PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Perceived risk of adverse neurodevelopmental outcomes in offspring related to psychotropics and mental illness exposure in pregnancy and breastfeeding: a cross-sectional survey of women with past or current mental illness
AUTHORS	Bjørndal, Ludvig D.; Tauqeer, Fatima; Heiervang, Kristin; Clausen, Hanne K.; Heitmann, Kristine; Lupattelli, Angela

VERSION 1 – REVIEW

REVIEWER	Glover, Vivette Imperial College London
REVIEW RETURNED	24-Feb-2022

GENERAL COMMENTS	This paper addresses an important subject and has a reasonable sample size. One weakness is in the references and the discussion of the relevant literature. The references are often old e.g 5,6,40-47. The safety of psychotropic drugs, and the effects of mental illness independent of medication are fast moving subjects, and it is important to have an up to date review of the literature. This references and review of the literature should be updated. Did the authors have data on whether the subjects actually took medication and how this was related to their attitudes? If they have such data the paper should include it. If not, this should be included as a limitation in the Discussion. Other points. What was the ethnicity of the subjects? Was this related to their attitudes? p9 line 42. "No patients could be involved in this study". It is not clear what this means. Pease clarify. p9 last para. Should be EPDS not EDPS.

REVIEWER	Alwan, Sura The University of British Columbia Department of Medical Genetics
REVIEW RETURNED	Alwan, Sura The University of British Columbia Department of Medical Genetics

GENERAL COMMENTS	This is an interesting analysis on the perception of risk among women with past or current mental illness (or who have been offered antidepressants) in the periconceptional and perinatal period. I rated the abstract as not fully accurate because in the objective, the authors should specify that this is not a perception of risk defined by the general population or among women of reproductive age in general, but specifically among women who are likely to have had or currently have mental illness. Targeting this group is what gives this paper its strength and uniqueness, and should be mentioned in the

	objective of the abstract, and clarified for the title of the manuscript as well. My other major concern for this paper: Although the design has been well carried out for the questionnaire in understanding the background and specifics of the targeted group and ensuring they fit the inclusion criteria, the part on the perception of risk of neurodevelopmental outcomes, in specific, is left at the end of the questionnaire and has not been adequately clarified. It is summarized in only one page and is extremely vague. Definition of neurodevelopmental outcome should be specified to the respondents. A definition for each specific neurodevelopmental outcome the authors are interested in should have been provided to the respondents before they rate their perception. There should have been specific questions to rate perception with regard to the many different neurodevelopmental outcomes (some maybe regarded as very adverse or hardly so). What does ADHD stand for? ADHD is different than autism and both are very different from other neurodevelopmental conditions, motor development, language and speech development, other learning disabilities and intellectual disability! Autism can be regarded by many as a social disability (and not even an adverse outcome)! The paper, therefore, is very weak in truly estimating the perception of risk among those women as it is not clear how these women could have been understanding the nature of neurodevelopmental outcomes in order to perceive a "risk". This point must be incorporated in the discussion as a major limitation of the study.

REVIEWER	Straub, Loreen Brigham and Women's Hospital Department of Medicine, Division of Pharmacoepidemiology, Department of Medicine
REVIEW RETURNED	01-Jul-2022

GENERAL COMMENTS	This is a very well conducted study that underlines how important it is to provide sufficient and tailored information on safety and effectiveness of psychotropic medication use in pregnancy. I have a few suggestions for the authors. Abstract: - Results: o It is not clear from the abstract what e.g., a mean score of 4.2 means – consider adding hat this was based on the scale from 0 to 10? o While the two exposure periods are (1) Prenatal and (2) breastmilk exposure, it reads like these two periods were just considered together as one exposure group. Maybe make this clear by adding e.g., (1) and (2) or similar. o Please include the type of analyses conducted to assess risk factors, and that the beta coefficient represents the mean difference in risk perception (on a scale from 0-10). o Consider adding some confidence intervals around the mean scores to make it easier for the reader to understand how much variation there was. o Given that a lot of women did not report on received risk for other psychotropic medications, this might be important to also add to the abstract, as it might mean that the risk reported for these conditions might not be directly comparable to the risk reported for antidepressants. - Conclusion: It would be great if the authors could emphasize here why it is so important to understand the women's perception, similar

