Reviewer's report

Title: Are self-reported gastrointestinal symptoms among older adults associated with increased intestinal permeability and psychological distress?

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Reviewer: Gerard Clarke

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Healthy aging is an important topic and further information on the links between gastrointestinal symptoms, intestinal barrier function and psychological distress. This study explores these factors in 3 groups of older adults. The main finding of the study is that older adults with more gastrointestinal symptoms displayed significantly higher levels of both zonulin and psychological distress. A PCA analysis revealed a separation between senior orienteering athletes and older adults with gastrointestinal symptoms on the basis of these differences. This is an interesting, well conducted and timely study that reports a number of interesting observations. I have the following queries and recommendations:

(1) The authors are careful in the manuscript to indicate that zonulin is an indirect marker of intestinal permeability. However, there is still some debate regarding the precise meaning of circulating zonulin since it may also be derived from sources other than the gut (e.g. see paper from Ohlsson et al., 2017 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5372598/#B2-ijms-18-00582). The discussion would therefore benefit from including this and other caveats surrounding this marker, particularly in the context of the increased cardiovascular disease in the older adults with GI symptoms. Can the authors also include the limit of detection and quantification and the intra-assay variability for the kit they used?

(2) If we accept the bonafides of zonulin as a readout for intestinal permeability, the fact that CRP levels are not elevated despite increased zonulin levels may indicate that the alteration noted is not sufficient to induce the immune activation necessary to back up aspects of the rationale for the study. If there are no inflammatory consequences of increased intestinal
permeability, is it a valid therapeutic target or are we just seeing the normal physiological range of intestinal permeability in old age? As the authors themselves note, cytokine levels would be beneficial here and add value to the study. Would it be possible to add this analysis to the current study?

(3) The authors have also been careful to link the HADS score to psychological distress apart from one instance in the results section on page 8 where they suggest that depression is higher in older adults with GI symptoms. This should be changed to indicate probable depression or alternative preferred description in line with the limited capacity of the HADS as a diagnostic tool for depression.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Yes

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