PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Systematic literature review on which maternal alcohol behaviors are related to Fetal Alcohol Spectrum Disorders (FASD).
AUTHORS	Roozen, Sylvia; Peters, Gjalt-Jorn; Kok, Gerjo; Townend, David; Nijhuis, Jan; Koek, Ger; Curfs, Leopold

VERSION 1 – REVIEW

REVIEWER	Victoria Coathup University of Oxford, UK
REVIEW RETURNED	23-May-2018

GENERAL COMMENTS	The authors describe a systematic review conducted to establish which maternal drinking behaviours are most strongly associated with FASD. Overall, the study poses an interesting research question and makes an important point regarding the consistency of reporting in alcohol research studies. However, I think there a few points that needs clarifying throughout the review. Abstract: It would be helpful to include the number of studies included in the review and to state your objective more clearly. Introduction: There are a number of systematic reviews that explore different patterns of maternal drinking and their associations with adverse offspring outcomes. However, this review is focused specifically on patterns of alcohol consumption and associations with a diagnosis of FASD, rather than outcomes such as IQ, birthweight, school results etc. which are often explored in relation to maternal alcohol consumption. I think this distinction needs to be made clearer in the introduction and in the methods section. Sentence in line 46 regarding binge drinking being a serious risk factor associated with severe forms of FASD. I think this might need further explanation (such as the levels of binge drinking that are associated with a diagnosis of FASD) as a lot of published research exploring binge drinking and offspring developmental outcomes report inconsistent results. Page 8, line 14: delete the word ‘such’ Methods: The open source repository is a fantastic resource and your search and data extraction process are obviously well documented. However, I find the methods a little bit difficult to follow because you refer to it many times throughout this section. I wonder whether it would be easier for the reader if you refer to the

	open source repository at the beginning of the methods, providing the website address, then refer to the actual document name in subsequent sections, as I found it difficult to identify the relevant document at times. Alternatively, include important documents as supplementary files rather than directing the reader to the open source website. The search is more than one year out of date now. If there are substantial amendments to be made, it might be worth re-running your search before publication to ensure that you have all relevant studies. I'm a little bit confused by your use of the term 'gray literature' in the search strategy section, as I don't think searching reference lists is considered a gray literature search. Did you mean that you searched reference lists of relevant studies for conference abstracts, reports or other gray literature? If so, why did you restrict your search of gray literature to the reference lists of included studies and not search specialised databases? I think the methods would benefit from a description of your inclusion and exclusion criteria, as it is not clear how you defined your exposures and outcome for the review. For example, you state records were included if studies reported maternal alcohol related behaviours associated with a FASD diagnosis, but you don't provide any additional details on what alcohol related behaviours you are looking at (any alcohol intake? During pregnancy or before? Studies that report timing, dose, length of exposure?), or how you defined an FASD diagnosis (diagnosis by a clinician? Or meeting particular criteria?). It is also not clear whether you included studies of a particular design. Did you exclude any studies based on their NOS results? It would be useful to include the number and reasons for studies being excluded on the flow chart. You refer to a 'slightly adapted version' of the Newcastle-Ottawa Scale. Could you explain what adaptations you made and why? 'Differences were settled by discussion' – is this discussion by the research team? Or between two reviewers? The data synthesis and statistical analysis is currently written like a protocol. I think this section needs to be re-written explaining what you did and why. Results: I think it would be helpful to provide a bit more detail about the NOS scores. How many were considered low quality and a brief explanation of the reasons. You refer to Table 1 as a supplementary file on page 12, line 45, but I couldn't find it. Only the prisma checklist was available as a supplementary file and table 1 included in the paper does not contain the information you describe in the brackets e.g. drinks per days, BAC levels etc.

	There are many references to the open source repository, but it is not clear what documents you are referring the reader to. You refer to table 2 as supplementary data, however, it is included as a table in the main text. I appreciate that there was a lot of heterogeneity between the reporting of alcohol consumption – this is a common issue within this field – and understand that a meta-analysis was not possible. However, the results read like a description of the different methods used, rather than any actual results. There is no mention of any results reported in the included studies. Was it possible to compare the results of a subset of papers that had more similar reporting measures, but without conducting a meta-analysis? (Henderson 2007, systematic review of the fetal effects of prenatal binge-drinking). Unfortunately I was unable to view the visualisations in the project area. It would be useful to include these as supplementary files. Discussion and conclusion: Page 17, line 51: 'much grams' to 'many grams' Page 18, line 9: 'studies was' to 'studies were' There is no discussion of the strengths and limitations of this review. The authors state recommendations clearly and the conclusions reflect the results reported in the review.