	as they did in the introduction, e.g., by saying that risk perception can affect decision-making regarding treatment, there might be confusion & conflicts regarding treatment etc. The first 2 sentences of the conclusion could in turn be considerably shortened to save words. Introduction: - Consider adding a few more examples of neurodevelopmental disorder other than autism (e.g., ADHD, language skills etc.) - "food items" – does this only refer to cranberries and alcohol? If so, consider clarifying. Methods: - Perception of risk: o Just as for the abstract, consider clarifying that the two exposure periods were: (1) prenatal and (2) breastfeeding - Mental health factors: o Was the cut-off of 13 previously used and validated? - Statistical analysis: o Describe what type of "descriptive statistics" were conducted – e.g., that frequency of covariates within the cohort was calculated and mean risk perception was assessed separately for each exposure. o Please consider adding a bit more information on the PCA and what the goal of this method is as the readers might not be familiar with this. - Association analysis: o " variables having no role (p-value > 0.05) or yielding a change smaller than 15% in the beta coefficients of the retained variables were removed " – was this requirement applied after all covariates from the univariate comparison with p<0.05 were included in one model? o Multiple imputation: assuming missingness at random might be quite a strong assumption, maybe the authors can add something on this in the discussion (see also my comments on the results section for the women reporting "unknown". Results: - Given that a lot of women reported "unknown" for the perceived risk of other psychotropics, did the authors also assess perceived risk & 95% CIs for each of these exposures only among women who reported perceived risk for each of these variables? - Similarly, did the authors assess whether women who reported "unknown" for the perceived risk of other psychotropics were different from those who did report a scale in terms of patient characteristics? Might the higher perceptive risk for the other psychotropics be potentially (in part) be a reflection of the cohort of women who did vs. did not report on everything? Also related to this, did the authors assess how much similarity in rating there was for each of the psychotropic exposures within the same woman? - Did the authors consider conducting the analyses from tables 3 and 4 also for other psychotropics (e.g., grouping all the others together) to see if findings/directions are similar to antidepressants?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Vivette Glover, Imperial College London

Comment 1: This paper addresses an important subject and has a reasonable sample size. One weakness is in the references and the discussion of the relevant literature. The references are often old e.g 5,6,40-47. The safety of psychotropic drugs, and the effects of mental illness independent of medication are fast moving subjects, and it is important to have an up to date review of the literature. This references and review of the literature should be updated.
Reply 1: We agree with the reviewer that some references in the original manuscript could be replaced by more recent references. In light of this comment, we conducted another literature search, to ensure we picked up recent references. We have therefore replaced a number of references with more recent ones.

Comment 2: Did the authors have data on whether the subjects actually took medication and how this was related to their attitudes? If they have such data the paper should include it. If not, this should be included as a limitation in the Discussion.
Reply 2: We agree with the Reviewer that use of specific psychotropics can be related to how women perceive their risk. However, this was not within the aims of this study. Having been offered an antidepressant in the past five years was a requirement for participating in the survey, and the majority of participants were using or had previously used this medication in our sample at some point (80%).

The study has information on use of antidepressants and other psychotropics, albeit for the latter medications the information collected is less granular than for antidepressants. We decided at the phase of study planning – as also stated in the registered statistical analytical plan - to focus on maternal health-related and sociodemographic factors that can shape women's risk perception, rather than on possible consequences of this risk such as psychotropic medication use. This decision was taken in order to aid clinicians in identifying women who are more likely to have an unrealistically elevated risk perception - who, consequently, may abruptly discontinue their medication treatment. We believe that the patterns of psychotropic use at the time around pregnancy are too complex to be included in this already extensive article. Indeed, many women discontinue their psychotropics at different time points in pregnancy, others continue or change the dose during pregnancy and while breastfeeding. For information, we are specifically working on how women's risk perception influences these different patterns of psychotropic medication use in a separate article. We hope the reviewer will understand and agree with our motivation.

