

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Neighborhood socioeconomic status modifies the association between anxiety and depression during pregnancy and preterm birth: A Community-based Canadian Cohort Study
AUTHORS	Adhikari, Kamala; Patten, Scott; Williamson, Tyler; Patel, Alka; Premji, Shahirose; Tough, Suzanne; Letourneau, Nicole; Giesbrecht, Gerald; Metcalfe, Amy

VERSION 1 – REVIEW

REVIEWER	Lesley Smith University of Leeds, UK
REVIEW RETURNED	14-May-2019

GENERAL COMMENTS	<p>This paper examines the association between depression, anxiety, the interaction with neighbourhood socioeconomic status and preterm birth. A major strength of the paper is the consideration of depression and anxiety symptoms alone and in combination. However, the paper does not adequately describe the study details fully and the modelling strategy, including dealing with missing data, are not appropriate, therefore I am unable to comment on the main findings and conclusions of the manuscript.</p> <p>When and how are the exposures, outcomes and other measures collected? When during pregnancy is the Edinburgh depression scale collected? Has it been validated for use during pregnancy to screen for both depression and anxiety? This is potentially a major issue/limitation</p> <p>The role of SES important, however further information on individual-level SES measures could be discussed further, no mention of implications of using area level measure at individual level in analysis. What is neighbourhood SES based on? Postcode of residence at time of questionnaire completion? Again lack of information on key exposure data.</p> <p>The methods also need refining to ensure appropriate confounder adjustment. Statistical models need more careful consideration of confounder adjustment and clarity of descriptions. Stepwise methods should not be used to select variables for inclusion in the adjusted model, the authors need to consider potential confounders based on the exposure and outcome relationship. Page 10, line 13-22, "variables were retained is they influenced the association", this is not clear and the statement "...improve the precision of the estimates" is incorrect. The modelling strategy is not clear "other variables selected based on literature" these do not appear to be included in the final adjusted model but in the text it reads like they are.</p>
-------------------------	--

	<p>More details on missing data should be included. For example 397 had missing data on gestation, is this related to SES, depression, anxiety and other confounders? The number of women with missing data for each variable should be included. If appropriate were methods to deal with missing data, such as multiple imputation, considered?</p> <p>Results first paragraph and Table 1 includes descriptive statistics about the study population – confidence intervals around percentages and mean values should not be included in these. More informative information about each study variable would be to include the range of values mean and SD, include all categories for categorical variables. A column that includes the total for the full study population would be useful. It would also be of interest to see the demographic characteristics by outcome.</p> <p>Minor comments Inconsistencies in the abbreviations EPDS and EDS both used. Page 7, line 8. “exposing women to health benefitting or risk elevating factors” such as? Authors could include some examples P9, line 10. “births” rather than “the births” P9, line 28. Deprivation fifth rather than quintile Other variables included in data analysis details are not included in the study variables section (for example how is BMI collected – at what point in pregnancy?) Page 11, lines 20-24. Mean scores (+/-) what are the +/- scores? Page 11, lines 38. Don’t include individual level p-values better to include overall test of significance</p> <p>Discussion. Page 13-14. It would be helpful to includes any similarities between study populations in other published work for comparative purposes Page 15, line 26-27. To make this point need to include (in methods?) details of the sampling strategy for the two included cohort studies used in the analysis. Table 1 How is drug abuse before pregnancy defined – seem high overall 14% ranging from 13% to 20% across anxiety and depression groups What ethnic groups does the non-white include? Table 2: Were there differences between unadjusted and adjusted model results?</p>
--	---

REVIEWER	Susanne Hesselman 1 Department of Women’s and Children’s health, Uppsala University, Uppsala, Sweden 2 Center for clinical research, Uppsala University, Falun, Sweden
REVIEW RETURNED	13-Oct-2019

GENERAL COMMENTS	This manuscript is clearly written and easy to follow with a focused research question i.e if anxiety and depression increase the risk of preterm birth alone or in conjunction and depending on neighborhood deprivation. Minor comments: 1) Even if the numbers were limited to allow for stratification of induced and preterm births, it could be interesting to know how many of the preterm births were spontaneous and iatrogenic among exposed and non-exposed.
-------------------------	--

	<p>2) Odds ratios are calculated but sometimes referred as risk. I think the word risk is better replaced by odds and or likelihood.</p> <p>3) Looking at OR. Although not significant, but it might be a question of power, depression but not anxiety seem to be associated with PTB. Any ideas of why these "stress" factor differs from each other?</p> <p>4) PTB is not easy to prevent. What targeting interventions do you suggest for deprived areas? Psychological care? Prevention of malnutrition and life style factors?</p> <p>Page 8 In 29. EDS change to EPDS</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Lesley Smith

Institution and Country: University of Leeds, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This paper examines the association between depression, anxiety, the interaction with neighbourhood socioeconomic status and preterm birth. A major strength of the paper is the consideration of depression and anxiety symptoms alone and in combination. However, the paper does not adequately describe the study details fully and the modelling strategy, including dealing with missing data, are not appropriate, therefore I am unable to comment on the main findings and conclusions of the manuscript.

