

March 29, 2015

Dear Editor,

Please find herewith enclosed the edited manuscript in Word format (file name: 16570-review.doc).

Title: Non-celiac gluten sensitivity: time for sifting the grain

Authors: Luca Elli, Leda Roncoroni, Maria Teresa Bartdella

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16570

The manuscript has been improved according to the reviewers' suggestions:

1 Format has been updated

2 Revision has been carried out according to the reviewers' suggestions.

Reviewer 1

Comment	Answer
There is absolutely no mention in the whole paper of the possible role of FODMAP sensitivity. As the authors certainly know, the paper by Biesiekierski et al. published in August 2013 represented a real paradigm shift in our thinking about NCGS, and one cannot avoid dealing with its conclusions. Thus, a proper acknowledgment and evaluation of that study in the context of NCGS is paramount and must be included.	As suggested, the article has been cited and described in the manuscript.
The statement about prevalence "Gluten-related disorders.... prevalence, increasing in the recent decades, ranges from 4% to 6% in Western countries" is unfounded. In fact, the authors provide no references for this, and this is not surprising, since one cannot estimate the prevalence of a disorder for which there is no accepted definition.	The statement has been rephrased.
Minor concerns	All minor concerns have been addressed.

Reviewer 2

Comment	Answer
the English language is slightly defective and a couple of Tables and/or a Figure might help the readers in following the article, thus it needs major modification.	The manuscript has been reviewed by an English mother tongue speaker.
The title gives the reader the impression that in the manuscript there is a real and novel explanation of gluten-related disorders, whilst the authors simply support the widely accepted criteria for diagnosis and	The title has been changed.

the current theories on the pathomechanisms of non-celiac gluten-sensitivity.	
First of all, a couple of Tables and/or a Figure possibly explaining the different clinical picture or mechanisms leading to gluten-related disorders are strictly required.	Accordingly, Table 1 has been included.
The possibility that this condition is due to wheat-sensitivity instead of gluten-sensitivity should be discussed.	This aspect has been discussed in the second paragraph.
More detail is required in order to explain the putative pathomechanisms leading to this disorder, with a mention to low-fermentable, poorly-absorbed, short-chain carbohydrates and polyols (so-called FODMAPs).	A section in the second paragraph has been added.
A mention about some diagnostic tests, such as the search for the anti-gliadin class G antibody, the cytofluorimetric assay revealing in vitro basophil activation by food antigens, and the frequent presence of eosinophils in the intestinal mucosa biopsies should be added in the text. ? Finally, the financial incentives for companies promoting gluten-free products represent an issue that deserves some discussion..	A paragraph dealing with the suggested topics has been added (page 9).
References: the following two important references should be inserted and discussed: - Biesiekirski JR, Peters SL, Newnham ED, Rosella O, Muir JG, Gibson PR. No effects of gluten in patients with self-reported non-celiac gluten sensitivity following dietary reduction of low-fermentable, poorly absorbed, short-chain carbohydrates. Gastroenterology 2013; 145:320–328. - Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology 2014; 146:67-75.	References have been inserted.

Reviewer 3

a nice, timely, and condensed manuscript reviewing the hot topic of non-celiac gluten sensitivity. I do not have major criticisms concerning the ms; however, the authors should describe a little more in-depth the possible histological findings of NCGS, focusing on the differences (if any) with celiac disease. Moreover, the authors could recognize that, by a histological point of view, this entity could be included in those encompassing the so-called microscopic enteritis.	We are grateful for the positive comments from Reviewer 3. Histology pictures and the possible presence of a microscopic enteritis, as described in the Bucarest consensus (now in the reference), has been inserted at page 9
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Some histological representative pictures are needed to stress the above points	
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3 Editor corrections have been included the audio core tip

Thank you again for publishing this manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'L. Elli', is positioned below the text 'Sincerely yours,'.

Luca Elli MD, PhD

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