We do however acknowledge this limitation in the Discussion section, which reads: "We did not consider how patterns of actual use of psychotropic medication were related to the woman's assessment of their risk"

Comment 3: Other points.
What was the ethnicity of the subjects? Was this related to their attitudes?
Reply 3: We did not collect data specifically on the ethnicity of participants. The collection of ethnicity data in Norway requires special ethical approval. However, we did ask respondents if Norwegian is their main language (in total, 405 answered 'Yes' and 42 'No') for this item. This variable was associated with higher antidepressant risk perception in both exposure periods among pregnancy planners (further described on p. 15).

Comment 4: p9 line 42. "No patients could be involved in this study". It is not clear what this means. Pease clarify.
Reply 4: We apologise for the confusing statement. We did not succeed in recruiting patient representatives for this specific project despite many efforts. We have rephrased and simplified this paragraph as follow: “The research team attempted to involve patient representatives in the development of the study protocol and the questionnaire, with the support of national mental health patient organisations. No patient representatives were willing to be involved in this study”.

Comment 5: p9 last para. Should be EPDS not EDPS.
Reply 5: We are grateful for the reviewer’s careful reading of our manuscript and have amended this error.

Reviewer: 2
Dr. Sura Alwan, The University of British Columbia Department of Medical Genetics

Comments to the Author:
Comment 1: This is an interesting analysis on the perception of risk among women with past or current mental illness (or who have been offered antidepressants) in the periconceptional and perinatal period.
I rated the abstract as not fully accurate because in the objective, the authors should specify that this is not a perception of risk defined by the general population or among women of reproductive age in general, but specifically among women who are likely to have had or currently have mental illness. Targeting this group is what gives this paper its strength and uniqueness, and should be mentioned in the objective of the abstract, and clarified for the title of the manuscript as well.
Reply 1: We thank the reviewer for this comment, which we fully agree with. In light of this comment, we have re-phrased the abstract to clearly state that our sample consists of women likely to have had or who currently have a mental illness (p. 3). Furthermore, we have rephrased our title to indicate that our findings concern this group (please see our reply 1 to the Editor for the amended title). Overall, we feel both the revised title and abstract more clearly convey the essential information of the study, as highlighted by the reviewer.

Comment 2: My other major concern for this paper: Although the design has been well carried out for the questionnaire in understanding the background and specifics of the targeted group and ensuring they fit the inclusion criteria, the part on the perception of risk of neurodevelopmental outcomes, in specific, is left at the end of the questionnaire and has not been adequately clarified. It is summarized in only one page and is extremely vague. Definition of neurodevelopmental outcome should be specified to the respondents. A definition for each specific neurodevelopmental outcome the authors are interested in should have been provided to the respondents before they rate their perception. There should have been specific questions to rate perception with regard to the many different neurodevelopmental outcomes (some maybe regarded as very adverse or hardly so). What does ADHD stand for? ADHD is different than autism and both are very different from other neurodevelopmental conditions, motor development, language and speech development, other learning disabilities and intellectual disability! Autism can be regarded by many as a social disability (and not even an adverse outcome)! The paper, therefore, is very weak in truly estimating the perception of risk among those women as it is not clear how these women could have been understanding the nature of neurodevelopmental outcomes in order to perceive a "risk". This point must be incorporated in the discussion as a major limitation of the study.
Reply 2: We thank the reviewer for raising this very important point. We agree that a definition of

