Reviewer's report

Title: The risk of childhood autism among second-generation migrants in Finland: a case-control study

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Reviewer: Emma Weisblatt

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This is a generally succinct and well-written paper and a useful contribution to the literature on aetiology of autism. The methodology is sound, detailed and well-described. The statistical analysis is to the best of my knowledge a reasonable one. The study raises a number of questions about the relationship between migration and autism which require further studies to answer, and thus contributes usefully to the literature. My further comments are numbered according to the questions in the guidance for reviewers.

1. Minor Essential Revision: - There is a general issue with defining the question being asked, in this important and interesting area of genetics and environment and how they may interact and correlate.

Specifically, on p3 – para 1 – the authors make a correct statement that there is strong evidence of genetic contribution “to autism” – the authors need to cite the heritability of autism of approximately 90%, and make explicit that this means not that 90% of the risk “for autism” is genetic, nor that 90% of cases of autism have a specific genetic cause, but that 90% of the variation in risk for autism, in a given population, can be explained by genetic factors. This is an important distinction not often made clearly in the literature – the best source for general references on behavioural genetics and heritability is Plomin et al’s book “Behavioural Genetics”. This does of course leave an important 10% of variation in risk attributable to environmental factors in the widest sense (nutrition, toxins, social environment, brain injury, infection and so on). The authors list some potential environmental factors in the same paragraph and do mention gene-environment interaction though not the equally-important gene-environment correlation (where the environment correlates with genotype rather than the genotype actually affecting the effect of the environment – this is likely to be relevant to the immigrant population studied). They also correctly mention that parents from different places may differ in terms of genetic risk and/or environmental risk, but do not set out how this study might be measuring one or other of these risks.

Finally, they mention obstetric complications and parental age as environmental risk factors – while potentially true, there is also evidence that obstetric complications can often be attributed to an abnormal foetus, and parental age may of course affect genetic and epigenetic factors. The interaction and correlation of genetic factors and prenatal environment is particularly relevant and these two-way interactions between gene and environment are an exciting
area for study.

Overall the paper needs to present a more balanced analysis of both the literature and the data collected, as regards the importance of genetic and environmental factors, bearing in mind the very high heritability of autism. This is an Essential Revision, in that it does require some rewriting and additional referencing but does not reflect on the actual quality of the data and the methodology of the study. The paper does analyse in some detail potential nutritional or chemical environmental factors.

2. Minor Essential Revision: The methods are very appropriate, making use of an extensive national database, with large sample size and well-matched controls. The methods are sufficiently well-described for the purposes of this paper. The statistical analysis, using conditional logistic regression, is appropriate for this type of data, with four categories of family immigration status and two groups. More explanation is needed of the relevance of maternal and paternal age as covariates, and in particular the specific ways in which the ages of parents vary between the groups.

3. This study is part of a set of studies in Finland looking at risk factors for autism, and as such is based on a well-renowned and extensive data set so to the best of my knowledge the data are sound.

4. I cannot comment on data deposition but the data are clearly reported without risk of revealing personal details or identities of participants.

5. The discussion addresses the issues of both genetic and environmental factors (and indeed how some environmental factors such as toxins themselves can affect the germ line). The main finding is that having an immigrant mother, but not father, is associated with an increased risk of autism overall. However on regional analysis there is also an effect of fathers, when born in Vietnam or former Yugoslavia. The authors correctly conclude that there is no evidence that immigration from countries where dark skin is common is associated with risk for autism, thus providing no evidence for lack of vitamin D (or indeed genetic factors) being involved in increasing the risk of autism in the immigrant population in Finland. This study does not directly allow for the estimation of contribution of genetic and environmental factors, and this is mentioned by the authors. The discussion thus does adequately cover the main issues.

6. Minor Essential Revision (Limitations of Study). The authors mention a number of limitations. More emphasis should be placed on the fact that migratory populations are not representative random samples of the population of the country of origin, socio-economically or genetically (there is extensive literature on this issue in schizophrenia). More importantly, parents, perhaps mothers in particular, might migrate because of factors associated with increased risk of autism in their offspring – rather than the proposed explanation that environmental exposures in the country of origin are causing increased risk of autism in the population as a whole in that country of origin. This is very briefly alluded to in para 3, p 9, but needs expansion and clarification - this is a compulsory revision as it addresses a potential flaw in the underlying assumption of the study. The limitation that migrant status may affect the diagnostic process
is appropriately mentioned.
7. To the best of my knowledge the authors acknowledge previous work, both their own and others’.
8. The title and abstract are clear and convey the main points of the study
9. The writing is of very acceptable standard and clarity with no significant errors.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests.