PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Variation in severe maternal morbidity according to socioeconomic position: a UK national case-control study.
AUTHORS	Lindquist, Anthea; Knight, Marian; Kurinczuk, Jenny

VERSION 1 - REVIEW

REVIEWER	Van Roosmalen, jos Leiden University Medical Centre, Obstetrics
REVIEW RETURNED	06-Mar-2013

RESULTS & CONCLUSIONS	this is a well researched important public health issue. My only worry is the way the aORs are presented: on page 10 "Following adjustment, compared with the controls, cases were 1.17 (95%CI 0.94-1.45) times more likely to be in the "intermediate' socioeconomic group than the 'managerial/professional group, etc .." No mention is made here of a non-significant increase, while on the same page, the authors write about BMI: After adjustment, cases had a non-significant 10% increase in the odds of having a BMI of 25 etc.'. Only by redistributing the relatively large group of missing socio-econmic observations into the unemployed group "produced a statistically significant aOR of 1.38 (95%CI 1.11-1.72). This artificially "produced" statistically significant aOR should be discussed in a way whether this redistribution is resembling "the truth".
REPORTING & ETHICS	In addition to what I wrote above, I still have a few remarks: 1. It would be helpful to give the timeframe of the different UKOSS studies in the methods 2. In the end of the discussion where the authors recommend further research, they could refer to the International Network of Obstetric Surveillance Systems, where the authors are the leading group. 3. In the conclusion of abstract and paper the authors state: the data "suggest" that etc. They continue to state that we should research why this association exists etc. I would say: we should first try to confirm the association and then investigate why etc. 4. There are a few typing errors in the manuscript: page 3 conclusion: omit 'an' before independently associated with an etc. page 4: "ethic' should be 'ethnic' page 6: in box 1 uterine rupture: 'explusion' should be 'expulsion' 5. Instead of ref. 26 you better refer to Eur j public health 2011; 21: 229-34 of the same authors which is specifically addressing ethnic disparities

REVIEWER	Laust H Mortensen Associate Professor of Epidemiology University of Copenhagen

REVIEW RETURNED	14-Mar-2013

| GENERAL COMMENTS | Thank you for the invitation to review this study, which I found to be well motivated and well written. The authors should be congratulated for this. As much as I liked the study, I fell that here are two major issues with this paper. I feel that the handling of missing values is inappropriate and should be changed before this manuscript is publishable. Also, I think that the authors overinterpret their statistically insignificant main findings. This should also be addressed in a revision. In some places the manuscript is a little unconventional in term of terminology (e.g. the way ORs are presented, labeling the study a cohort, the definition of confounding etc.), but these are minor things that can easily be fixed.

General comments:
1. Abstract and title: It is a little unclear why the study design is described as a cohort study. I believe that the study design is a case-control design and not a cohort design.
2. Summary: (line 28-33) I believe the confounder control is inappropriate (see below).
3. Method: It is not clear to me why the missing categories are included in the analyses. First, to me the applicability of these estimates is not clear. Second, it is my conviction that the missing-indicator method (MIM) should not be used to handle missing confounder data because it gives a biased estimation of the OR of the association between exposure and outcome. The missing category is a mix of actual levels of the variable and if the variable is a confounder such a category can lead to biased estimates of the overall effect of the study exposure. This holds for even small percentages of missing values. Moreover, the direction of the bias is unpredictable as the direction and magnitude of the bias depends on the pattern in the missing values. Also, the inclusion of a missing-category in e.g. BMI does not imply that the effect size is not underestimated (as stated on page 8: “BMI was included as a categorical variable due to the high proportion of missing data and the concern that by including it as a continuous, women with missing data would be excluded and the effect size underestimated”).
The implications of inclusion of missing categories (also in relation to exposure) should be addressed and I think a discussion of the choice of applying MIM is important, if the authors use this approach. An improved method with less restrictive assumptions could be applied to handle missing values, e.g. multiple imputation (MI).
Also, I think that several of the factors stated as potential confounders are more likely to be mediators between occupation and severe maternal morbidity, e.g. smoking and BMI. I miss an argument for including multiple pregnancy as a confounder. Also, if it is believed that socioeconomic position affects the risk of these pregnancy complications (which is the hypothesis of the study) adjustment for previous pregnancy conditions could imply bias. This should be discussed. For more information on adjustment for pregnancy history see e.g. Hernán et al. Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects. EpidemiologyAm J Epidemiol 2002;155:176–84.
4. Design: It seems that the medical notes of cases are generally more closely examined in relation to covariates (less missing values among cases, except from BMI) (table 1). As information about covariates is obtained by a physician knowing the outcome status of the women, the missing values and/or potential misclassification |