Response: Thank you for your comments. We have addressed these comments in the revised manuscript as described below.

-When and how are the exposures, outcomes and other measures collected? When during pregnancy is the Edinburgh depression scale collected? Has it been validated for use during pregnancy to screen for both depression and anxiety? This is potentially a major issue/limitation.

Response: The measurement time (at pregnancy) and methods of exposures, outcome and other variables (such as anxiety and depression, neighborhood SES, preterm birth, and BMI) have been added in method section (variable sub-section: page 8, 9, and 10). The Edinburgh depression scale had been previously validated in postpartum period and recommended for use to screen for both depression and anxiety. We have explained this in method section. We were not able to validate the Edinburgh depression scale in our data for use during pregnancy as we did not have reference scale for this purpose. We agree that using a measure that has not been validated for use during pregnancy is a limitation of this study. This issue has been acknowledged in the discussion section (page 17, paragraph 1).

-The role of SES important, however further information on individual-level SES measures could be discussed further, no mention of implications of using area level measure at individual level in analysis. What is neighbourhood SES based on? Postcode of residence at time of questionnaire completion? Again lack of information on key exposure data.

Response: Information on the type of analysis used (analysis section: page 10 and 11), neighborhood SES measure (variable subsection: page 9), and role of individual-level SES measures (analysis section: page 10) have been described in method section.

We used a multilevel logistic regression model to examine the effect modification of neighborhood SES on the association between anxiety and/or depression and PTB. Multilevel analysis is an appropriate analytical approach for the hierarchical nature of data as it assumes the lack of independence of observations and accounts for the variation between groups/neighborhoods in addition to the adjustment for individual level variables. Whereas, classical logistic regression

assumes independence of observations and fails to account for the hierarchical nature of data and may produce standard errors that are too small (thus increasing the chance of a type I error or spuriously significant associations).

Neighborhood SES was based on the aggregated proportion of persons without high school diplomas, the average personal income, and the rate of unemployment at the dissemination area level. The neighborhood SES was assigned to each cohort based on their postal code of residence at the time of cohort recruitment. This has been explained in method section (page 9 and 10, last paragraph). Furthermore, the implication of using area-based variables (i.e., neighborhood SES) has been discussed (page 17, last paragraph).

-The methods also need refining to ensure appropriate confounder adjustment. Statistical models need more careful consideration of confounder adjustment and clarity of descriptions. Stepwise methods should not be used to select variables for inclusion in the adjusted model, the authors need to consider potential confounders based on the exposure and outcome relationship. Page 10, line 13-22, "variables were retained is they influenced the association", this is not clear and the statement "...improve the precision of the estimates" is incorrect. The modelling strategy is not clear "other variables selected based on literature" these do not appear to be included in the final adjusted model but in the text it reads like they are.

Response: Regarding modeling strategy, we identified potential confounders based on their association with outcome and exposure: parity, ethnicity and BMI were significantly associated with both preterm birth and anxiety/depression and therefore were included in the multivariable model for the adjustment. Other variables (i.e., smoking, social support, and maternal education and household income) were also initially selected to include in the model: considering that they may change/confound the exposure-outcome association in the multivariable model (if so they require adjustment) as they were found to be associated with both preterm birth and anxiety/depression in literature. However, these variables were later dropped from the model as they did not change/confound the association. Enhanced descriptions of the modeling strategy are revised in method section (analysis subsection: page 10 and 11).

-More details on missing data should be included. For example, 397 had missing data on gestation, is this related to SES, depression, anxiety and other confounders? The number of women with missing data for each variable should be included. If appropriate were methods to deal with missing data, such as multiple imputation, considered?

Response: The number of women with missing data for each variable (including PTB, SES, depression and anxiety, and other confounders) and how the missing data were managed have been added in method section (missing data subsection: page 11 and 12).

Maternal ethnicity, parity, BMI, neighborhood SES, anxiety, and depression were significant with missing data on PTB. We have undertaken a multiple imputation for 3 variables that contained $\geq 5\%$ missing data (preterm birth, BMI, and neighborhood SES). Results based on multiple imputation are now reported (Table 3 and 4) as the primary findings although the results were not different from the analyses restricted to complete cases.