neurodevelopmental outcomes should have been provided and that the examples given are very heterogeneous. At the same time, explaining all possible developmental domains and ask women to rate each developmental outcome in relation to each drug/item of interest, would have resulted in a very long section in the questionnaire. The latter format would have enhanced missing responses and study drop-out. Prior research on teratogenic risk perception of medications has also grouped all possible malformation types into a broad category; so, we adapted our risk perception question to the context of developmental outcomes based on prior research (Gils et al, DOI: 10.1186/s12884-016-1025-6; Petersen et al, doi: 10.1136/bmjopen-2014-007390; Widnes et al, doi: 10.1007/s40264-013-0035-9). Our methodological choice was a compromise between a reasonable questionnaire length and accurate data collection.
However, we fully agree with the Reviewer that we cannot rule out the possibility that the formulation of the question for the risk perception influenced our estimates of perceived risk, as highlighted by the reviewer. We have incorporated this as a limitation, acknowledging its importance, in the Limitations section (p. 22 and p. 23), which reads: “An important limitation of the study is that we did not provide a specific definition of all individual ‘neurodevelopmental outcomes’ in the questionnaire, but rather presented a few substantially heterogeneous examples. This may have affected the accuracy of women’s reporting on the perceived risk of psychotropics and mental illness on the broader, unspecific domain of child neurodevelopment. We cannot rule out the possibility that the lack of clarity in these items influenced our estimates of perceived risk and associations”. We have also added this to the list of Limitations in the “Article summary” (p. 5), which reads “A specific definition of all possible neurodevelopmental outcomes was not provided to respondents, and women rated their perceived drug risk on the broad, unspecific spectrum of child neurodevelopment”.

Reviewer: 3
Dr. Loreen Straub, Brigham and Women's Hospital Department of Medicine

Comments to the Author:
Review of Manuscript: bmjopen-2022-061159
This is a very well conducted study that underlines how important it is to provide sufficient and tailored information on safety and effectiveness of psychotropic medication use in pregnancy. I have a few suggestions for the authors.

Comment 1: Abstract:
- Results:
o It is not clear from the abstract what e.g., a mean score of 4.2 means – consider adding that this was based on the scale from 0 to 10?
Reply 1: We agree with the reviewer and have added the 0-10 scale to increase clarity in the abstract (p. 3). We have further clarified in the Methods section what score 0 and 10 meant more specifically. The revised text now reads: “Participants were asked to rate (from 0 to 10, where 0 corresponds to ‘not harmful’ and 10 to ‘very harmful’) the perceived harmfulness of substances…”

Comment 2:
o While the two exposure periods are (1) Prenatal and (2) breastmilk exposure, it reads like these two periods were just considered together as one exposure group. Maybe make this clear by adding e.g., (1) and (2) or similar.
Reply 2: We have included (1) and (2) as suggested by the reviewer to clarify that these were two separate exposure groups.

Comment 3:
o Please include the type of analyses conducted to assess risk factors, and that the beta coefficient represents the mean difference in risk perception (on a scale from 0-10).
Reply 3: We have specified in the Abstract that associations were examined using general linear models and that the β represents the mean difference in the risk perception score between groups.

Comment 4: o Consider adding some confidence intervals around the mean scores to make it easier for the reader to understand how much variation there was.
Reply 4: We have now added the 95% CI of the mean score for antidepressants in both exposure periods.

Comment 5:
o Given that a lot of women did not report on received risk for other psychotropic medications, this might be important to also add to the abstract, as it might mean that the risk reported for these conditions might not be directly comparable to the risk reported for antidepressants.
Reply 5: We agree with the reviewer that this is an important point and have added it to the abstract (p. 3). The added text reads “Many participants were unfamiliar with psychotropics other than antidepressants.”

Comment 6: Conclusion: It would be great if the authors could emphasize here why it is so important to understand the women’s perception, similar as they did in the introduction, e.g., by saying that risk perception can affect decision-making regarding treatment, there might be confusion & conflicts regarding treatment etc. The first 2 sentences of the conclusion could in turn be considerably shortened to save words.
Reply 6: We agree with the reviewer that this should be highlighted in the abstract and have incorporated this (p. 4). We have also shortened the first two sentences, as recommended by the reviewer. The revised conclusion now reads “In women with past/current mental illness, the perceived risk of antidepressant exposure on child neurodevelopment was lower than that for maternal mental illness. Other psychotropic medications were perceived as more harmful. As medication risk perception influences the decision-making regarding treatment of mental illness, pre- and pregnancy counselling should target women with characteristics associated with higher perceived risk.”