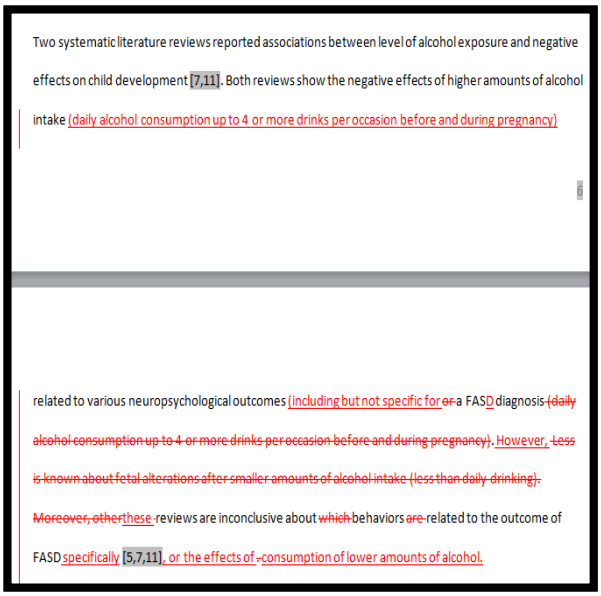
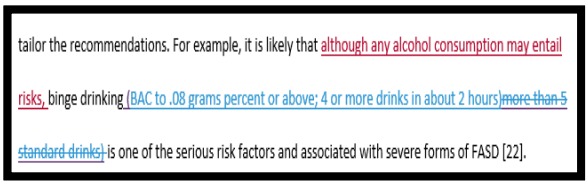
REVIEWER	Raja Mukherjee UK National FASD clinic, Surrey and Borders Partnership NHS Foundation Trust,UK
REVIEW RETURNED	05-Jul-2018

GENERAL COMMENTS	Overall this is a good review that adds to the literature and should eventually be accepted for publication however there are some issues, I believe can be easily amended, that will even need to be anemed in order to clarify and contextualise the findings. My main concern relates to the fact that whilst this study focuses on human literature, which is appropriate, the minimal subsequent reference either in the introduction or the discussion to wider animal work which was used to prove teratogenic causality of prenatal alcohol is not really mentioned. To the casual reader, rather than the experienced reader of the FASD world, this will appear that the causal relationship between alcohol and teratogenic effects overall are yet to be established. In fact it is the mechanism and translation from animal research to human presentations that is still being evaluated not the fact that alcohol can cause direct harm. Were it is mentioned, it is very brief and is not explicit. My concern is that to the casual reader this potentially, without reference to this earlier work, has the potential to put the field back many years and will be used in a way the authors do not intend. This is not requiring a significant addition but I believe an important one for the casual reader with less familiarity towards FASD. More detailed comment

	there are a few areas where a factual statement is made but would benefit from a reference. For example line 12 on page 6 after a list of effects of alcohol was no reference where there should be. line 34 page 6 states that several reviews have identified maternal alcohol consumption to be an important risk factor for FASD. This implies there are more. Again whilst this review is trying to keep an open mind, it needs to highlight therefore what these others might be as currently it is making implication without clarification leading again the casual reader to question what else might be involved. A similar situation can be seen online 43 where a list of wider risk factors is noted with the term environmental factors stated. This can be extensive therefore an example of one or two in parentheses would help the casual reader who is less familiar with FASD to understand what the authors are implying without adding too much to the word count. Page seven line 14 the authors introduce a controversial statement about prenatal alcohol not being the only cause of FASD. This is internationally still under debate. Changes that are prenatal in origin which have paternal or transference from grandparents are genetic or epigenetic in origin, they are not directly teratogenic. The debate that is currently raging is whether they should be defined under the broader Fetal alcohol spectrum or whether they are mechanistically different and should be termed separately. This is a complex debate and is addressed only very briefly in this article. Whilst it is appropriate considering the nature of the study to highlight this, the article does not make clear that it is not a settled position at this time. It will be helpful again to the casual reader when making statements which are complex and not internationally agreed that this is recognised. Page 8 below figure 1, when talking about individual dose response, it is important to take into consideration that there is known individual vulnerabilities. For example something as simple as alcohol dehydrogenase and its different subtypes affect the rates of metabolism and can change a person's response from alcohol. Whilst that is not necessary to be included explicitly, the individual vulnerabilities and variability should be noted and does not appear to be highlighted as a factor influencing the differences. Also people's behaviour and understanding of alcohol levels impacts on risk as much as knowledge and this should be highlighted. The methods used seem appropriate costume measures used to conduct the analysis. Tables and referencing seem appropriate my main concern about the discussion is stated in the major concern the nature of how the work is presented without some brief context being given to suggest that whilst this is focus on humans there has been some evidence of the teratogenic effects being established.

