Psychological Medicine

cambridge.org/psm

Correspondence

Cite this article: Arnone D (2023). Increased levels of intestinal-type fatty acid-binding protein (I-FABP) in mood disorders. *Psychological Medicine* **53**, 4827–4828. https://doi.org/10.1017/S0033291722001970

Received: 22 May 2022
Revised: 9 June 2022
Accepted: 12 June 2022
First published online: 21 July 2022

Key words:
Bipolar disorder; I-FABP; intestinal-type fatty acid-binding protein; intestine permeability; major depression; mood disorders; zonulin

Author for correspondence:
Danilo Arnone,
E-mail: danilo.arnone@kcl.ac.uk

Increased levels of intestinal-type fatty acid-binding protein (I-FABP) in mood disorders

Danilo Arnone[1,2]

[1]Centre for Affective Disorders, Psychological Medicine, Institute of Psychiatry, Psychology and Neurosciences, King's College London, London, UK and [2]Department of Psychiatry, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates

I read the recent review published by Borkent et al. with great interest (Borkent, Ioannou, Laman, Haarman, & Sommer, 2022). The authors provide an excellent description of the role of the gut microbiome in three major psychiatric disorders including major depression, bipolar disorder and schizophrenia and present putative gut–brain mechanisms involved in these conditions.

Findings from this work support the notion that the gut–brain axis could contribute to mood disorders and schizophrenia, whilst interventions focused on ameliorating gut microbiota could bring significant health benefits to patients. The authors also report on the contradictory nature of some of the results across the studies, which impedes reaching definitive conclusions regarding the presence and direction of some of the effects, such for example in the case of gut permeability.

To better understand and substantiate empirical evidence of the role of gastrointestinal permeability, it was possible to combine in a meta-analysis the studies listed by Borkent et al. when a minimum of three datasets were available to calculate a meaningful summary effect size (Alvarez-Mon et al., 2019; Kılıç, Işık, Demirdaş, Doğuç, & Bozkurt, 2020; Ohlsson et al., 2019; Stevens et al., 2018). These included studies that evaluated measurements of peripheral levels of zonulin and intestinal-type fatty acid-binding protein (I-FABP), primarily in patients with major depression and bipolar disorder. Random-effect meta-analyses were carried out with STATA 17 (Stata Corp, College Station, Texas, USA) based on the combination of median/mean peripheral levels of zonulin and I-FABP and interquartile ranges/standard deviation across the studies as a measure of statistical dispersion for cases and healthy controls. As previously described, standardised mean difference (S.M.D.) and confidence interval (CI) for each analysis were calculated by using Cohen's d statistic, level of heterogeneity with the Q test and I^2, and publication bias by using the Egger's test with an overall significance level set at $p \leqslant 0.05$ (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012).

Results by using this approach (see Fig. 1) suggest that the overall size of the contribution of zonulin to mood disorders is likely to be in the small range with non-significant differences in peripheral levels between patients and controls (S.M.D.: 0.31; CI: −0.70–1.32), a high level of heterogeneity in the analysis due to unaccounted factors ($I^2 = 92.8\%$, $p \leqslant 0.001$) and absence of publication bias ($p = 0.98$).

The analysis of I-FABP on the contrary indicated a significant increase in the peripheral level of I-FABP in mood disorders compared to healthy controls (S.M.D.: 0.58; CI: 0.09–1.07) in the absence of significant heterogeneity ($I^2 = 57.4\%$, $p = 0.071$) and publication bias ($p = 0.57$). The overall size of this effect appeared more substantial compared to zonulin and in the medium range.

It is important to highlight that the patients included in the primary studies were overall quite heterogeneous with recurrent forms of illness and often received medication. Furthermore, the studies were not controlled, used different methodological approaches and were small in their overall number and size. Hence, it is important to exercise caution when interpreting the results of these meta-analyses and consider the possibility of the contribution of confounders and of small studies bias to the measured effects, even in the absence of publication bias (Arnone et al., 2012).

In conclusion there is evidence that increased peripheral levels of I-FABP might contribute to gastrointestinal permeability in mood disorders. Although recruitment in mood disorders can be challenging especially in case of highly selected samples (Wise et al., 2016), it is essential to design larger controlled studies to sufficiently power statistical analyses to confirm or exclude the role of possible markers of gastrointestinal permeability. Investigating the relationship between the gut–brain axis and other peripheral and brain-based candidate biomarkers involved in mood disorders could also bring useful insights for the development of novel

