Author's response to reviews

Title: A large nationwide population-based case-control study of the association between intussusception and later celiac disease

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Author's response to reviews: see over
We would like to thank the journal for allowing us to revise our paper. We have attached our response to the peer reviewers. The requested changes have improved the paper and we hope that the revised paper is acceptable for publication.

**Reviewer 1: Kalle Kurppa**

**Reviewer:** A study by Ludvigsson et al. investigated the possible association of intussusception and celiac disease. The text is clear and well-written. There are some (mainly minor) issues that should be clarified.

*Level of interest:* An article whose findings are important to those with closely related research interests

*Quality of written English:* Acceptable

**Reply:** We thank Dr Kurppa for his encouraging remarks

**Minor Essential Revisions**

**Reviewer:** 1. Introduction, paragraph 2, line 3. I recommend that world “small-bowel mucosal” or “intestinal” is added before “inflammation”.

**Reply:** Done

**Reviewer:** 2. Methods, Celiac disease, line 9. The authors should clarify what means “positive for CD serology”? Positive to EmA, TG2-ab or antigliadin antibodies? The latter are well-known of their poor specificity

**Reply:** We agree that antigliadin-antibodies have a poorer specificity than Ema or TG2. The sentence has been re-written and now reads (new words in italics):

“We did not require patients to have a positive antibodies against tissue transglutaminase (TTG), endomysium (EMA), or gliadin for a CD diagnosis, but in a random subset of patients with VA and available data on CD serology about 88% were positive for either of these antibodies at the time of biopsy”

**Reviewer:** 3. Methods, Post-hoc analysis, last two lines. I wonder if it really was necessary to perform post-hoc power calculation, as the usefulness of such retrospective analysis is controversial

**Reply:** In the revised paper we have omitted the following text:

“A post-hoc power calculation (significance level 0.05) showed that this study had 80% power to detect an OR of 1.67.”

**Reviewer:** 4. Results, Subanalyses, paragraph 2. I do not particularly like this paragraph;
there were really no statistical differences. In my opinion the paragraph should be reformulated or omitted. Also, it is possible that the “especially high” OR before 1990 is more likely caused by surveillance bias.

Reply: Regarding the 2nd paragraph in the discussion we have omitted some of the text:

“Restricting our exposure to intussusception with either radiological intervention or surgery, the OR for future CD was 1.27 (95%CI=0.60-2.69). The OR for CD was especially high in patients with intussusception and intervention before 1990 (Table III), although it failed to attain statistical significance, partly due to lack of statistical power in this subanalysis (Table III).”

Reviewer: 5. Discussion, paragraph 2, last four lines. I believe that the authors may read the full article of Reilly et al. (online first version) from the journals’ website.

Reply: We thank the reader for drawing our attention to the publication of the paper. We have read the full paper online and have cited it accordingly.

Old version of our manuscript:
“The discrepancy between our study and that of Reilly et al[14] may be due to different source populations (nationwide approach vs. tertiary institution), or different numbers of patients (29,096 vs. 252). Since Reilly et al did not present any 95%CI for their findings in their abstract (that we could access) it is possible that the suggested association between intussusception and CD in their study did not attain statistical significance.”

Revised version
“Reilly et al reported that 1.2% of their celiac children had experienced a known intussusception[Reilly, 2013, 22832512] but since the authors do not present any statistical comparison with the general population this may or may not represent an increase. Our study differs from that of Reilly et al [Reilly, 2013, 22832512] by different source populations (nationwide approach vs. tertiary institution), and larger number of celiac patients (29,096 vs. 254).”

Reviewer: 6. Discussion, last paragraph. Maybe it should be addressed that the modern rotavirus vaccine is not associated with an increased risk of intussusception.

Reply: We agree. We have added the italicized text:
“Early versions of Rotavirus immunizations….”

Reviewer: 7. Table 1. Since the number of the subjects is shown, it should expressed with “n” (= Age 0-19, n (%))

Reply: Done

Reviewer: 8. Additional File 1. In my opinion this table is unnecessary and could be omitted.

Reply: This file has been omitted and we do not refer to it in the revised paper.
Reviewer 2: Kamran Rostami

Reviewer: In study by Ludvigsson et al., retrospectively investigated the possible correlation between intussusception and later biopsy-verified celiac disease in a large nationwide case-control study in Swedish population. The authors used the available database which was published before. The paper is well written and statistically analyzed very well.

Reply: We would like to thank the reviewer for his kind comments.

Reviewer: I’m not entirely convinced that large database can allow us to analyse some similar variables accurately. This might be the reason that the authors did not find an association between intussusception and CD.

Reply: We agree that large databases have inherent weaknesses (which we discuss in greater detail in the revised manuscript). However, we feel that the consistently neutral relationship seen between prior intussusception and later CD is plausible, and supported by the findings of a number of sensitivity analyses (e.g. examining the association between CD and two earlier records of intussusception). In Sweden, intussusception is diagnosed in hospital, and hence our study based on nationwide data on inpatient and hospital-based outpatient data is likely to detect intussusception.

However, due to limited statistical power, despite a large number of patients, we cannot rule out a small risk increased (the upper 95% CI was 1.67). We have commented on that in the discussion, and added the following lines:

“Finally, despite the large number of patients, we cannot rule out a weak association between intussusception and later CD since the upper 95% CI reached 1.67.”

Reviewer: The authors did not talk much about the limitation and the weakness of this study that I suggest to be added in discussion.

Reply: In the original study we mentioned the following limitations and weaknesses in the discussion:

1. We did not screen individuals with intussusception for CD (intussusception □ CD)
2. We did not have access to radiological data such as computed tomography and could therefore not confirm the intussusception diagnosis.
3. Neither did we screen individuals with CD for intussusception (CD □ intussusception)
4. We lacked data on Rota virus immunization (which has been linked to intussusception, while Rotavirus infection has been suggested as a risk factor for CD).

We believe this is a fair list of limitations. To this list we have now added a fifth limitation about limited power (5. Finally, despite the large number of patients, we cannot rule out a
A weak association between intussusception and later CD since the upper 95% CI reached 1.67.

We hope Dr Rostami and the editors now feel that our revised paper gives a balanced view of strengths and limitations, but if the editor requires us to list more limitations we will do so.

Reviewer: I also would like to see a better justification for exploring the association of celiac disease and intussusception in the introduction.

Reply: We state two reasons for exploring the association between CD and intussusception:

1. Undiagnosed CD is characterized by small bowel inflammation[5] and will sometimes cause small bowel wall edema,[6] intestinal lymph node swelling[7] and dysmotility[7] but also ulcers and strictures[8]. It has therefore been suggested that untreated CD may be linked to intussusception.

2. A number of case-reports and case series substantiate this hypothesis.[9-14] .....

However, due to small numbers or lack of controls, none of these studies have estimated relative risks or odds ratios (ORs).

Hence we feel that ongoing inflammation in CD (mostly before diagnosis, but to some extent also after diagnosis) may constitute an anatomical cause of intussusception. This has been suggested by a number of studies but none of them have had the power needed to confirm an association. Therefore we felt there was a need for our paper.

We feel these two arguments justify our study but should Dr Rostami and the editors request additional text to support the study this will be added; but in order to limit the length of the study we have not extended the introduction further.