Comment 7: Introduction:
- Consider adding a few more examples of neurodevelopmental disorder other than autism (e.g., ADHD, language skills etc.)
Reply 7: We have now made more examples, specifically for ADHD and scholastic skills. A new reference to recent literature has been added in relation to scholastic skill outcomes.

Comment 8:
“food items” – does this only refer to cranberries and alcohol? If so, consider clarifying.
Reply 8: We have clarified that food items refer to cranberries and alcohol (p. 7).

Comment 9:
Methods:
- Perception of risk:
o Just as for the abstract, consider clarifying that the two exposure periods were: (1) prenatal and (2)

breastfeeding
Reply 9: We have clarified that there were two separate exposure periods, as suggested by the reviewer (p. 8).

Comment 10:
- Mental health factors:
o Was the cut-off of 13 previously used and validated?
Reply 10:
The Edinburgh Postnatal Depression Scale has been validated in multiple languages and different cultural settings (see Cox J and Holden J. Perinatal Mental Health: A Guide to the EPDS. Publisher : RCPsych Publications; 1st edition (January 1, 2003)). Cox et al. have proposed and validated a cut-off for 'probable depression' at 12/13, and for 'possible depression' at 9/10 (Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry 1987;150:782–786). Because in our study we measured the EPDS only once, we used a more conservative cutoff of 13 (instead of 9/10, or 12) to classify women possibly having "probable depression" at the time of study participation.
We have now provided the rationale for this choice of the cut-off value in the Methods, which reads: "The choice of cut-off 13 is conservative, as it reflects the higher end of the validated cut-off for "probable depression".

Comment 11:
- Statistical analysis:
o Describe what type of "descriptive statistics" were conducted – e.g., that frequency of covariates within the cohort was calculated and mean risk perception was assessed separately for each exposure.
Reply 11: In this section, we refer to the descriptive results for the mean risk perceptions. The previous paragraph describes the sociodemographic characteristics/covariates. We have rephrased the first sentence of the 'Statistical analysis' section to clarify that we assessed mean risk perceptions descriptively and separately for each exposure, as suggested by the reviewer (p. 11).

Comment 12:
o Please consider adding a bit more information on the PCA and what the goal of this method is as the readers might not be familiar with this.
Reply 12: We have rephrased this to also state that we aimed to use PCA to reduce the number of outcome variables and group them into fewer factors (p. 11). The revised text now reads: "Principal Component Analysis (PCA) was conducted to assess if the risk perception of the various substances could be grouped into fewer factors for analyses; due to the large proportion of women who indicated psychotropic drugs other than antidepressants as 'unknown', the PCA caused substantial data loss. As a result, the grouping of psychotropic drugs other than antidepressants was hindered, and we focused subsequent analyses on the perceived risk of antidepressant and maternal mental illness exposure only."

Comment 13:
- Association analysis:
o " variables having no role (p-value > 0.05) or yielding a change smaller than 15% in the beta coefficients of the retained variables were removed " – was this requirement applied after all covariates from the univariate comparison with p<0.05 were included in one model?
Reply 13: Yes, that is correct. We have rephrased this passage in the methods to enhance clarity. It

now reads: “Candidate variables were first selected based on a p-value < 0.15 in a univariable linear regression model. Selected candidate variables were then included in the multivariable model; at this stage, variables having no role (p-value > 0.05) or yielding a change smaller than 15% in the beta coefficients of the retained variables were removed”.