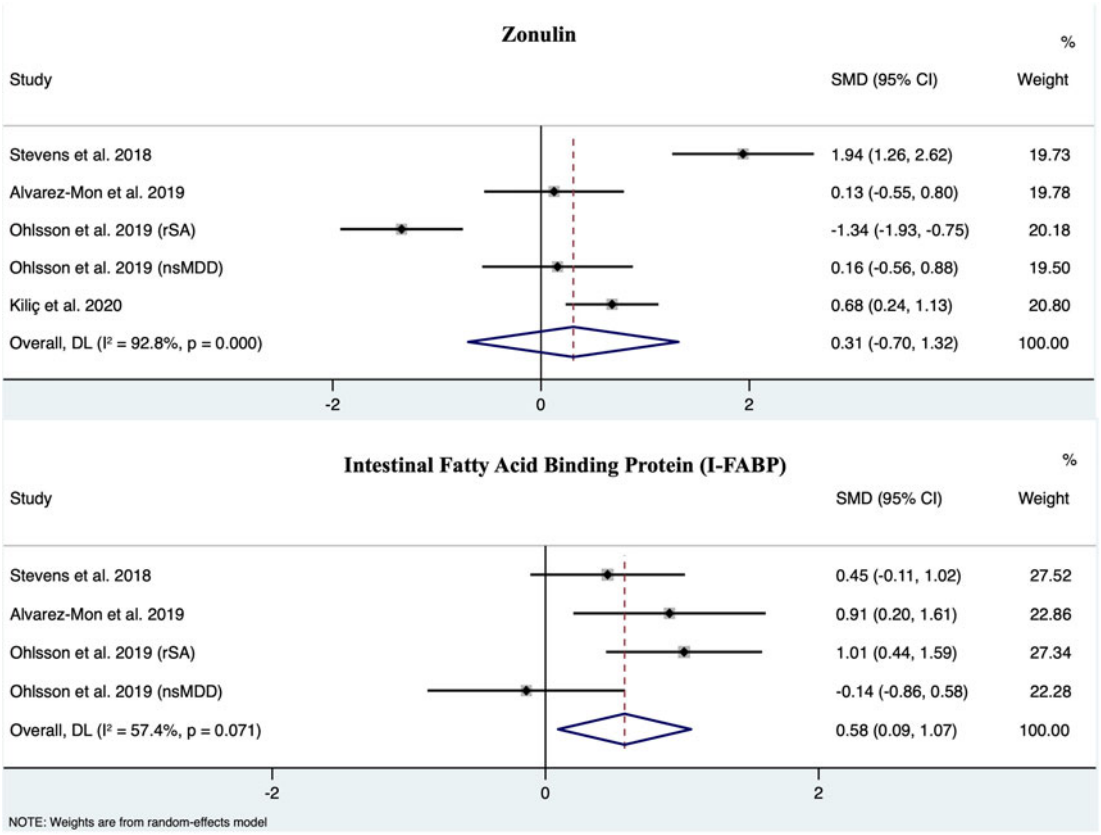

Fig. 1. Forest plots representing comparisons of peripheral levels of zonulin and intestinal fatty acid binding protein (I-FABP) between patients with mood disorders and healthy controls. The study by Ohlsson et al. (2019) included patients with a recent suicide attempt (rSA) and non-suicidal patients with major depression (nsMDD).

treatments, especially if the investigations were conducted in relation to treatment effects (Cheng et al., 2017; Dutta et al., 2019).

Conflict of interest. None.

References

Alvarez-Mon, M. A., Gómez, A. M., Orozco, A., Lahera, G., Sosa, M. D., Diaz, D., … Alvarez-Mon, M. (2019). Abnormal distribution and function of circulating monocytes and enhanced bacterial translocation in major depressive disorder. *Frontiers in Psychiatry*, *10*, 812. https://doi.org/10.3389/fpsyt.2019.00812.

Arnone, D., McIntosh, A. M., Ebmeier, K. P., Munafò, M. R., & Anderson, I. M. (2012). Magnetic resonance imaging studies in unipolar depression: Systematic review and meta-regression analyses. *European Neuropsychopharmacology*, *22* (1), 1–16. https://doi.org/10.1016/j.euroneuro.2011.05.003.

Borkent, J., Ioannou, M., Laman, J. D., Haarman, B. C. M., & Sommer, I. E. C. (2022). Role of the gut microbiome in three major psychiatric disorders. *Psychological Medicine*, *52*(7), 1222–1242. https://doi.org/10.1017/S0033291722000897.

Cheng, Y., Xu, J., Arnone, D., Nie, B., Yu, H., Jiang, H., … Xu, X. (2017). Resting-state brain alteration after a single dose of SSRI administration predicts 8-week remission of patients with major depressive disorder. *Psychological Medicine*, *47*(3), 438–450. https://doi.org/10.1017/S0033291716002440.

Dutta, A., McKie, S., Downey, D., Thomas, E., Juhasz, G., Arnone, D., … Anderson, I. M. (2019). Regional default mode network connectivity in major depressive disorder: Modulation by acute intravenous citalopram. *Translational Psychiatry*, *9*(1), 116. https://doi.org/10.1038/s41398-019-0447-0.

Kılıç, F., Işık, Ü., Demirdaş, A., Doğuç, D. K., & Bozkurt, M. (2020). Serum zonulin and claudin-5 levels in patients with bipolar disorder. *Journal of Affective Disorders*, *266*, 37–42. https://doi.org/10.1016/j.jad.2020.01.117.

Ohlsson, L., Gustafsson, A., Lavant, E., Suneson, K., Brundin, L., Westrin, Å., … Lindqvist, D. (2019). Leaky gut biomarkers in depression and suicidal behavior. *Acta Psychiatrica Scandinavica*, *139*(2), 185–193. https://doi.org/10.1111/acps.12978.

Stevens, B. R., Goel, R., Seungbum, K., Richards, E. M., Holbert, R. C., Pepine, C. J., & Raizada, M. K. (2018). Increased human intestinal barrier permeability plasma biomarkers zonulin and FABP2 correlated with plasma LPS and altered gut microbiome in anxiety or depression. *Gut*, *67*(8), 1555.2-1557. https://doi.org/10.1136/gutjnl-2017-314759.

Wise, T., Arnone, D., Marwood, L., Zahn, R., Lythe, K. E., & Young, A. H. (2016). Recruiting for research studies using online public advertisements: Examples from research in affective disorders. *Neuropsychiatric Disease and Treatment*, *12*, 279–285. https://doi.org/10.2147/NDT.S90941.

https://doi.org/10.1017/S0033291722001970 Published online by Cambridge University Press