



# Response to: Commentary: Sex Differences in the Peripheral Immune System in Patients with Depression

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A commentary on

**Commentary: Sex Differences in the Peripheral Immune System in Patients with Depression**

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We would like to thank Breidenstein and colleagues for writing a commentary on our study titled “Sex Differences in the Peripheral Immune System in Patients with Depression” and appreciate the positive comments (1). We agree that even though our study points toward women showing higher levels of inflammation during depression, it is not possible to draw inferences about causality from our results due to the cross-sectional nature of the study. Therefore, a longitudinal study is warranted to determine the causal relationship between inflammation and major depressive disorder (MDD) (2).

With regard to interleukin-6 (IL-6), Breidenstein et al. pointed out that we did not identify elevated levels of IL-6 in depressed women compared with controls after controlling for body mass index nor a positive correlation between IL-6 and depression severity. However, our study did find elevated IL-6 in depressed females when compared with depressed males after controlling for body mass index (2). To further support this, one of our previous studies found higher circulating levels of IL-6 in MDD, which was largely explained by obesity (3). Although numerous correlative studies have found elevated IL-6 in depressed patients relative to controls, a recent meta-analysis using longitudinal studies showed that the weighted-mean effect size for IL-6 was relatively small (unadjusted  $r = 0.045$ ,  $p = 0.007$ ; adjusted  $r = 0.097$ ,  $p = 0.06$ ) (4). In addition, elevated circulating IL-6 has been reported in several animal models of depression in which chronic mild stress or learned helplessness was applied to establish depressive-like symptoms (5). Taken together, studies in humans and animal models have provided strong evidence that inflammation is altered and IL-6 may be elevated in a subset of depressed patients or animals that are exposed to stress. However, the role of elevated IL-6 levels in depressed patients may need to be interpreted in a sex-specific manner as well as to include other confounding factors such as obesity. Thus, more rigorous and longitudinal studies in humans are needed to establish the sex–IL-6 relationship in depressed patients.

Breidenstein et al. raise an important issue regarding the relationship between gonadal hormones and inflammation that referred to a paper focusing on an immune system-related disease, i.e., rheumatoid arthritis, instead of the observations in depression (6). Indeed, recent studies indicate that the relationship between gonadal hormones and cytokines is complicated and their relationship varies from disease to disease. For example, several clinical and experimental studies have showed a gender dimorphism of the immune and organ responsiveness in the susceptibility to and morbidity from shock, trauma, and sepsis. Specifically, studies indicate that androgens are responsible for the immunodepression after trauma hemorrhage in males. By contrast, female sex steroids seem to exhibit immunoprotective properties after trauma (7). Furthermore, postmenopausal women have higher basal levels of IL-6 and a larger IL-6 stress response than age-matched men in response to

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acute stress (8). Although gonadal hormones are not in the scope of our current study, we would like to include gonadal hormone measurements in future studies to explore its complicated roles in depression and to determine if those effects are sex and age dependent.

Another issue raised by Breidenstein et al. is the role of psychosocial stress as a possible mediator in the relationship between inflammation and MDD, as well as the hypothalamic–pituitary–adrenal (HPA) axis in the pathogenesis of MDD. Two other studies from our group have suggested that childhood maltreatment is positively correlated with elevated inflammatory markers (9, 10). Our observations were consistent with Mondelli et al.'s reports (11) that psychosocial stress was one of the main factors determining neuroinflammation. Stress is a major risk factor for depression and the HPA axis mediates stress response. Altered HPA axis activity in depressed patients has been associated with both childhood maltreatment and acute stress responses. One of our prior studies suggests that individuals with childhood maltreatment showed suppressed HPA axis activity measured by cortisol awakening curve; this effect was independent of depression (9). Our observations were supported by other research groups who found early life adverse experiences were associated with decreased salivary cortisol responses to awakening (12). Both Holsboer et al. and Gold et al. reported that depressed women with and without childhood trauma exhibited blunted adrenocorticotrophic hormone response to corticotropin-releasing factor (13, 14). By contrast, Heim et al. reported that women with a history of childhood abuse with and without current major depression exhibited increased adrenocorticotrophic hormone but normal cortisol responses to stress compared with controls (15). Taken together,

an interconnected relationship between inflammation, HPA axis, and depression might be present, which definitely warrants further investigation in humans and in animal models.

To summarize, our study demonstrated that inflammation is related to depression; however, the association is sex specific. Understanding the influence of inflammation on women's mental health may help enhance our understanding of the sex differences in depression as well as help clinicians choose effective antidepressants in the future. More longitudinal studies are needed to answer the causal relationship between inflammation and MDD. Currently, more studies are ongoing in our department to understand the link between sex, depression, inflammation, and the HPA axis. We thank Dr. Breidenstein and group for the thoughtful comments, which focus our attention to be careful as we describe and interpret our outcome measures, and helpful to design future studies.

## AUTHOR CONTRIBUTIONS

BB and LL wrote, edited, and approved the submission. RS and EA edited and approved the submission.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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