might be differential according to outcome. This could be discussed.
5. I miss a short comment in the introduction on the hypothesis linking socioeconomic position and severe maternal morbidity.
6. The interpretation of the ORs is unconventional. I suggest rephrasing the interpretations. As an example: (page 10, line 23) “compared with controls, cases were 1.17 […] times more likely to be in the ‘intermediate’ socioeconomic group than..” could be rephrased: “..women in the intermediate group had a 17 % higher odds of experiencing severe maternal morbidity compared to women in the managerial/professional group.”
7. I think the authors overinterpret the results. None of the relevant socioeconomic groups yields statistically significant estimates and hence it might be strident to state that e.g. a group in need is clearly identified (page 13, line 8).
Specific comments:
1. Page 2, line 10: I suggest adding ‘defined by occupation’ after socioeconomic position
2. Page 2, line 18: I suggest to use previous instead of past (making it implicit that it is not ‘after’ pregnancy complications)
3. Page 2, line 32: maybe ‘or’ should be ‘and’?
4. Page 2, line 45: settings?
5. Page 3, line 18: 2.256 ◊ 2,256
6. Page 3, line 37: I think it would be nice if you added ‘managerial/professional’ as reference group
7. Page 3, line 50: erase ‘an’
8. Page 4, line 37: add an ‘n’ in ethnic
9. Page 4, line 49-51: I’m not sure what is confounded? I suggest writing: Because minority ethnic groups are often disproportionately represented in lower socioeconomic groups, results attributed to ethnic differences are likely to be confounded by socioeconomic differences. If that is what is meant.
10. Page 6, line 25: a following programme? (Sentence construction?) I do not understand the sentence.
11. Page 8, line 21-26: The argumentation is not correct in relation to missing values and BMI.
12. Page 9, line 6: add a full stop after controls.
13. Page 9, line 18: table 2. Presented estimates are adjusted odds ratios, not adjusted odds.
14. Page 10, line 13-15: it could be argued that some of the conditions in the pre-existing medical condition group might be effects (causal or non-causal) of socioeconomic position, and hence are mediators, not confounders.
15. Page 10, line 32: erase ’be’.
16. Page 10, line 34: add ’95%CI’ in the parenthesis
17. Page 10, line 38: add ’of’ after the odds
18. Page 12, line 20-24: or it might be mediated through lifestyle factors differing across socioeconomic groups.
19. Page 13, line 43-58: I completely fail to understand this paragraph.
20. Page 15, line 5: I do not believe the findings can be interpreted as evidence of a causal pathway.
21. Page 15, conclusion: I suggest to state that the findings were not statistically significant. Likewise, I suggest to add this in the abstract conclusion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Jos van Roosmalen
Leiden University Medical Centre, Obstetrics

This is a well-researched important public health issue. My only worry is the way the aORs are presented: on page 10 "Following adjustment, compared with the controls, cases were 1.17 (95%CI 0.94-1.45) times more likely to be in the "intermediate' socioeconomic group than the 'managerial/professional group, etc .." No mention is made here of a non-significant increase, while on the same page, the authors write about BMI: After adjustment, cases had a non-significant 10% increase in the odds of having a BMI of 25 etc.'.
Only by redistributing the relatively large group of missing socio-economic observations into the unemployed group "produced a statistically significant aOR of 1.38 (95%CI 1.11-1.72). This artificially "produced" statistically significant aOR should be discussed in a way whether this redistribution is resembling "the truth".
Thank you for pointing out these inconsistencies in our presentation. We have revised the results in the light of this comment to make them consistent. We have indicated with all results whether or not they are statistically significant. We have quite clearly stated that our redistribution of the missing group of socio-economic observations is a sensitivity analysis only; we have revised our discussion to take account of this.

