Reviewer’s report

Title: Familial autoimmunity: a meta-analysis

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Reviewer: Pascal Meier

Reviewer’s report:

The authors report on a systematic review and meta-analysis on familial aggregation of autoimmunity in five major autoimmune disease groups (rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disease (AITD), multiple sclerosis and type 1 diabetes mellitus).

They included 47 studies and found significant familial aggregation regarding the specific disease but also regarding autoimmune disease in general with odds ratios between 1.77 to 1.96.

The authors conclude that familial autoimmunity is a consistent condition observed in the major ADs.

This is an interesting topic and the authors have put in a lot of work here.

Major compulsory revisions:

1. Did you consider unpublished data? And if so, please label them accordingly.

2. The conclusion needs to be adjusted "It's study will help to decipher the common mechanisms of ADs.". It is not clear what the authors mean. The conclusion should be based on the results found in this paper. Did the authors mean that THIS study will help to decipher the common mechanisms of AD? I don’t think that this is the case.

3. The abstract results should clearly show the likelihood (odds ratios) for the familial aggregation of the specific disease (for example, how much more likely is it to have MS if another family member has MS) and the odds ratios for the familial aggregation of autoimmune disease in general (how much more likely is it to have an autoimmune disease if another family member has an autoimmune disease). These 2 aspects should be the backbone of this paper, and also be mentioned in the results section of the abstract (briefly).

4. Statistics: The transformation of effect sizes is explained in a rather lengthy but still not sufficiently clear way. Was the aim to finally have all effect sizes as odds ratios? Please state how you transformed risk ratios to odds ratios, etc.

5. Statistics: You state that "Additional meta-analyses were done for studies with complex data structure and noncumulative results since the information for the different effects was not totally independent." This needs further explanation. What do you mean with complex
data, and what do you mean with non-cumulative results? What kind of meta-analyses did you do in this situation?

6. Statistics: Fixed and random effects models were both used. I would prefer to use random effects models in general, unless we can assume that there is neglectable between study heterogeneity which is rarely the case. You state that "The selection of the computational model was done based on the expectation that the studies shared a common effect size." This sentence should be re-written or deleted, it is not very clear what it means here. A common effect size is assumed in a fixed effects model. I am not sure whether this is what you wanted to explain? Again, in general I would prefer random effects models.

7. The method used for the fixed or random effects model needs to be mentioned (for example, DerSimmonian&Laird approach?)

8. In the abstract, you use odds ratios, in the result section, there are risk ratios. This is confusing. I would prefer consistent effect size measures throughout. If there were also case-control studies included and not only prospective studies as described in the method section, risk ratio is not appropriate effect size measures.

9. The paper evolved from a narrative review which influenced its current shape. Nevertheless, the manuscript should be written more concisely and more clearly. The introduction should be shorter, the results section should focus more on the meta-analysis.

10. Table 2: number of studies is smaller than number of subgroups. What was the unit of analysis, the subgroups or the entire studies?

11. Table 2: Subject "FDR" versus "proband" is confusing. The proband is the index patient? The association is between index patient and his first degree relatives FDR? What does "subject" mean here?

12. Table 2: what exactly does table 2 show? The association between a specific disease and any autoimmune disease in a FDR?

13. Table 3: worldwide prevalence of autoimmune disease. This is very important and interesting information but we have to make sure it is accurate. Worldwide would mean that the studies include a very broad range of countries, we know that AID vary considerably among different countries, for example MS prevalence with its north-south decrease etc. Second, you calculated a mean value based on ranges. This may be possible if you had confidence intervals, but for a range, this seems a little questionable, without any information on data distribution.

14. Table 3: the statistical section does not describe how you calculated the pooled worldwide prevalence values.

15. Table 4: This is very difficult to read and understand. The idea of a meta-analysis is to pool, summarise and digest current evidence. What do these numbers mean? You state that these are aggregations lambda. What does that
mean exactly? The reader needs to see, what the likelyhood of first degree relative is, if the index patient has a certain autoimmune disease.

16. It is not clear how many patients were included in these studies.

17. Forest plots: for figure 5 and 6 for example, it seems as if you have used subgroups as the unit of analysis. I am not sure why occasionally two subgroups have the exactly same characteristiscs (same Proband disesae and same disease in FDR). What is the difference between these subgroups?

18. A table with baseline characteristics of the individual studies (size, setting, design such as case-control or cohort study, etc) would help to get a better understanding and overview for the reader.

Minor discretionary revisions:

1. Abstract: multiple sclerosis (S), I would prefer to use MS as abbreviation for MS which makes more sense and is used in general.

2. Page 19: be consistent with decimal marker/separator, sometimes you use a comma, sometimes points ("a p-value 2-tailed: 0,047",...)Since the manuscript is written in American English, it should be points (0.047).

Quality of written English: Needs some language corrections before being published

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

Declaration of competing interests:

None