-Results first paragraph and Table 1 includes descriptive statistics about the study population – confidence intervals around percentages and mean values should not be included in these. More informative information about each study variable would be to include the range of values mean and SD, include all categories for categorical variables. A column that includes the total for the full study population would be useful. It would also be of interest to see the demographic characteristics by outcome.

Response: The Table 1 and its description (result section: page 12) have been revised. Table 2 has been added to illustrate the demographic characteristics by outcome or preterm birth.

Minor comments

-Inconsistencies in the abbreviations EPDS and EDS both used.
Response: This has been revised.

-Page 7, line 8. “exposing women to health benefitting or risk elevating factors” such as? Authors could include some examples
Response: Examples are added to clarify the “exposing women to health benefitting or risk elevating factors” (page 7). The examples include access to healthy foods, quality health services, opportunities for leisure activity, and social support and exposure to societal stressors, crimes, and poor air and water quality.

-P9, line 10. “births” rather than “the births”
Response: This has been revised.

-P9, line 28. Deprivation fifth rather than quintile
Response: This has been revised as advised.

-Other variables included in data analysis details are not included in the study variables section (for example how is BMI collected – at what point in pregnancy?)
Response: When and how the variables were measured have been added in the study variables section (page 8, 9, and 10). Briefly, study variables such as age, ethnicity, maternal SES, parity, BMI, smoking status, depression, and anxiety were measured at <27 weeks of gestation in the APrON study and at <25 weeks of gestation in the AOF study. BMI was calculated based on self-reported height and weight before the pregnancy. Additionally, depression and anxiety were measured during the third trimester.

-Page 11, lines 20-24. Mean scores (+/-) what are the +/- scores?
Response: “+/-“ was used as a symbol to denote. Now, it has been replaced by the word “standard deviation”

-Page 11, lines 38. Don’t include individual level p-values better to include overall test of significance
Response: This has been revised as suggested.

-Discussion: Page 13-14. It would be helpful to includes any similarities between study populations in other published work for comparative purposes
Response: The discussion on similarities or comparison is included in page 14 (interpretation subsection: paragraph 1).

-Page 15, line 26-27. To make this point need to include (in methods?) details of the sampling strategy for the two included cohort studies used in the analysis.
Response: The two cohort studies were community-based pregnancy cohorts. Their sampling strategy has been added in methods section (page 15, paragraph 2). Citations are also provided for readers interested in a more detailed description.

-Table 1: How is drug abuse before pregnancy defined – seem high overall 14% ranging from 13% to 20% across anxiety and depression groups
What ethnic groups does the non-white include?
Response: The drug abuse was broadly defined based on maternal self-reported any street or recreational drugs use before the current pregnancy. The definition may explain the observed high prevalence of drug abuse before pregnancy.
Non-white ethnic group included all non-Caucasian women.

-Table 2: Were there differences between unadjusted and adjusted model results?

Response: The unadjusted ORs were slightly different from the adjusted ORs. For transparency, both unadjusted and adjusted ORs are presented in Table 3.

Reviewer: 2

Reviewer Name: Susanne Hesselman

Institution and Country

1 Department of Women's and Children's health, Uppsala University, Uppsala, Sweden

2 Center for clinical research, Uppsala University, Falun, Sweden

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This manuscript is clearly written and easy to follow with a focused research question i.e if anxiety and depression increase the risk of preterm birth alone or in conjunction and depending on neighborhood deprivation.

Minor comments:

1) Even if the numbers were limited to allow for stratification of induced and preterm births, it could be interesting to know how many of the preterm births were spontaneous and iatrogenic among exposed and non-exposed.

Response: We were unable to distinguish spontaneous or iatrogenic preterm birth due to the data limitation. This has been acknowledged in discussion as a limitation of this study (page 17, paragraph 1).

2) Odds ratios are calculated but sometimes referred as risk. I think the word risk is better replaced by odds and or likelihood.

Response: This is revised as suggested when it is applicable.

3) Looking at OR. Although not significant, but it might be a question of power, depression but not anxiety seem to be associated with PTB. Any ideas of why these "stress" factor differs from each other?

Response: We agree that non-significance of depression might have been related to the power of the study, which has been acknowledged in discussion section (page 17, paragraph 1). The possible explanations for the difference of preterm birth across these stress factors, anxiety and depression could be: depressive symptoms negatively affect women' self-care and physical functionality, leading to less able to meet the demand of pregnancy, whereas, some level of anxiety during pregnancy increases the self-awareness regarding the demand of pregnancy or motivates the women to stay more focus to maintain the health of her baby and herself.

4) PTB is not easy to prevent. What targeting interventions do you suggest for deprived areas? Psychological care? Prevention of malnutrition and life style factors?

Response: We agree that PTB is not easy to prevent. We suggest that timely psychological screening and management as a targeted intervention for vulnerable group of women may help to reduce the risk of PTB (page 17, conclusion). However, they would need to be evaluated before implementation.

