Reviewer’s report

Title: The relation between celiac disease, nonceliac gluten sensitivity and irritable bowel syndrome

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Reviewer: Imran Aziz

Reviewer’s report:

1. The paragraph on IBS & CD connection. The authors report that the prevalence of AGA in IBS has varied from 5-17% to as high as 50%....the 50% had been shown in NCGS patients, so that should be mentioned. Also they should mention when discussing NCGS and IBS that in patients with NCGS who are AGA positive, a GFD led to clinical and serological remission thereby supporting its diagnosis (Effect of gluten free diet on immune response to gliadin in patients with non-celiac gluten sensitivity. Caio G, Volta U, Tovoli F, De Giorgio R. BMC Gastroenterol. 2014 Feb 13;14:26)

2. The paragraph on is gluten responsible for NCGS? I believe for reference 106 (Biesiekierski et al) the paragraph needs to be slightly rephrased in that particular section as it can be misinterpreted as it stands. It currently reads that that a placebo-controlled crossover study in IBS patients on a GFD found symptom improvement with a low FODMAP...This low FODMAP part was not DBPC but open-label dietary intervention as a run-in period. The DBPC crossover was commenced later with low-dose gluten, high-dose gluten, placebo.

3. The paragraph on is gluten responsible for NCGS? The authors mention for reference 106 that following a low FODMAP diet in NCGS there was symptom improvement, and the re-introduction of low-dose/high-dose gluten/placebo did not worsen symptoms. However, the study reported did show a worsening of symptoms in all 3 arms but no difference between them, suggesting a nocebo effect. Hence I think the authors would be better re-phrasing this sentence and stating that there was no specific or dose-dependent effect of gluten. Please see comment 2.

4. The paragraph on is gluten responsible for NCGS? The authors can also discuss other non-gluten constituents that may trigger symptoms, such as the new players in amylase-trypsin inhibitors. This work can be found on Pubmed under Schuppan D 2015, Junker Y 2012

5. The abstract and manuscript regularly mention the word “compelling” evidence for FODMAPS in NCGS. This appears too strong a word as no DBPC study with FODMAPs in NCGS has yet been done to my knowledge. The effects to a low-FODMAP in NCGS have been shown in an open-label manner, and the DBPC effects of a FODMAP in IBS patients. So maybe leave as “evidence” only given that it is still an area confounded by uncertainty with FODMAPs, gluten, amylase-trypsin inhibitors.
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'