VERSION 1 – AUTHOR RESPONSE

Comments Reviewer 1	**Response Authors**
Abstract:	Good point; this is now included (see page 4).

It would be helpful to include the number of studies included in the review and to state your objective more clearly.	
Introduction: There are a number of systematic reviews that explore different patterns of maternal drinking and their associations with adverse offspring outcomes. However, this review is focused specifically on patterns of alcohol consumption and associations with a diagnosis of FASD, rather than outcomes such as IQ, birthweight, school results etc. which are often explored in relation to maternal alcohol consumption. I think this distinction needs to be made clearer in the introduction and in the methods section.	This was indeed insufficiently clear in the manuscript. We have now amended a section in the introduction (see page 6-7) 
Sentence in line 46 regarding binge drinking being a serious risk factor associated with severe forms of FASD. I think this might need further explanation (such as the levels of binge drinking that are associated with a diagnosis of FASD) as a lot of published research exploring binge drinking and offspring developmental outcomes report inconsistent results.	Thank you for the suggestion. We have provided an example as follows (see also page 8):  To our knowledge, there is evidence consistent with models of alcohol metabolism that indicates that binge drinking is considerably more likely to be harmful than distributed consumption of small amounts of alcohol (as an extreme example, eating a dessert with a bit of alcohol every day for a month versus drinking two bottles of one on one day). Our interpretation of the evidence indicates that any alcohol consumption may be harmful, but that risks further increase as alcohol consumption is more concentrated in a small period of time. However,

	perhaps there is evidence that we are unaware of that does indicate that perhaps binging does not exacerbate the risks. We assume that perhaps we have not phrased this assumption sufficiently clearly, and have therefore amended the text as follows (see also page 8): tailor the recommendations. For example, it is likely that although any alcohol consumption may entail risks, binge drinking (BAC to .08 grams percent or above; 4 or more drinks in about 2 hours)~~more than 5 standard drinks)~~ is one of the serious risk factors and associated with severe forms of FASD [22].
Page 8, line 14: delete the word 'such'	Thank you, this was removed (see page 8) to completely eliminate their alcohol intake, for example because of personal factors ~~such~~ as self-regulation skills, or environmental factors such as social pressures. ~~.~~Given that a total abstinence
Methods: The open source repository is a fantastic resource and your search and data extraction process are obviously well documented. However, I find the methods a little bit difficult to follow because you refer to it many times throughout this section. I wonder whether it would be easier for the reader if you refer to the open source repository at the beginning of the methods, providing the website address, then refer to the actual document name in subsequent sections, as I found it difficult to identify the relevant document at times. Alternatively, include important documents as supplementary files rather than directing the reader to the open source website.	This is an excellent idea. We have fundamentally restructured and cleaned up the OSF repo (and connected it to a GitHub repo), as well as numbered all directories. This way, everything should be more easily findable and usable by others. We will use these numbers to refer to resources throughout the manuscript (see page 9 and further). *Protocol and data repository* Data will be reported following the ~~The~~ PRISMA guideline ~~was followed~~ [24]. All materials and supporting documents are ~~will be made~~ publically available at ~~, also available at~~ the Open Science Framework repository at ~~for this study~~ https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950 (NOTE TO REVIEWERS, EDITOR AND TYPESETTERS: THIS WILL BE REPLACED WITH THE PUBLIC, NON-ANONYMIZED URL ON ACCEPTANCE). In this repository, we have numbered the directories that organize the materials. Hereafter, we will refer to materials in this repository as "resource 1" through "resource 8", which correspond to these directories.

