Reviewer's report

Title: A step beyond the hygiene hypothesis – immune-mediated classes determined in a population based study

Version: 0 Date: 11 Jan 2019

Reviewer: Mikael Knip

Reviewer's report:

This is an interesting paper setting out to (i) to develop an integrated approach to immune system programming by classifying comorbidity patterns of childhood infections and atopic diseases together with adverse childhood events using the latent class analysis (LCA) as the statistical model, and (ii) to characterize the immune-mediated classes established based on white blood cell (WBC) counts and inflammatory markers as well as their association patterns with other groups of diseases and sociodemographic variables. The database came from CoLaus|PsyCoLaus, a large epidemiological study in Switzerland, in which 6734 35-75-year-old subjects took part in the baseline examination in 2003-2006 and 5064 in the second survey in 2009-2012. The authors report that sharing a specific immune-mediated class different from the neutral class [resilient, atopic, mixed or adverse childhood experiences (ACE class)] modifies the risk for most chronic inflammatory diseases and neurodevelopmental / mental disorders. In particular, the mixed class emerged as a new and unanticipated phenomenon. The LCA analysis was based on infectious childhood diseases, atopic diseases and childhood adversities and came up with five classes.

Comments:

1. What is the evidence for the statement on page 25 that immune-mediated classes consolidate during the first years of life? What is the impact later immunological insults?

3. All inflammatory markers analyzed are proinflammatory measures, and no anti-inflammatory markers. e.g. IL-10 have been analyzed. The authors had no possibility to influence the selection of immunological markers in the current setting, but in the Discussion section it would be appropriate to discuss the selection of immunological markers and its potential impact on the outcome of the LCA.

4. The section of statistical analysis is not very transparent, and therefore this reviewer proposes that an expert on the LCA analysis should review that part.
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.

Not applicable

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

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

**Quality of written English**
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