When does selection generate bias in clinical samples?

We welcome the opportunity to respond to the letter by Höfler and Trautmann (2019) entitled "When does selection generate bias in clinical samples?" Höfler and Trautmann argue there are limitations of our study which compromise the validity of our findings. There are three main concerns raised by Höfler and Trautmann. First that our findings conflict with a well-established body of theory which emphasises the broad problem of selection bias and its impact on research findings. Second, that our findings are population based and may have little relevance to "clinical' samples. Third, our findings may not be generalizable to many studies.

We will respond to each of these concerns but begin where perhaps we should have begun in our paper. Bias, we argue, should be interpreted in the context of a specific research question. If the research question is whether childhood sexual abuse "causes" mental illness, then the population from which those affected come is likely the appropriate sampling frame. A clinical sample of persons (however comprehensively selected) who are receiving treatment for mental illness is inherently "biased" and is unlikely to provide an accurate answer to the research question. On the other hand asking a question about proportion of those being treated for a mental illness who have previously experienced childhood sexual abuse can be answered using clinical samples, but the answer has no direct relevance to the first question. Bias should be understood as a finding which is misleading in the context of a specific question which is being addressed. In our paper we address the question of whether adversity and/or economic disadvantage are associated with mental illness. We use a population based sample. The majority of those in our study who have symptoms of mental illness do not seek or receive clinical treatment. Given the research question we address (does loss to follow-up (LTFU) affect the estimates of association between adversity/economic disadvantage and mental illness?), our sampling is appropriate.

First then, Höfler and Trautmann are concerned that an established body of theoretical literature suggests that LTFU may lead to biased estimates of association. We agree and refer to some of these papers in our literature review (Fewtrell et al., 2008; Zhao et al., 2009). However, this literature is mute on the obvious questions which follow. How much bias is generated by different rates of LTFU? What is the extent to which selective LTFU in both the predictor and/or outcome variables affect findings and generate misleading results? In the absence of relevant empirical research some scholars use an arbitrary criterion eg. 20% (Fewtrell et al., 2008), or even a variable percentage depending upon the topic or preference of a particular researcher, to suggest that findings may be biased. This is not only an arbitrary criterion but potentially has unintended and possibly destructive consequences. Many papers with valid findings will be rejected based on an arbitrary and empirically unsupported standard. While we accept the theoretical case that LTFU may lead to misleading findings, we argue that the blanket application of an arbitrary criterion based upon theoretical considerations is itself a serious error with likely negative consequences. The theory that underpins our understanding of LTFU and bias is important but, as it is presently not guided by a body of data, an imprecise guide to whether a specific set of findings are affected.

Second, the focus of the letter is on clinical research and selection bias as it may affect clinical findings. The counterpart to our baseline estimates in a clinical sample would be the sample recruited to the study. The selection of clinically relevant samples raises a particular subset of concerns about bias. For example, for randomised clinical trials the comparison groups should not differ (due to the randomisation process). Participants in both control and treatment group are ideally exposed to similar types of treatment. In population samples this problem of having similar comparison groups is addressed by statistical control for confounding. In general, the questions being addressed in clinical and population samples are often different. Clinical and population samples may have a similar set of concerns about the possible ways selection bias might impact on findings, but will have somewhat different ways of addressing these effects. It is also likely that the perceived consequences of a misleading finding may be different. Clinical samples may generally be smaller, more narrowly selected and have more intensive follow-up than do population samples. Treatment trials, in particular, may adopt sampling procedures that recruit individuals who are most likely to optimise risk/benefit considerations relevant to a specific health problem. Despite these differences we see no reason why our findings would not extend to clinical and/or treatment samples.

Finally, it is suggested that our findings may be limited to our sample or method of analysis and not be able to be generalised. While this latter suggestion cannot be dismissed it seems unlikely because (i) other studies using other samples and methods of analysis have reported similar findings (Gerrits et al., 2001; Greene et al., 2011; Howe et al., 2013), (ii) we have not been able to find (nor does the letter cite) studies with findings that conflict with ours (iii) the important finding in our paper that while LTFU may be biased on both predictor and outcomes variables (that is data are not missing at random), the estimates of association (particularly in the group LTFU) remain effectively unaffected. While our data confirm that those LTFU have substantially higher rates of both economic disadvantage and mental illness, the estimates of the association in those who remain in the study and those LTFU are remarkably similar. Further, the specific rate of LTFU does not appear to be related to evidence of "biased" findings. This latter finding is arguably unexpected.

We acknowledge the threat to findings posed by LTFU in longitudinal studies. We agree that, when estimates of association are considered, misleading results possibly attributable to LTFU may occur, but our findings suggest these are infrequent and generally estimates of association appear to be unaffected. We agree with Höfler and Trautmann's sensible suggestion that sensitivity analyses should be undertaken to assess the potential effect of bias under different LTFU assumptions. However, we argue that blanket rejection of papers on the

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basis of an arbitrary level of LTFU may involve the misguided application of an arbitrary criterion and consequently lead to the rejection of a good deal of important research. As a next step we need to have better information about the specific circumstances in which LTFU leads to misleading findings.

Conflicts of interest

None.

Availability of data and material

The data sets are held by the principal investigators. They are available on request, contact Professor Jake Najman in the first instance. MUSP welcomes interest in international collaborations. Contact details: j.najman@uq.edu.au.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.02.011.

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