In addition to what I wrote above, I still have a few remarks:
1. It would be helpful to give the timeframe of the different UKOSS studies in the methods
This has been added to the Table on definitions of the UKOSS conditions studied.

2. In the end of the discussion where the authors recommend further research, they could refer to the International Network of Obstetric Surveillance Systems, where the authors are the leading group.
We have added this as suggested

3. In the conclusion of abstract and paper the authors state: the data "suggest" that etc. They continue to state that we should research why this association exists etc. I would say: we should first try to confirm the association and then investigate why etc.
We have amended the conclusion as suggested.

4. There are a few typing errors in the manuscript: page 3 conclusion: omit 'an' before independently associated with an etc. Amended

page 4: "ethic' should be 'ethnic'. Amended

page 6: in box 1 uterine rupture: 'explusion' should be 'expulsion'. Amended

5. Instead of ref. 26 you better refer to Eur j public health 2011; 21: 229-34 of the same authors which is specifically addressing ethnic disparities
We have added this reference as suggested

Reviewer: Laust H Mortensen
Associate Professor of Epidemiology
University of Copenhagen

Thank you for the invitation to review this study, which I found to be well motivated and well written. The authors should be congratulated for this. As much as I liked the study, I fell that here are two major issues with this paper. I feel that the handling of missing values is inappropriate and should be changed before this manuscript is publishable. Also, I think that the authors overinterpret their statistically insignificant main findings. This should also be addressed in a revision. In some places the manuscript is a little unconventional in term of terminology (e.g. the way ORs are presented, labelling the study a cohort, the definition of confounding etc.), but these are minor things that can easily be fixed.

General comments:
1. Abstract and title: It is a little unclear why the study design is described as a cohort study. I believe that the study design is a case-control design and not a cohort design.
We have made this correction

2. Summary: (line 28-33) I believe the confounder control is inappropriate (see below).
See response below to point 3.

3. Method: It is not clear to me why the missing categories are included in the analyses. First, to me the applicability of these estimates is not clear. Second, it is my conviction that the missing-indicator method (MIM) should not be used to handle missing confounder data because it gives a biased estimation of the OR of the association between exposure and outcome. The missing category is a mix of actual levels of the variable and if the variable is a confounder such a category can lead to biased estimates of the overall effect of the study exposure. This holds for even small percentages of missing values. Moreover, the direction of the bias is unpredictable as the direction and magnitude of the bias depends on the pattern in the missing values. Also, the inclusion of a missing-category in e.g. BMI does not imply that the effect size is not underestimated (as stated on page 8: "BMI was included as a categorical variable due to the high proportion of missing data and the concern that by including it as a continuous, women with missing data would be excluded and the effect size underestimated"). The implications of inclusion of missing categories (also in relation to exposure) should be addressed and I think a discussion of the choice of applying MIM is important, if the authors use this approach. An improved method with less restrictive assumptions could be applied to handle missing values, e.g. multiple imputation (MI).
Also, I think that several of the factors stated as potential confounders are more likely to be mediators between occupation and severe maternal morbidity, e.g. smoking and BMI. I miss an argument for including multiple pregnancy as a confounder. Also, if it is believed that socioeconomic position affects the risk of these pregnancy complications (which is the hypothesis of the study) adjustment for previous pregnancy conditions could imply bias. This should be discussed. For more information on adjustment for pregnancy history see e.g. Hernán et al. Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects. Epidemiology Am J Epidemiol 2002;155:176–84.

The pattern of missing data was explored extensively in the initial analysis but the paper length restricted how much of this analysis and the findings could be included. Exploration of the missing data demonstrated that the data were not 'missing at random' but that there were in fact systematic differences between the women with complete data and those with missing data, in particular for socioeconomic position. Use of a proxy indicator for 'missing' also showed that women with missing data had different ORs to women with complete data – in particular for socioeconomic position where women with missing data had a higher OR than any other group. Although Multiple Imputation has become popular in recent years in dealing with missing data, it is based principally on the assumption that the missing data are 'missing at random' and cannot be used if there is evidence that this is not the case, as in our study. Wes therefore felt that in the case of a non-random pattern of missing data, Multiple Imputation was not an appropriate method to use and proxy indicators were instead used to demonstrate the OR amongst women with missing data for each variable. A brief explanation of why MI was not used has now been included in the paper methods.

