

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prenatal Alcohol Exposure and Childhood Balance Ability: Findings from a UK Birth Cohort Study
AUTHORS	Humphriss, Rachel; Hall, Amanda; May, Margaret; Zuccolo, Luisa; Macleod, John

VERSION 1 - REVIEW

REVIEWER	Wendy Kalberg, M.A., LED University of New Mexico Center on Alcoholism, Substance Abuse and Addictions Albuquerque, New Mexico United States I am not the most appropriate reviewer of this manuscript as my bias is toward the importance of conveying the message of dangers to unborn children when mothers drink during pregnancy. I am certainly happy to recuse myself from this review as a result.
REVIEW RETURNED	26-Feb-2013

RESULTS & CONCLUSIONS	This manuscript is well written and the research clearly presented. I do not think the authors considered previous evidence of deleterious effects of prenatal alcohol exposure enough in their presentation of their results. The overall message of the paper is that, in fact, drinking during pregnancy can result in better outcomes on balance at age 10, despite the fact that there was low test-retest reliability in measuring balance. Given all the previous research done on the topic of prenatal alcohol exposures and the issues of neurobehavioral issues resulting in children with prenatal alcohol exposure, I believe the message conveyed in this paper could do more harm than good. Animal studies and human studies over the past 30 years have shown the deleterious effects of prenatal alcohol exposure on development; particularly in the areas of neurocognitive functioning. Balance at age 10 is not that significant given that context.
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REVIEWER	Abel, Ernest Wayne State University
REVIEW RETURNED	08-Mar-2013

THE STUDY	Many relevant references for prenatal alcohol have been omitted,
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	<p>e.g., Alcohol, 1991, 8, 21; 1995, 12, 1; Life Sciences, 1991, 48, 1, Neurotoxicology and Teratology, 1993, 15, 445;</p> <p>Balance reference in animals, Physiol. Behav. 1995, 57, 429</p>
GENERAL COMMENTS	<p>The key message is too apologetic. There is no need to feel that this study is in any way inferior to others. the fact that data was obtained from fathers at the same time as mothers is a very needed approach and should be positively discussed in more detail. Most studies of paternal drinking are based on what women say their significant others were drinking.</p> <p>p. 6 2nd para "maternal alcohol use..." is awkward. Same para. Why is this paradoxical?</p> <p>p. 7. cont'd from p. 6. "with maernal alcohol...not specifically maternal. Last sentence is unclear as to meaning.</p> <p>p. 7 Methods. "use of genetic data" What genetic data?</p> <p>p10. Genetic data. how were these obtained, and how determined. What bodily samples were used.</p> <p>General comment: Should include weights and heights of children if available.</p>

REVIEWER	<p>Bjørn Bay M.D, Ph.d. Fellow Dept. of epidemiology School of Public Health Aarhus Universitet & Dept. of Obstetrics and Gynecology Institute of clinical medicine Aarhus University Hospital</p>
REVIEW RETURNED	17-Mar-2013

THE STUDY	<p>The exclusion criteria are not fully described. E.g. 59 children are excluded due to teacher evaluated physical disabilities - are there balance problems among these?</p> <p>The patients are not representative of actual patients the evidence might affect - but the authors describe this very well.</p>
GENERAL COMMENTS	<p>This study investigates the association between manternal alcohol consumption during pregnancy and development of balance skills in the offspring. The study is large and appropriate adjusted and the manuscript is well written. It adds knowledge to the current evidence showing that low-to-moderate maternal alcohol consumption in pregnancy most likely do not affect the long-term development of the child.</p> <p>Minor Comments:</p> <p>1) Abstract: The definitions of moderate, high, binge etc should be included in the abstract.</p>

	<p>2) Article summary, p.4, l.10: Should the statement be: "High alcohol consumption has been found...?"</p> <p>Introduction, p. 7, line 7: ADH1B should not be completely abbreviated the first time it is mentioned.</p> <p>Methods p. 8, line 46: The dichotomization of SBEO is confusing and should be elaborated on or clarified.</p> <p>Methods p. 9, line 14: Alcohol consumption is categorized into low, medium and high. In table 2 and in the abstract the word Moderate is used. One of these should be used stringent.</p> <p>Methods p. 11, line 5: The analyses is based on complete case. Here would a description of the missings be appropriate.</p> <p>Results: Since the outcomes are based on quartiles and a maximum score it would be good to see the absolute proportions having "good balance" in each group.</p> <p>Results p. 18, line 18: "All balance outcomes were better...." Is this data shown?</p> <p>Discussion: The authors account well for the limitations in this study (self-reported exposure, low test reliability and differences between participaters and non-participaters).</p>
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VERSION 1 – AUTHOR RESPONSE