The search is more than one year out of date now. If there are substantial amendments to be made, it might be worth re-running your search before publication to ensure that you have all relevant studies.	We have rerun the query, and updated the manuscript accordingly (see also page 10): before submitting the manuscript ~~including databases up to~~in ~~April 2017~~August 2018 and performed a cursory inspection to scan for newly added papers. Moreover, we applied the ascendancy approach by ~~gray literature was~~ inspecting ~~ed through~~ the reference lists of included articles (the complete queries are included in reseourcse 1~~for further inspection see the Open Science Framework repository for this~~
I'm a little bit confused by your use of the term 'gray literature' in the search strategy section, as I don't think searching reference lists is considered a gray literature search. Did you mean that you searched reference lists of relevant studies for conference abstracts, reports or other gray literature? If so, why did you restrict your search of gray literature to the reference lists of included studies and not search specialised databases?	You are right, this was wrong. We meant the ascendancy approach, and have amended the manuscript accordingly. In fact, omission of grey literature was a weakness of this review (it was deliberate omission, due to limited resources, but still) (see page 10). *Search strategy ~~and criteria~~* A search was conducted in PubMed, PsychINFO, PsychARTICLES, ERIC, CINAHL, EMBASE and MEDLINE databases up to August 2015 using an extensive query consisting of keywords related to FASD, pregnancy and behavior (e.g., fetal alcohol syndrome, pregnancy, alcohol use, risk factor). We reran the query just before submitting the manuscript ~~including databases up to~~in ~~April 2017~~August 2018 and performed a cursory inspection to scan for newly added papers. Moreover, we applied the ascendancy approach by ~~gray literature was~~ inspecting ~~ed through~~ the reference lists of included articles (the queries are included in recourse 1~~for further inspection see the Open Science Framework repository for this study https://osf.io/whq45/?view_only=6d5fddfeb71e493f999036753326c950~~).
I think the methods would benefit from a description of your inclusion and exclusion criteria, as it is not clear how you defined your exposures and outcome for the review. For example, you state records were included if studies reported maternal alcohol related behaviours associated with a FASD diagnosis, but you don't provide any additional details on what alcohol related behaviours you are looking at (any alcohol intake? During pregnancy or before? Studies that report timing, dose, length of exposure?), or how you defined an FASD diagnosis (diagnosis by a clinician? Or meeting particular criteria?).	This is a good suggestion and needed more clarification. Given the extensive query we made a clear link in the manuscript to direct the interested reader to the criteria in resource 2 (see page 10). concerned reviews or meta-analysis, or concerned studies that involved non-human subjects were excluded. An extensive list of inclusion and exclusion criteria is located in the screening instructions (resource 2).

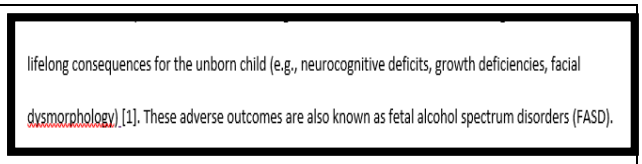
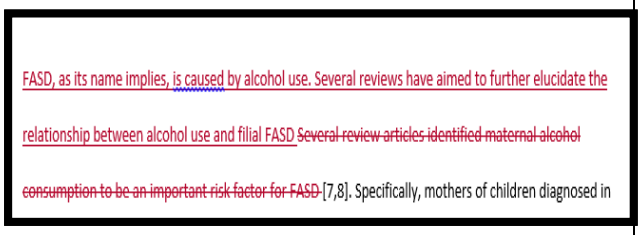
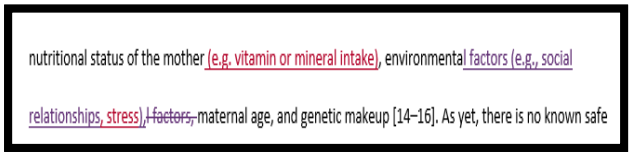
It is also not clear whether you included studies of a particular design.	Thank you for this additional point. We have now provided clear directions towards the relevant file in the repository (see page 10). concerned reviews or meta-analysis, or concerned studies that involved non-human subjects were excluded. An extensive list of inclusion and exclusion criteria is located in the screening instructions (resource 2).
Did you exclude any studies based on their NOS results?	We acknowledge that this might have caused some confusion. We made the text on page 11-12 concerning the NOS more explicit. publication was assessed by two independent reviewers (inter rater reliability = 80%) who ~~furthermore~~ settled differences by discussion. ~~Differences were settled by discussion~~. No studies were excluded based on this quality assessment.
It would be useful to include the number and reasons for studies being excluded on the flow chart.	We have now made it more explicit by adapting the caption beneath the figure. See also the caption of Figure 2. Figure 2. Flow chart of publications measuring maternal behavior(s) related to FASD included in the review. Details regarding the screening procedure and number of exclusions per exclusion criterion ~~Considerations during the inclusion and exclusion process~~ can ~~also~~ be inspected at resource 2 ~~at https://osf.io/whq45/?view_only=6d5fddfeb71c493f999036753326c950~~
You refer to a 'slightly adapted version' of the Newcastle-Ottawa Scale. Could you explain what adaptations you made and why?	This is an excellent idea. We have created a file that compares both versions and included it in the repository (see page 12):

