Author's response to reviews

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

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Author's response to reviews: see over
Dear Editor,

We wish to thank the Editor for the possibility to revise the manuscript and the Reviewers for their valuable comments. We have done our best to answer the comments and to revise the manuscript accordingly. Changes to the revised manuscript are highlighted in bold font.

Yours sincerely,
Professor Andre Sourander, the corresponding author

Response to Reviewer 1:

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 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.

We agree with the Reviewer that more emphasis should be placed on genetic factors. The first paragraph of the Introduction has been revised and new references have been added (p.3):

“There is strong evidence of genetic contribution including both inherited factors and de novo mutations [1, 2]. Heritability rate as high as over 90% has been suggested for childhood autism [3]. This indicates that most of the variation in risk for childhood autism in the studied populations can be explained by genetic
factors, but it does not, however, give information on the genetic contribution to individual's phenotype [4]. Environmental factors, possibly through gene-environment interactions and correlations influence the risk of autism as well [2, 5, 6]."

We also agree that environmental factors may not be independent of genetic effects and have included the following addition (p.3):

"Examples of potential environmental risk factors are advanced parental age, obstetric complications, dietary factors, lack of vitamin D, and different mutagenic chemicals [5, 7, 8], which may also reflect underlying genetic effects and interaction or correlation with genetic 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.

More information on parental age has been included (p.6):

"Parental age was considered to be a possible confounder. Table 1 shows that the age of immigrant parents differs from Finnish parents especially in families with both an immigrant mother and father. Advanced parental age as a risk factor for childhood autism has been described in more detail in a previous study based on FIPS-A [28]."

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.

We thank the Reviewer for this important comment. It is true that this is a crucial limitation which was not
“Immigrant parents may not represent the general population of their country of origin for several reasons. The resources needed for employment-based migration in particular may only be available to a selected group of people. On the other hand, especially those refugees who are selected in the refugee quota often represent the most vulnerable parts of the population. Autistic traits in the family or other risk factors associated with autism in offspring may also influence the decision to migrate. Thus we cannot conclude if the increased risk of autism in certain immigrant populations could be explained by factors associated with their country of origin or by selective migration.”

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.

Response to Reviewer 2

Reviewer’s report:

This is a scientifically sound and well-written paper which applies a suitable statistical model to a large data set in order to address a valuable research question.

Discretionary Revisions

1. I believe that the method used to select potential confounders to be controlled for is not ideal. It is possible for the results to be affected by confounding even in cases in which there fails to be a significant relationship between the potential confounder and both the exposure and the outcome. I believe that the final results found would be much stronger if all the potential confounders were controlled for in the final model.

Including more covariates would decrease statistical power, because the included study population would be smaller due to missing data. This is problematic concerning the regional analysis in particular. That is why we prefer including only covariates that are significantly associated with both the exposure and the outcome.

However, we conducted the analysis shown in the Table 2 using all six covariates shown in the Table 1. The changes were very small. The adjusted odds ratios and their confidence intervals remained the same for those with an immigrant mother or an immigrant father (OR 1.8, 95% CI 1.2–2.7 and OR 1.3, 95% CI 0.8–2.1, respectively). For those with two immigrant parents the new adjusted odds ratio was 1.9 (95% CI 1.2–2.8) (compared with OR 1.8, 95% CI 1.2–2.7 when adjusted only for parental age).

2. The fact that socio-economic status has not been controlled for is of concern. The authors cite the unreliability of the data on SES for immigrants as the reason for this omission; however it would probably be better to control for this factor -- even using imperfect data -- than to omit this important potential confounder altogether. Where SES cannot be assigned reliably, it might be worth considering using multiple imputation.

The information we have in our dataset on maternal SES is categorized into four groups: upper white collar workers, lower white collar workers, blue collar workers and others. “Others” includes entrepreneurs and people outside the labor force such as students, housemothers and unemployed people. There are more mothers who belong to the group “others” among immigrants compared with Finnish mothers. In families with two immigrant parents most mothers belong to this group. This is because they are often outside the labor
force and information on their level of education is not always available. It is not easy to define if people in this group are of lower or higher SES than in the other three groups. Thus we think that maternal SES is not a useful covariate. No information is available on fathers’ SES. We know, however, that maternal SES is not associated with childhood autism in the FIPS-A birth cohort (unpublished data) and we agree with the Reviewer that this supports the idea that it is not a confounder.