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Letter to the Editor

Author reply – Letter to the Editor "Antidepressant use, chronic inflammatory comorbidities and behavioral disinhibition"

Dear Editor:

We are grateful to Dr. Gau et. al for their interest in our recent article (Shi et al., 2022) and appreciate this opportunity to provide additional information.

We agree that chronic inflammatory diseases and immune-related pharmacotherapy may confound our analyses. Therefore, we corrected for the effects of representative chronic multi-morbidities in the regression analyses by utilizing self-reported somatic diseases, including cardiovascular diseases, cancer, or diabetes as covariates, although not comprehensive to cover all inflammatory conditions. Furthermore, sensitivity analyses after excluding participants with those problems indicated consistent findings in the mediation analysis. Also, for each immune biomarker, we excluded participants with levels lying outside of 3 standard deviations of the mean, which was higher than 9.06 mg/L for C-reactive protein (CRP) in the UK Biobank (UKB) dataset. In healthy participants, plasma CRP level is usually lower than 10 mg/L, and $>$ 10 mg/L are generally regarded as heightened (Pope and Choy, 2021). The elevated CRP can be persistently observed in some of the patients with rheumatoid arthritis and other inflammation-associated disorders (Kilcher et al., 2018). Therefore, our analysis to a large extent accounted for the potential confounding caused by inflammatory dysfunction. Last but not least, in an unpublished pre-analysis, we adjusted our analyses for the presence of allergic diseases diagnosed by doctors. The results showed that the correction did not attenuate the overall final results; in contrast, the association became more robust after correction.

Dr. Gau also highlighted the use of medication, such as selective serotonin reuptake inhibitors (SSRIs), as a possible confounder. Concerning this, we further performed two supplementary analyses of the self-reported use of antidepressants in the UKB dataset (Data field 20546). The results showed a significant association between medication use and disinhibition score (standardized estimates 0.55 [0.53,0.59], $P < 0.001$). Yet, several pro-inflammatory biomarkers, such as leukocytes (0.087 [0.082,0.092], $P < 0.001$), CRP (0.041 [0.036,0.047], $P < 0.001$) and INFLA-score (0.063 [0.053,0.068], $P < 0.001$) remained significantly associated with increased disinhibition after additional adjustments for medication coadministration within all participants (N = 157,316), though attenuation existed. Similar findings were obtained in both men (N = 68,243) and women (N = 89,073). Likewise, mediation analyses corrected for comedication showed that the estimates remained consistent for all models, with a significant indirect effect of INFLA-score in prudent diet-disinhibition association (−0.006 [−0.007, −0.005], $P < 0.001$) and in meat-based diet-disinhibition association (0.0012 [0.00087, 0.0015], $P < 0.001$), and for both sexes. While the results thus demonstrated a correlation between the use of antidepressants and behavioral disinhibition, it is unlikely that our reported effects were driven by a confounding effect of antidepressant use. Moreover, the significant results were also replicated in a subsample (N = 122,995) after excluding those who had ever used medication.

In conclusion, our results and mediation models stay to be robust when controlling for co-occurring inflammatory aberrations and the use of antidepressant medication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

For the data of UK Biobank, please visit https://www.ukbiobank.ac.uk/.

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