	nonrandomized studies for further meta-analysis with a maximum of 10 stars [26] (see resource 4 for the complete assessment and comparison to the original version) ~~(for more detailed information see the~~
'Differences were settled by discussion' – is this discussion by the research team? Or between two reviewers?	This indeed needed some clarification. The text was adjusted accordingly (see page 12) publication was assessed by two independent ~~-~~reviewers (inter rater reliability = 80%) who ~~furthermore~~ settled differences by discussion. ~~Differences were settled by discussion.~~ No studies were excluded based
The data synthesis and statistical analysis is currently written like a protocol. I think this section needs to be re-written explaining what you did and why.	We closely re-read the 'Integration' section in the Results sections (which is where the synthesis occurs – note that we refrained from meta-analysis after consulting three independent experts in alcohol research, as documented in this 'Integration' section). However, we feel like this comment may have referred to something else: this section seems to mostly document our decisions and justifications for those decisions, rather than constitute a protocol-like description of tasks. Could you perhaps pinpoint which section you mean, exactly?
Results: I think it would be helpful to provide a bit more detail about the NOS scores. How many were considered low quality and a brief explanation of the reasons.	We are reluctant to draw readers' attention to the NOS scores for two reasons. First, since synthesis was mostly impossible, these NOS scores did not play a large role in the study. Second, the NOS was not very applicable to our research question; it was largely designed for clinical studies (e.g. 'case definition' is not easily translatable given that the target subjects in this review were the mothers, not the children; studies with controls were *excluded*; alcohol use, the behavior of interest, can hardly be redefined as 'exposure', etc). Given this relatively low applicability (note, however, that to our knowledge no equivalent exists that addresses our situation better; this seemed the 'least worst' option), combined with the fact that the NOS scores are not used as synthesis was not possible, we prefer not to emphasize the NOS.
You refer to Table 1 as a supplementary file on page 12, line 45, but I couldn't find it. Only the prisma checklist was available as a supplementary file and table 1 included in the paper does not contain the information you describe in the brackets e.g. drinks per days, BAC levels etc.	This reference to the supplemental materials was erroneous; this was actually simple Table 1. This has been corrected at multiple places in the manuscript. We apologize for the inconvenience (see page 13).

