Reviewers report

Title: Landmark models to define the age-adjusted risk of developing Stage 1 type 1 diabetes across childhood and adolescence

Version: 0 Date: 18 Feb 2019

Reviewer: Peter Colman

Reviewer's report:

Background

The rationale for the study is well explained - with the increase in testing for preclinical type 1 diabetes it is very important to have accurate information to provide participants about the diabetes risk that this signifies. However, it is also important to know at which age testing for autoantibodies should be undertaken and whether the risk of developing autoantibodies changes over time. This study makes important observations regarding these factors.

Methods

The studies are well described. There is reanalysis of long term antibody and diabetes development in these two related first degree relative antibody testing and follow up studies. The BABYDIET study included a dietary intervention but as this did not effect development of diabetes this has no bearing on the use of the data for this description of natural history. The antibodies used in the study are standard and well described. For comparative purposes it would be good to briefly document their performance in the DASP/IASP workshops over the long period of time of the study follow up.

Results

The number of children followed is substantial and allows the conclusions drawn

Is the data shown in figure 4 for single and multiple antibodies - presumably not. Can the results include information about single or multiple autoantibody status?

The figures (both in the paper and supplementary data) are clear and well explained.
Discussion

The discussion refers to 'risk of asymptomatic diabetes'. It would be better to use the new classification nomenclature and refer to this as Stage 1 type 1 diabetes.

On line 229 on page 11, there is discussion of the 'single-phase decay function' suggested to be related to the homogenous nature of the cohort 'which comprised children with a FDR and who were followed from birth'. This seems not to be factually correct. Weren't a large number recruited well after birth?

The description of the practical use of the data in counselling parents about the meaning of a negative antibody test at different ages is well described and useful.

The speculations regarding the implications of the observed exponential risk decay for pathogenesis are interesting but of course only speculation. The real value of the manuscript is in the practical information it supplies regarding antibody development risk according to age and the utility of this information for discussions with families and its implications for future public health prevention and intervention measures for type 1 diabetes.

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.

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

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I have collaborated with several of the authors on previous studies. Not this one.

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