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Effects of bias on the association between post-traumatic stress disorder and interleukin-6

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A recent meta-analysis by Passos et al.¹ investigated the relationship between inflammatory markers and post-traumatic stress disorder (PTSD). This paper is a valuable resource, and likely to remain so, since effect estimates were obtained in several cases by contacts with original authors, when they could not be estimated directly from published papers. However, the question of bias could have been more thoroughly addressed and we suspect that effects may have been overestimated. Here, we present additional investigations of bias, focussing on IL-6, since this outcome had the greatest number of studies investigated ($k = 15$).

Data from Passos et al. were re-coded by one investigator (GN). Following Passos et al., we performed a meta-analysis using R^2 with the metafor package³. All data and code are openly available at [dx.doi.org/10.5281/zenodo.44726](https://doi.org/10.5281/zenodo.44726). Reanalysis produced a standardised mean difference summary estimate of 0.88 [95% CI 0.40, 1.35], $p = 0.0003$, replicating the original results. A funnel plot revealed considerable heterogeneity and a skewed distribution (figure 1). One study (Guo et al. 2012) appeared to be an outlier. Exclusion of this outlier reduced the overall effect estimate to 0.66 [0.35, 0.97], and Egger's test was significant among the remaining non-outlier studies, $b = 3.31$, $z = 2.34$, $p = 0.019$. As one possible adjustment for bias, we performed a cumulative meta-analysis with studies sorted by precision. The four largest studies gave an aggregate estimate of 0.33 [0.14, 0.53] (figure 1).

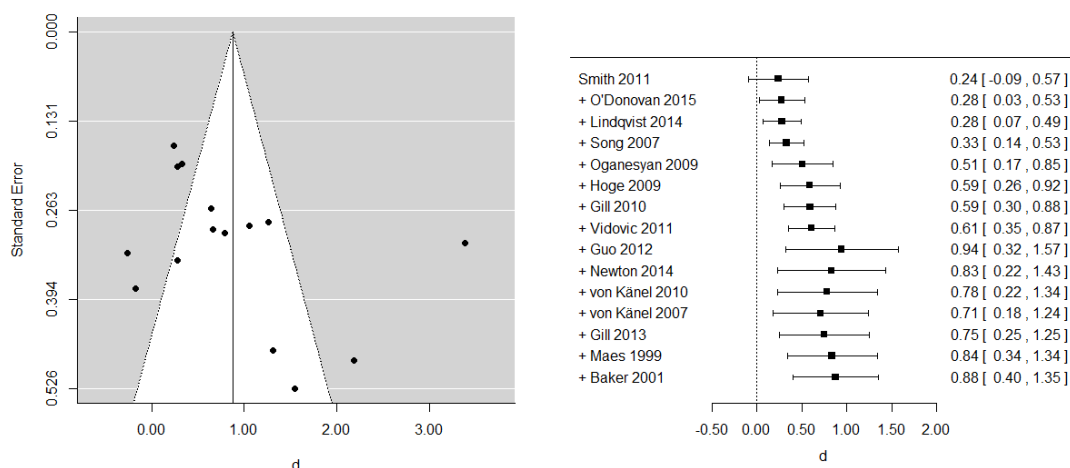


Figure 1. Left: Funnel plot. Right: Cumulative meta-analysis with studies sorted by precision.

Passos et al. addressed heterogeneity by meta-regression on depression and medication status. Meta-regression on either of these variables resolved some heterogeneity, but these predictors were highly correlated. Sample size is another possible moderator, reflecting small-study effects. We suspect that small-study effects may contribute to an overestimation of the association between PTSD and IL-6, but because sample size was highly correlated with depression and medication status, it is hard to tell which of medication, comorbid MDD, or research bias truly predicts observed effect size.

Aside from small-study effects, we are also concerned about the risk of confounding, as the meta-analysis concerns observational associations. Of particular concern is possible confounding by pretraumatic vulnerability or by burden of somatic diseases associated with elevated inflammatory markers. Whereas Passos et al. propose that trauma induces chronic low-grade inflammation, an alternative and testable explanation is that this apparent association may instead be due to one or more unobserved additional variables.

In conclusion, our results suggest that the association between PTSD status and circulating IL-6 may have been overestimated by Passos et al, and that it is difficult to disentangle the effects of medication, comorbid MDD, and possible research bias in the available data. We recommend that clinical implications be treated with caution. While the putative connection between immune activation and PTSD is very interesting, the observational data analysed here are not evidence for causal mechanisms, and, in our view, do not yet warrant clinical trials of anti-IL-6 agents against PTSD.

Authors' contributions

Initiated the study: GN. Analysed data: GN, JH. Interpreted data: GN, JH, FA, ML. Drafted the manuscript: GN, JH, FA. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors report no conflicts of interest.

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Ethics committee approval

Ethics committee approval was not required.

References

1. Passos, I.C., Vasconcelos-Moreno, M.P., Costa, L.G., Kunz, M., Brietzke, E., Quevedo, J., Salum, G., Magalhães, P.V., Kapczinski, F., Kauer-Sant'Anna, M., 2015. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry* 2, 1002–1012. doi:10.1016/S2215-0366(15)00309-0
2. R Core Team, 2015. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
3. Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software* 36, 1–48.