PTSD is associated with elevated inflammation: any impact on clinical practice?

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ABSTRACT FROM: Passos IC, Vasconcelos-Moreno MP, Costa LG, *et al.* Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry* 2015;2:1002–12.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Accumulating evidence indicates that elevated inflammation may play a causal role in the development of post-traumatic stress disorder (PTSD) symptoms, and in PTSD-related increased risk for cardiovascular, autoimmune and neurodegenerative diseases.[1 2] At the same time, studies examining levels of inflammatory markers in individuals with PTSD have had mixed results, with most showing higher but others showing similar or even lower levels of inflammation in individuals with PTSD compared with healthy controls.[1] To summarise and make sense of this literature, Passos *et al* compared levels of inflammatory markers between people with and without PTSD using meta-analytic techniques.

METHODS OF THE STUDY

All potentially eligible cross-sectional or longitudinal studies published between January 1960 and April 2015 were identified in PubMed, Embase, Scopus, Web of Science, PsycINFO and in the reference lists of relevant papers. From 8058 identified articles, the authors included data from 20 papers that reported basal levels of peripheral blood inflammatory markers in adults with and without PTSD; used validated diagnostic criteria for diagnosing PTSD; and excluded individuals with bipolar, psychotic and severe medical or inflammatory disorders. Meta-analysis and metaregression were conducted and a random effects model with restricted maximum-likelihood estimator was used to synthesise the effect size across studies. Outcomes included mean and SDs of inflammatory markers and information on heterogeneity among studies.

WHAT THIS PAPER ADDS

- This first meta-analysis of inflammatory markers in PTSD represents a critical contribution to research due to the conflicting results of prior studies.
- Among the 11 inflammatory markers examined, this meta-analysis indicated that interleukin-6 (IL-6), IL-1β and interferon-γ levels (IFN-γ) are significantly higher in individuals with versus without PTSD. Standardised mean differences (SMDs) indicated moderate-to-large effect sizes for these group differences (IL-6: SMD 0.88, 95% CI 0.40 to 1.35; IL-1β: SMD 1.42, 0.03 to 2.81; IFN-γ: SMD 0.49, 0.18 to 0.81).
- In contrast, levels of IL-2, IL-4, IL-8, IL-10, soluble IL-2 receptor (sIL-2R), sIL-6 receptor (sIL-6R), C reactive protein and tumour necrosis factor-α (TNF-α) were not significantly different between individuals with versus without PTSD overall. However, levels of TNF-α were significantly higher in individuals with PTSD in subgroup analyses including only medication-free (SMD 0.69, 0.35 to 1.02) or depression-free (SMD 1.32, 0.13 to 2.50) participants.
- Results indicated that greater illness duration was associated with higher levels of IL-1β in medication-free individuals ($p<0.0001$), and that greater severity of PTSD symptoms was associated with higher levels of IL-6 ($p=0.04$).
- Study heterogeneity was high ($I^2>75\%$) for all inflammatory markers apart from IFN-γ ($I^2=0\%$), largely accounted for by comorbid major depression, use of psychotropic medication, type of assay used and time of day for blood sampling.

LIMITATIONS

- As with all meta-analyses, there is a risk that publication bias and the 'file-drawer effect' are skewing results.
- PTSD and depression are highly comorbid and in fact, patients who meet criteria for severe PTSD also typically meet criteria for major depression. Thus, although the authors attempt to do so here, it is difficult to understand the association between PTSD and inflammation independent of depression. Very large studies including people with and without PTSD and with and without depression will be needed to clarify.
- For sIL-2R, sIL-6R and IFN-γ, results were based on only two studies each, yielding small sample sizes ranging from 22 to 79 patients with PTSD.

WHAT NEXT IN RESEARCH

This meta-analysis raises important questions for future research. First, results highlighted that levels of some but not all inflammatory markers are increased in PTSD. Future research should focus on uncovering the precise transcriptional control mechanisms underlying elevated inflammation in PTSD, as in prior small studies.[3] Anti-inflammatory treatments for psychiatric disorders will need to be highly targeted at specific transcriptional control pathways because inflammation plays a critical role across bodily systems. Second, it is clear that not all individuals with PTSD show elevated inflammation. Given the multitude of symptom combinations that can underlie PTSD,[4] it will be important to identify if only some subtypes of PTSD are associated with elevated inflammation. For example, perhaps only individuals with higher levels of threat sensitivity will show elevated inflammation.[2] Finally, the field must uncover causal mechanisms of the relationship between inflammation and PTSD, possibly using targeted anti-inflammatory agents in randomised clinical trials.

DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

No. Even though the present study provides the strongest evidence to date that inflammation is elevated in PTSD, these results are unlikely to have an immediate impact on clinical practice. It remains premature to prescribe anti-inflammatory treatments for patients with PTSD because we do not know which treatments would be beneficial, nor for whom. However, reducing inflammation is another reason to recommend and facilitate a healthy lifestyle in patients with PTSD, particularly with regard to sleep, physical activity and diet.[5]

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