PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	PREVALENCE OF AUTISM SPECTRUM DISORDERS IN AN ICELANDIC BIRTH COHORT
AUTHORS	Saemundsen, Evald; Magnússon, Páll; Georgsdóttir, Ingibjörg; Egilsson, Erlendur; Rafnsson, Vilhjálmur

VERSION 1 - REVIEW

REVIEWER	Emily Simonoff MD, FRCPsych Professor of Child and Adolescent Psychiatry King's College London, Institute of Psychiatry, UK I have no conflicts of interest
REVIEW RETURNED	06-Mar-2013

GENERAL COMMENTS	This paper reports on the prevalence of autism spectrum disorder (ASD) amongst children born between 1994 and 1998 in Iceland. The authors report a prevalence rate of 1.2% with just under half having an intellectual disability and 17% showing at least one medical condition. The method used for case identification is that of clinical diagnosis; the authors explained that all ASD diagnoses are made in two tertiary care centres in which research-standard evaluations are used as part of the clinical workup in the overwhelming majority of cases. The prevalence rate reported and associated characteristics are very much in line with those described in the majority of other recent prevalence studies and therefore are essentially a replication. However, this study wais carefully and robustly undertaken and the findings are an important substantiation of those already available in the literature. Furthermore, the authors were able to look specifically at differences between the populations who are diagnosed early (before 2005) and later (between 2005 and 2009) and this represents a useful insight. The paper is clearly written and the tables are well-presented. The background literature is well covered in a succinct manner. In general, the methods in the study are clearly described. However, I did have a few questions about new clarification. A bit more detail on the method of population definition and ascertainment would be helpful. It is implied that the population considered is a birth cohort of 1994-1998 and the denominator is calculated based on all children in Iceland born between those dates and still living in Iceland. More clear explication of this, however, would be helpful. Furthermore, a brief discussion regarding migration would be helpful. In the Discussion, the authors indicate that the change in prevalence rates between the two time periods assessed cannot be explained by migration differences but the evidence to substantiate this is not given. In terms of clinical characterizing the population, more details of the range of cognitive assessments used to determine an intellectual

	disability should be included. It would also be helpful, if possible, to have the age at which intellectual ability was determined; this is because measures in very young children can be inaccurate. Similarly a broader description of the standard assessments done to determine associated medical conditions would be helpful. In particular, the authors should describe the type of genetic testing that was undertaken and whether it was done in all cases or only in some. Did the clinics have an operational definition of epilepsy? If so, could the authors please give that. A minor comment, on page 12, line 30. The authors suggest that the prevalence of epilepsy is low in their population. However, as implied but not stated subsequently, the onset of epilepsy in autism is frequently reported to be in adolescence and nearly all of the children included in the present study may not have passed through the age of risk. This is because I am assuming that epilepsy is noted if recorded at the time of diagnostic assessment. If this was based on date collected subsequently as well, it would be helpful if the authors highlighted this.

REVIEWER	Mats Cederlund, M.D., Ph.D Child neurologist Sahlgrenska academy Gillberg Neuropsychiatric Centre Kungsgatan 12 411 19 Göteborg Sweden
REVIEW RETURNED	21-Apr-2013

THE STUDY	The abstract could be better defined an structured, and the same is true for article focus and key messages. There is no comment in the limitations of this study. In the present version I do not find the standard of English good enough for publication. Under Methods (page 6) there is a far to long and inadequate description of the health care/educational and social services in Iceland that needs major revision
RESULTS & CONCLUSIONS	The presentation is not entirely to my liking. It deals with the results, but at several instances it is a bit unfocused and it is then difficult to follow what the authors try to say. The Discussion section would have benefitted from a broader discussion about previous findings, not just a reference to the list of references.
REPORTING & ETHICS	There is no report on research ethics in the paper.
GENERAL COMMENTS	I find this an interesting study, however there are issues that need to be adressed. The paper needs a major revision and the standard of the English must be improved.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Emily Simonoff MD, FRCPsych
Professor of Child and Adolescent Psychiatry
King's College London, Institute of Psychiatry, UK

I have no conflicts of interest

This paper reports on the prevalence of autism spectrum disorder (ASD) amongst children born

between 1994 and 1998 in Iceland. The authors report a prevalence rate of 1.2% with just under half having an intellectual disability and 17% showing at least one medical condition. The method used for case identification is that of clinical diagnosis; the authors explained that all ASD diagnoses are made in two tertiary care centres in which research-standard evaluations are used as part of the clinical workup in the overwhelming majority of cases. The prevalence rate reported and associated characteristics are very much in line with those described in the majority of other recent prevalence studies and therefore are essentially a replication. However, this study wais carefully and robustly undertaken and the findings are an important substantiation of those already available in the literature. Furthermore, the authors were able to look specifically at differences between the populations who are diagnosed early (before 2005) and later (between 2005 and 2009) and this represents a useful insight.

The paper is clearly written and the tables are well-presented. The background literature is well covered in a succinct manner. In general, the methods in the study are clearly described. However, I did have a few questions about new clarification.
A bit more detail on the method of population definition and ascertainment would be helpful. It is implied that the population considered is a birth cohort of 1994-1998 and the denominator is calculated based on all children in Iceland born between those dates and still living in Iceland. More clear explication of this, however, would be helpful.

AR: The comprehensive population registries and the easy access to these in Iceland are self-evident to us, and we apologize for not being clear here. We have now added clarification in Methods, page 8, paragraph 2, on this point. This comment by Dr Simonoff is related to the next one concerning migration.

