Reviewer's report

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

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Reviewer: Petra Ina Pfefferle

Reviewer's report:

The report submitted by Ajdacic-Gross et al. presents a novel comprehensive approach to better characterize the complex network of immune programming in childhood in the context of infectious, atopic and mood disorders based on a latent class analysis (LCA) in males and females, separately. Data were obtained from CoLaus/PsyColaus a population based study conducted in Switzerland. LCA revealed five major classes corresponding to a resilient, neutral, atopic, infectious/atopic and an ACE (adverse childhood experiences) type.

General comment.

LCA emerged within the last years as a potent statistical method to characterize clinically relevant pattern in large study populations. LCA thereby serves as tool to better understand the so far latent network between basic physiological pathways and clinical signs, somatic as well as psychiatric manifestations. The report is thereby timely and ambitioned. Based on the postulates of the hygiene hypothesis, this report aims to contribute to the ongoing discussion of common roots in somatic and psychiatric disorders mediated by the immune system and stimulated by exogenous exposures such as ACE and infections. It is not surprising that the LCA confirms the currently mostly accepted opinion of a relationship between early immune programming and later disease development. Moreover, the immune mediated classes identified and comprehensively discussed in this report fitting well to the principles of the hygiene hypothesis and subline relationship between chronic inflammatory processes and mood disorders and, vice versa, resilience in association with balanced immune response.

In sum, as stated by the authors, the LCA serves as a pattern recognition tool based on the reduction of dimension and thereby might simplify reality. Nevertheless, this report contributes new evidence to the field of early immune programming and disease development.

Special comments:

1. The report is fluently written, the introduction allocates the basic hypothesis and the aim of the study vividly. In the method section the authors concisely describe both questionnaires and statistical operations used in this study. The main part of the results
are presented adequately, namely, the last paragraph should not be presented in bullets and in more detail as this part is the clinically the most relevant aspect. The figures should be edited and improved in quality. The discussion section highlights the specific attributes of the five classes precisely and well substantiated by literature references. I highly appreciate and support the rationale between the positive association ulcer, H. pylori -infection status and the "Old friends" hypothesis and the decreased susceptibility for mental disorders in the resilient class.

2. The authors should give some brief information about the CoLaus-study, e.g. the survey is based on instruments in French language. Is the study also conducted in German, Italian and/or Rhaeto-Romantic parts?

3. Were somatic disorders surveyed by explicitly questioning for doctor's diagnosis or just self-reported?

4. The authors report to assess hsCrP. Why not CrP? As nearly every subject displays low levels of CRP without any signs of inflammation the assessment of high-sensitive CrP is questionable in the clinical and epidemiological context.

5. WBC strongly depends on some life-style factors that might act as confounders such as smoking. Were models based on WBC adjusted for common confounders?

**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.

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