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Inflammatory biomarkers in PTSD: A look at the fineprint

To the Editor,

we read with interest the recent report on a putative role of proinflammatory molecules in promoting suicidality of women with a diagnosis of PTSD (Kawanishi et al., 2023). As for the putative effects of candidate genetic markers, however, some caveats are justified.

From a clinical point of view, it is unfortunate that neither the criteria used to diagnose PTSD nor the expertise of the respective physicians have been addressed. Substantial changes have marked the transition from DSM-IV to DSM-5 over the past decade, including the elimination of the subjective component to the definition of trauma, the explication and tightening of the definitions of trauma and exposure to it, the increase and rearrangement of the symptoms criteria, and changes in additional criteria and specifiers. In other words, conceptualization of PTSD is quite different now from what it used to be when recruitment began in 2015 (Pai et al., 2017).

With regard to the putative CRP biomarkers investigated, the authors have essentially presented a reanalysis of their earlier study of rs2794520 using a slightly enlarged sample (Otsuka et al., 2021) of which, however, 16% of genotypes are missing in controls. No mention is made of the previously claimed association with serum levels of CRP. Has this association been replicated, or rather refuted? It would seem that it is now obsolete, as the putative serum and genetic markers fail to predict the same phenotypes.

The newly claimed phenotype-genotype association for *IL6* marker rs1800796, in turn, appears questionable. As the authors have correctly pointed out, genotype data are ordinal, i.e. increasing numbers of alleles confer increasing probabilities to be in a particular phenotypic group, therefore testing for overall association is not recommended. For a 2x3 genotype contingency table, trend tests are employed, e.g. the Cochran-Armitage test (Cochran, 1954). When the trend test is applied, significance for rs1800796 is lost ($p = 0.11$).

Finally, in the light of multiple known confounders of mood swings and suicidality in the target population (Nilsonne et al., 2016), any tentative predictions would appear to be obscured by interference from menstrual-cycles, failure to control for physical exercise, and the pooling of samples collected both long before and during the COVID-19 pandemic. Given these unresolved issues, we encourage the authors to readdress the role of proinflammatory molecules in shaping the behaviour of women with PTSD in a larger, more homogenous sample.

Declaration of competing interest

There is no conflict of interest for all authors.

Data availability

No data was used for the research described in the article.

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