Ernest Abel

1. Many relevant references for paternal alcohol have been omitted, e.g., Alcohol, 1991, 8, 21; 1995, 12, 1; Life Sciences, 1991, 48, 1, Neurotoxicology and Teratology, 1993, 15, 445;
- We think it is important to note that the animal evidence highlighted by Professor Abel relates to paternal alcohol use and does not relate to offspring balance outcomes. Our focus was on maternal alcohol use in relation to balance outcomes and we cite relevant animal evidence. Within the above caveat we have now added citations to Professor Abel's work in para 1 (Introduction, p6)

2. The key message is too apologetic. There is no need to feel that this study is in any way inferior to others. The fact that data was obtained from fathers at the same time as mothers is a very needed approach and should be positively discussed in more detail. Most studies of paternal drinking are based on what women say their significant others were drinking.
- sentence added to para 2, p22, to highlight the strength of our paternal measures

3. p. 6 2nd para "maternal alcohol use..." is awkward. Same para. Why is this paradoxical?
- sentence rephrased; "paradoxical" deleted

4. p. 7. cont'd from p. 6. "with maternal alcohol...not specifically maternal. Last sentence is unclear as to meaning.
- "maternal" deleted
- final sentence of para 1, p7 rephrased to improve clarity.

5. p. 7 Methods. "use of genetic data" What genetic data?
- specific description of this added (sentence 1, p8)

6. p10. Genetic data. how were these obtained, and how determined. What bodily samples were used.
- more information including a new reference added to para 1, p11

7. General comment: Should include weights and heights of children if available.
- Professor Abel does not indicate the value he feels that additional consideration of offspring height and weight would add to our analyses, he simply suggests we incorporate these data if they are available. Height and weight data are available in ALSPAC but several points are relevant. First, unless there is a priori reason to suspect that offspring height and weight may either confound or mediate an association between maternal alcohol use and offspring balance (or that because of some interaction with offspring height and weight such an association may only be apparent in certain subgroups) there seems no strong rationale to include offspring height or weight in our analyses. Professor Abel does not advance any argument of this kind and we are not aware of any evidence supporting such an argument. Second, though height and weight measures are available in

ALSPAC they may not be contemporaneous with balance measures constraining their usefulness in this context. Third, to obtain height and weight measures on the individuals that our analyses are based on would involve submission of a new request for ALSPAC data to the study Executive Committee. Whilst it is likely that such a request would be agreed this would incur further costs and inevitable delay. Taking all the above into consideration we feel that it is not appropriate for us to repeat our analyses including offspring height and weight. If the Editor felt it important that we did reanalyse our data in this way we would be prepared to reconsider this decision. We would also be prepared to highlight the fact that we had not considered offspring height and weight in our section on study strengths and weaknesses – however, as discussed above, we are currently unclear as to how this omission represents a “weakness”.

Bjørn Bay

1. The exclusion criteria are not fully described. E.g. 59 children are excluded due to teacher evaluated physical disabilities - are there balance problems among these?
- further clarification added to para 2, p8
2. Abstract: The definitions of moderate, high, binge etc should be included in the abstract.
- definitions now added where appropriate (p2)
3. Article summary, p.4, l.10: Should the statement be: "High alcohol consumption has been found...?"
- This statement is not restricted to “high” alcohol consumption as there is some evidence of deleterious effects on neurodevelopmental outcomes at low-moderate levels of exposure
4. Introduction, p. 7, line 7: ADH1B should not be completely abbreviated the first time it is mentioned.
- We have now added the abbreviation ADH when we introduce the alcohol dehydrogenase gene family, on the same line as mentioning ADH1B for the first time, which is a member of the family.
5. Methods p. 8, line 46: The dichotomization of SBEO is confusing and should be elaborated on or clarified.
- clarification has been added (top of p9)
6. Methods p. 9, line 14: Alcohol consumption is categorized into low, medium and high. In table 2 and in the abstract the word Moderate is used. One of these should be used stringent.
- “moderate” is now used throughout the paper
7. Methods p. 11, line 5: The analyses is based on complete case. Here would a description of the missings be appropriate.
- a description of the untested part of the cohort is given in Table A1
8. Results: Since the outcomes are based on quartiles and a maximum score it would be good to see the absolute proportions having "good balance" in each group.

- this information has been added to the sentence at the top of p9

9. Results p. 18, line 18: "All balance outcomes were better...." Is this data shown?

- this information is shown in Table 4