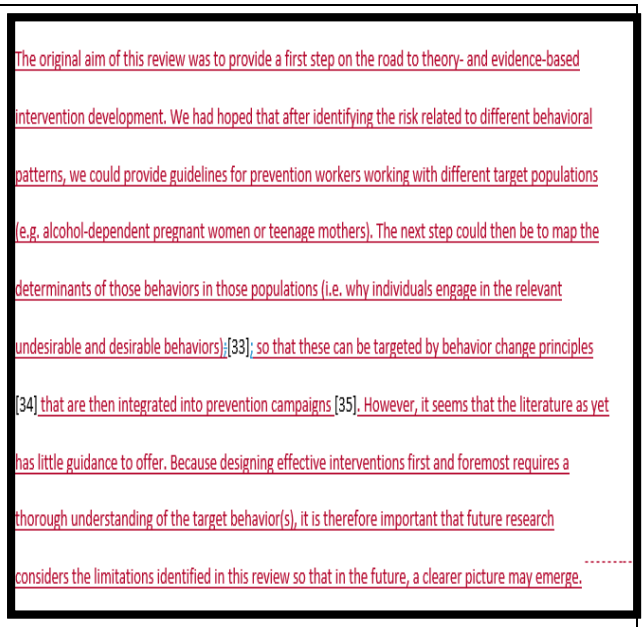
	dichotomous measures~~drinks per drinking day, BAC levels~~; a complete table can be found in ~~the supplemental materials,~~ Table 1): in fact, no two studies used the same measure. Some studies reported
There are many references to the open source repository, but it is not clear what documents you are referring the reader to.	We hope to have resolved this as explained in response to your earlier comment.
You refer to table 2 as supplementary data, however, it is included as a table in the main text.	This has also been fixed; our apologies. heavy), or interval variables (e.g., percentage). The original author's conclusions on maternal drinking behaviors & FASD can be inspected in ~~the supplemental materials,~~ Table 2.
I appreciate that there was a lot of heterogeneity between the reporting of alcohol consumption – this is a common issue within this field – and understand that a meta-analysis was not possible. However, the results read like a description of the different methods used, rather than any actual results. There is no mention of any results reported in the included studies. Was it possible to compare the results of a subset of papers that had more similar reporting measures, but without conducting a meta-analysis? (Henderson 2007, systematic review of the fetal effects of prenatal binge-drinking).	We have now included a reference to these details (see page 16) Because aggregation of the evidence was not possible, we instead sought to explore the heterogeneity exhibited by the included studies (note that all 230 extracted effect sizes are available in file 'effectsizes.csv', and an overview of the used operationalisations in 'Alcohol use variables.csv', both in resource 6). Given the small number of included studies, we decided to inspect visualizations of the Note that we prefer to *not* include these effect sizes in the manuscript for two reasons. First, it takes up a lot of space for results that are relatively irrelevant (and, available online anyway). Second, we want to prevent readers from basing conclusions on cursory inspection of this table.
Unfortunately I was unable to view the visualisations in the project area. It would be useful to include these as supplementary files.	We have now restructured the repository, and included all figures in resources 6 (and those in the manuscript, in resource 7 – but these should be available to you as the journal management software should normally append those to the manuscript file after we separately uploaded them).
Discussion and conclusion: Page 17, line 51: 'much grams' to 'many grams'	We have corrected this, thank you!

	studies did use continuous measures, studies often did not report how ~~much~~ many grams of alcohol
Page 18, line 9: 'studies was' to 'studies were'	We have corrected this, thank you! One of the reasons for this heterogeneity may be that none of the included studies w~~a~~eres conducted
There is no discussion of the strengths and limitations of this review.	We realized that this was unclear; we have now clearly labelled this section (see page 19). *Strengths and limitations*

Comments Reviewer 2	**Response Authors**
My main concern relates to the fact that whilst this study focuses on human literature, which is appropriate, the minimal subsequent reference either in the introduction or the discussion to wider animal work which was used to prove teratogenic causality of prenatal alcohol is not really mentioned.	We have made this clearer in the manuscript by adding the following paragraph on page 9: Animal models have provided some evidence as to potential dose-response relationships. However, such models are not fully translatable to humans [16], and especially given that the present research question concerns not simply whether a dose-response relationship exists, but what the *nature* of this relationship is, relying on animal models does not seem appropriate.
There are a few areas where a factual statement is made but would benefit from a reference. For example line 12 on page 6 after a list of effects of alcohol was no reference where there should be.	This is a good point. Reference was added accordingly:

	 lifelong consequences for the unborn child (e.g., neurocognitive deficits, growth deficiencies, facial dysmorphology) [1]. These adverse outcomes are also known as fetal alcohol spectrum disorders (FASD).
line 34 page 6 states that several reviews have identified maternal alcohol consumption to be an important risk factor for FASD. This implies there are more. Again whilst this review is trying to keep an open mind, it needs to highlight therefore what these others might be as currently it is making implication without clarification leading again the casual reader to question what else might be involved	We have now made clear that FASD is, as its name (and definition) suggests, is caused by alcohol use, in the introduction of the discussion of these reviews. Note that we here do not go in too much depth by explaining that other risk factors (e.g. smoking) moderate the relationship between maternal alcohol use (or, potentially, paternal alcohol use) and filial FASD; in our view, this would require too much explanation for a relatively peripheral point (see page 6):  FASD, as its name implies, is caused by alcohol use. Several reviews have aimed to further elucidate the relationship between alcohol use and filial FASD ~~Several review articles identified maternal alcohol consumption to be an important risk factor for FASD~~ [7,8]. Specifically, mothers of children diagnosed in
A similar situation can be seen online 43 where a list of wider risk factors is noted with the term environmental factors stated. This can be extensive therefore an example of one or two in parentheses would help the casual reader who is less familiar with FASD to understand what the authors are implying without adding too much to the word count.	This is an excellent suggestion; we have added two examples for each group of factors (see also page 6):  nutritional status of the mother (e.g. vitamin or mineral intake), environmental factors (e.g., social relationships, stress), ~~factors,~~ maternal age, and genetic makeup [14–16]. As yet, there is no known safe
Page seven line 14 the authors introduce a controversial statement about prenatal alcohol not being the only cause of FASD. This is internationally still under debate. Changes that are prenatal in origin which have paternal or transference from grandparents are genetic or epigenetic in origin, they are not directly teratogenic. The debate that is currently raging is whether they should be defined under the broader Fetal alcohol spectrum or whether they are mechanistically different and should be termed separately. This is a complex debate and is addressed only very briefly in this article. Whilst it is appropriate considering the nature of the study to highlight this, the	This is again an excellent point. We have thought about a way to clearly explain this without paradoxically confusing exactly that casual reader too much (see page 7):

article does not make clear that it is not a settled position at this time. It will be helpful again to the casual reader when making statements which are complex and not internationally agreed that this is recognised.	[19,20], but as yet, it remains undecided whether paternal and grandparental consumption should also be included in the FASD definition (effects of paternal and grandparental consumption are considered necessarily either genetic or through influencing maternal alcohol consumption, whereas maternal alcohol consumption has a direct teratogenic effect). However, for the sake of this review, we limited
Page 8 below figure 1, when talking about individual dose response, it is important to take into consideration that there is known individual vulnerabilities. For example something as simple as alcohol dehydrogenase and its different subtypes affect the rates of metabolism and can change a person's response from alcohol. Whilst that is not necessary to be included explicitly, the individual vulnerabilities and variability should be noted and does not appear to be highlighted as a factor influencing the differences. Also people's behaviour and understanding of alcohol levels impacts on risk as much as knowledge and this should be highlighted.	We have made this explicit (as briefly as possible) by including the following text (see page 9) weekly maternal alcohol consumption and risk of filial FASD for a given individual (note that individual vulnerabilities can vary). The left panel shows a sigmoid relationship, where risk remains low if less than Regarding the second point: this is a very good point, and one we share completely. In fact, we are currently engaged in another review to synthesize what is known about the different determinants of alcohol consumption (e.g. knowledge, risk perception, attitude, norms, self-efficacy, etc etc). This is in fact such an important point that we have added a new paragraph to the discussion to place this review in the wider picture of FASD prevention (see page 20):

	
my main concern about the discussion is stated in the major concern the nature of how the work is presented without some brief context being given to suggest that whilst this is focus on humans there has been some evidence of the teratogenic effects being established.	We hope the reviewer agrees that the improvements we implemented in response to the earlier excellent suggestions have also resolved this point.

VERSION 2 – REVIEW

REVIEWER	Victoria Coathup University of Oxford, UK
REVIEW RETURNED	31-Oct-2018

GENERAL COMMENTS	I think the paper has been greatly improved and all my previous comments have been addressed by the authors.

REVIEWER	Raja Mukherjee National FASD Specialist Behaviour Clinic, Surrey and Borders NHSFT, Redhill
REVIEW RETURNED	19-Oct-2018

GENERAL COMMENTS	The Authors appear in my opinion to have modified the paper based on prior comments and is now acceptable for publication

VERSION 2 – AUTHOR RESPONSE

Thank you and the reviewers for the approval of the manuscript. The minor revisions have been added to the document. As such, the URL to the repository has been changed accordingly. Also, a funding and conflict of interests statement have been added to the end of the manuscript.