Furthermore, a brief discussion regarding migration would be helpful. In the Discussion, the authors indicate that the change in prevalence rates between the two time periods assessed cannot be explained by migration differences but the evidence to substantiate this is not given.

AR: We have now supplemented the discussion on migration, which was not clear; by referring to the National Registry (see Discussion, page 12, paragraph 4).

In terms of clinical characterizing the population, more details of the range of cognitive assessments used to determine an intellectual disability should be included.

AR: To meet this comment we have now added references for five cognitive tests and two versions of the same instrument measuring adaptive behaviour, all of which are relevant for the assessment of the children in this cohort (see page 7, paragraph 4, and in References).

It would also be helpful, if possible, to have the age at which intellectual ability was determined; this is because measures in very young children can be inaccurate.

AR: It is already stated on page 7, paragraph 2, that “The majority of children diagnosed early during the preschool years were reassessed before beginning elementary school.” We have added the age of the children for a better understanding of this point (see page 7 end of paragraph 2). Also, we have added a sentence (page 7, paragraph 4) explaining that for the diagnosis of intellectual disability two successive cognitive tests are needed.

Similarly a broader description of the standard assessments done to determine associated medical conditions would be helpful.

AR: We have added information on this point in Methods, page 8, paragraph 1. Also, we have added

information to the same paragraph explaining that the paediatrician selected the medical condition to be reported from diagnoses obtained by record linkage with the hospital registry and the records at the SDCC. This was done by taking into consideration neurological abnormalities, neuro-developmental conditions, genetic and congenital syndromes, and epilepsy without assuming an etiological role between the condition and ASD for the individual case.

In particular, the authors should describe the type of genetic testing that was undertaken and whether it was done in all cases or only in some.

AR: The genetic testing was not done systematically but according to clinical indications by different tests through the period of the study (see above, page 8, paragraph 1). In Results (page 9, paragraph 3) we already indicated the number of children (n=122) with genetic tests and chromosomal analyses with a special focus on fragile X.

Did the clinics have an operational definition of epilepsy? If so, could the authors please give that.

AR: Yes, the definition was two unprovoked seizures, and this has been added to the Methods section, page 8, paragraph 1.

A minor comment, on page 12, line 30. The authors suggest that the prevalence of epilepsy is low in their population. However, as implied but not stated subsequently, the onset of epilepsy in autism is frequently reported to be in adolescence and nearly all of the children included in the present study may not have passed through the age of risk. This is because I am assuming that epilepsy is noted if recorded at the time of diagnostic assessment. If this was based on date collected subsequently as well, it would be helpful if the authors highlighted this.

AR: We admit that we were not clear on this point and it was not possible to find out when the epilepsy was diagnosed from our submission and we did not collect this information. This is also true for the other medical conditions reported here, but the record linkage with the hospital registry marks the upper time limits when the diagnoses and the medical conditions were recorded. The diagnoses were recorded gradually during the lifetime of the children or from 1994 to the end of year 2009 at the SDCC and the LUH. It is now clearly stated in Discussion (page 12, paragraph 3) that we are talking about lifetime prevalence of epilepsy to end of the year 2009, when the children were 11 to 15 years old. As we do not have the exact time when the medical conditions were recorded we have mentioned this as one of the limitations of our study (Discussion, page 14, paragraph 2), confer the second comment of Dr Cederlund.

Reviewer: Mats Cederlund, M.D., Ph.D
Child neurologist
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411 19 Göteborg
Sweden

The abstract could be better defined an structured, and the same is true for article focus and key messages.

AR: We have now made the Abstract more determined (page 2), confer comment from the Managing Editor.

There is no comment in the limitations of this study.

AR: Some limitations were mentioned in the Article Summary and at the end of Discussion, page 14. Further, we have now added to the Discussion (page 14) a comment regarding the fact that the follow up in the hospital registry was until the children were 11 to 15 years old, which does not preclude that new medical conditions may be discovered later (after 2009). This point is related to Dr Simonoff's last comment.

In the present version I do not find the standard of English good enough for publication.

AR: We have now read the manuscript carefully, and it was read by an English native speaking editor for language review prior to its submission.

Under Methods (page 6) there is a far to long and inadequate description of the health care/educational and social services in Iceland that needs major revision

AR: To meet this point, we have now made this paragraph shorter (see Methods, page 6, paragraphs 3 and 4).

The presentation is not entirely to my liking. It deals with the results, but at several instances it is a bit unfocused and it is then difficult to follow what the authors try to say.
The Discussion section would have benefitted from a broader discussion about previous findings, not just a reference to the list of references.

AR: We have now added several improvements to the manuscript in order to make it more focused: a change in the title with a corresponding change in the running head and the Abstract; Methods pages 6, 7, and 8; Discussion pages 12 and 14.

There is no report on research ethics in the paper.

AR: The ethics approval was indicated in the manuscript after the Acknowledgements, page 16, and maybe the reviewer has missed this. We have now added a statement of ethics approval at the end of Methods, page 8.

I find this an interesting study, however there are issues that need to be adressed. The paper needs a major revision and the standard of the English must be improved.

AR: These are our responses to the Reviewers comments, and we want to repeat that we appreciate them very much and we think that our manuscript has been considerably improved. We hope that we have managed to meet the comments in an acceptable manner.

VERSION 2 – REVIEW

REVIEWER	Emily Simonoff, MD, FRCPsych Professor of Child and Adolescent Psychiatry and Head of Department Child and Adolescent Psychiatry King's College London, Institute of Psychiatry London SE5 8AF UK I have no conflicts of interest to report.
REVIEW RETURNED	24-May-2013

GENERAL COMMENTS	The authors have responded adequately to all the issues I have raised in the previous review of this paper