Comment 14:
• Multiple imputation: assuming missingness at random might be quite a strong assumption, maybe the authors can add something on this in the discussion (see also my comments on the results section for the women reporting “unknown”.
Reply 14: We agree with the reviewer that “missing at random” may be a strong assumption. However, assuming data are “missing completely at random” – and thereby conducting a complete case analysis – is an even stronger assumption that should be avoided in epidemiological research. We believe it is important to state the underlying assumption on pattern of missingness when multiple imputation is conducted. Our assumption was driven by the observed distribution of missing data in our study. We have now added a sentence in the Limitation section addressing this: “We assumed data to be missing at random when conducting the association models; however this assumption is not testable and it was based on the patterns of missingness in our population.”

Comment 15:
Results:
- Given that a lot of women reported “unknown” for the perceived risk of other psychotropics, did the authors also assess perceived risk & 95% CIs for each of these exposures only among women who reported perceived risk for each of these variables?
Reply 15: We thank the reviewer for proposing these additional descriptive analyses, to assess potential differences between those who reported perceived risks for all substances (N = 125) versus those who only reported risks for a subset of substances (or none). We report the results for these analyses in the revised Supplementary (e-Only Table 4) and made reference to these results in the Results section. The table shows that the pattern of perceived risks for this group of participants is similar to that of all participants (as reported in the manuscript). One slight difference is for alcohol, where the group of participants responding to all items evaluated alcohol as slightly less harmful (for both exposure periods). The differences are small, however, and the 95% CIs contain the values reported in the main manuscript.

Comment 16:
- Similarly, did the authors assess whether women who reported “unknown” for the perceived risk of other psychotropics were different from those who did report a scale in terms of patient characteristics? Might the higher perceptive risk for the other psychotropics be potentially (in part) be a reflection of the cohort of women who did vs. did not report on everything? Also related to this, did the authors assess how much similarity in rating there was for each of the psychotropic exposures within the same woman?
Reply 16: We have compared the distribution of key characteristics (i.e. age, education, occupation, number of reported mental illnesses, and having Norwegian as native language) in women who reported “Don’t know” on the perceived risk for all psychotropic medications, in relation to those with only one “Don’t know” response, and those with “Don’t know” for all psychotropic medications. Results are presented in e-Only Table 5. We have now referred to this table in the Results section and added a Limitation, which reads: “However, unfamiliarity with psychotropic medications was more common among women not working as a healthcare professional and those with lower education. This could have influenced our descriptive and association results, although the latter were all adjusted for the educational level of the woman”.

There is indeed a correlation between item-response within each woman. We have now reported in the Results section the consistency of women's responses across the risk perception items for psychotropics specifically, which reads: "The consistency of women's responses across the risk perception scores for psychotropics were 0.73 (pregnancy exposure) and 0.78 (breastfeeding exposure)."

Comment 17:
- Did the authors consider conducting the analyses from tables 3 and 4 also for other psychotropics (e.g., grouping all the others together) to see if findings/directions are similar to antidepressants?
Reply 17: We did consider these analyses; understanding factors related to other risk perceptions was also the rationale for doing a principal component analysis in the attempt to reduce the number of medication groups into fewer variables. As the Reviewer has seen, we have three different population groups (pregnant, planners, mothers) and risk perception scores for two separate exposures (pregnancy and breastfeeding). Doing same analysis from Table 3 and Table 4 for all remaining, individual medications would create an extensive amount of data and results. Because – according to the PCA results – we cannot group all other psychotropics into a single variable, we would like to keep the focus on antidepressant and maternal psychiatric illness risk perception when it comes to associated risk factors. We believe this is reasonable since one inclusion criterion in the study was having been offered an antidepressant and having a mental illness. We hope the Reviewer understands our motivation.

VERSION 2 – REVIEW

REVIEWER	Alwan, Sura The University of British Columbia Department of Medical Genetics
REVIEW RETURNED	09-Sep-2022

GENERAL COMMENTS	Thanks for your revision and responses.

REVIEWER	Straub, Loreen Brigham and Women's Hospital Department of Medicine, Division of Pharmacoepidemiology, Department of Medicine
REVIEW RETURNED	16-Aug-2022

GENERAL COMMENTS	No additional comments. This is a very nice paper.