5) Page 8 In 29. EDS change to EPDS

Response: This is revised.

VERSION 2 – REVIEW

REVIEWER	Lesley Smith University of Leeds, UK
REVIEW RETURNED	19-Nov-2019

GENERAL COMMENTS	<p>The authors have tried to address the points I raised previously, however the methods to deal with confounder adjustment have still not been addressed sufficiently.</p> <p>The authors state: “However, these variables did not change or confound the association in the multivariable model and were thus dropped from the model”</p> <p>The selection of confounders to include in the model should not be based on model-based selection methods (as currently described in the paper) as this does not account for the underlying causal structure of the hypothesis. See for example https://www.atsjournals.org/doi/pdf/10.1513/AnnalsATS.201808-564PS</p> <p>The authors may want to consider the use of a direct acyclic diagram to explain their underlying hypothesis and confounder justification.</p> <p>Minor point 2. Article summary section– check grammar in second point</p>
-------------------------	--

REVIEWER	<p>Susanne Hesselman Center for Clinical research Dalarna Womens and Children's Health Uppsala University Sweden</p>
REVIEW RETURNED	28-Nov-2019

GENERAL COMMENTS	<p>Thank you for the revision. I think my previous comments has clearly been addressed and the manuscript improved.</p> <p>Minor comment</p> <p>1) "Both studies recruited pregnancy cohorts between 2008 and 2012 from maternity clinics, high schools, public places, etc. and followed them up". Was it by posters? care providers?</p> <p>2) I assume that women contributed with only one pregnancy in the cohort. If they had more than one delivery during the study period, was the first or second pregnancy included?</p> <p>3) "However, these variables did not change or confound the association in the multivariable model and were thus dropped from the model". I suggest to say that it did not changed the estimates.</p>
-------------------------	--

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Lesley Smith

Institution and Country: University of Leeds, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The authors have tried to address the points I raised previously, however the methods to deal with confounder adjustment have still not been addressed sufficiently.

The authors state:

“However, these variables did not change or confound the association in the multivariable model and were thus dropped from the model”

The selection of confounders to include in the model should not be based on model-based selection methods (as currently described in the paper) as this does not account for the underlying causal structure of the hypothesis. See for example

<https://www.atsjournals.org/doi/pdf/10.1513/AnnalsATS.201808-564PS>

The authors may want to consider the use of a direct acyclic diagram to explain their underlying hypothesis and confounder justification.

Response: Thank you for your comments. The confounder selection is now done based on our prior knowledge or conceptual understanding that the selected variables meet the traditional definition/criteria of confounder. Accordingly, the variables that are associated with both outcome (i.e., preterm birth) and exposure (i.e., anxiety and/or depression) but are not in the causal pathway, based on our prior knowledge (i.e., conceptual understanding based on literature), are now included in the model (page 10). The underlying hypothetical relationship of the variables have been shown using a direct acyclic diagram (supplementary file: Figure 1)

Minor point

2. Article summary section– check grammar in second point

Response: This is corrected.

Reviewer: 2

Reviewer Name: Susanne Hesselman

Institution and Country:

Center for Clinical research Dalarna

Womens and Children's Health Uppsala University

Sweden

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for the revision. I think my previous comments has clearly been addressed and the manuscript improved.

Minor comment

1) "Both studies recruited pregnancy cohorts between 2008 and 2012 from maternity clinics, high schools, public places, etc. and followed them up". Was it by posters? care providers?

Response: Both studies recruited pregnancy cohorts using community-based recruitment strategies. This included face-to-face recruitment in maternity clinics by research assistants or nurses and recruitment in public places using posters, pamphlets, and brochures. This is now described in page 8.

2) I assume that women contributed with only one pregnancy in the cohort. If they had more than one delivery during the study period, was the first or second pregnancy included?

Response: Yes, women contributed only one pregnancy in the cohort (page 7).

3) "However, these variables did not change or confound the association in the multivariable model and were thus dropped from the model". I suggest to say that it did not change the estimates.

Response: This statement has been now deleted as the confounders were selected based on our prior knowledge or conceptual understanding that they fit the criteria of confounders (an acceptable approach to address confounding) as suggested by reviewer 1.

VERSION 3 – REVIEW

REVIEWER	Lesley Smith University of Leeds, UK
REVIEW RETURNED	06-Jan-2020

GENERAL COMMENTS	I am happy that the authors have addressed all my previous comments
REVIEWER	Susanne Hesselman Center for Clinical research Dalarna Institution for Womens and Children's Health Uppsala University
REVIEW RETURNED	31-Dec-2019
GENERAL COMMENTS	My questions has been adressed by authors.