Note that we also conducted a complete case analysis as a sensitivity analysis (final paragraph of the results section) and this did not produce materially different estimated odds ratios associated with socioeconomic position than the proxy indicator model.

With regards to multiple pregnancy as a confounder, we included multiple pregnancy in the analysis as a potential confounder on the basis that the two strongest predictors of multiple pregnancy (maternal age at conception and IVF conception) are both strongly socially patterned in the UK and thus multiple pregnancy is socially patterned. Multiple pregnancy is a known risk factor for pregnancy complications and severe maternal morbidity.

4. Design: It seems that the medical notes of cases are generally more closely examined in relation to covariates (less missing values among cases, except from BMI) (table 1). As information about covariates is obtained by a physician knowing the outcome status of the women, the missing values and/or potential misclassification might be differential according to outcome. This could be discussed.
We have added this to the first paragraph of the discussion as suggested.

5. I miss a short comment in the introduction on the hypothesis linking socioeconomic position and severe maternal morbidity.
We note in the introduction that "Because minority ethnic groups are often disproportionately represented in lower socioeconomic groups, results attributed to ethnic differences are likely to be confounded by socioeconomic differences. The aim of the analysis reported here was to explore whether there is an independent risk of severe maternal morbidity associated with socioeconomic position in the UK."

6. The interpretation of the ORs is unconventional. I suggest rephrasing the interpretations. As an example: (page 10, line 23) "compared with controls, cases were 1.17 […] times more likely to be in the 'intermediate' socioeconomic group than.." could be rephrased: "..women in the intermediate group had a 17 % higher odds of experiencing severe maternal morbidity compared to women in the managerial/professional group."
We understand the referees preferences, however, we feel it would be better to retain our current phrasing, as this describes the relationship in a more comprehensible way to a clinical audience, given the study design.

7. I think the authors overinterpret the results. None of the relevant socioeconomic groups yields statistically significant estimates and hence it might be strident to state that e.g. a group in need is clearly identified (page 13, line 8).
We have revised our phrasing and interpretation extensively in the light of this comment and those of reviewer 1.

Specific comments:
1. Page 2, line 10: I suggest adding 'defined by occupation' after socioeconomic position Amended
2. Page 2, line 18: I suggest to use previous instead of past (making it implicit that it is not 'after' pregnancy complications). Amended
3. Page 2, line 32: maybe 'or' should be 'and'? Amended
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7. Page 3, line 50: erase 'an'. Amended
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9. Page 4, line 49-51: I'm not sure what is confounded? I suggest writing: Because minority ethnic groups are often disproportionately represented in lower socioeconomic groups, results attributed to ethnic differences are likely to be confounded by socioeconomic differences. If that is what is meant.

We have revised this as suggested.

10. Page 6, line 25: a following programme? (Sentence construction?) I do not understand the sentence.
This should read “a rolling programme”; we have corrected.

11. Page 8, line 21-26: The argumentation is not correct in relation to missing values and BMI.
We have corrected.

12. Page 9, line 6: add a full stop after controls. Amended

13. Page 9, line 18: table 2. Presented estimates are adjusted odds ratios, not adjusted odds.
Amended

14. Page 10, line 13-15: it could be argued that some of the conditions in the pre-existing medical condition group might be effects (causal or non-causal) of socioeconomic position, and hence are mediators, not confounders.
This is a possible hypothesis. However, it does not apply to all these conditions. Also, since the distribution of these conditions was so different between cases and controls, and they are known to be associated with severe maternal morbidity, we felt that not including them in the model would potentially invalidate any observed association with socioeconomic position

15. Page 10, line 32: erase ’be’. Amended

16. Page 10, line 34: add ’95%CI’ in the parenthesis. Amended

17. Page 10, line 38: add ’of’ after the odds. Amended

18. Page 12, line 20-24: or it might be mediated through lifestyle factors differing across socioeconomic groups.
We have commented on this as suggested

19. Page 13, line 43-58: I completely fail to understand this paragraph.
This paragraph referred to the unique capacity for the UKOSS studies to be aggregated in order to explore ‘severe maternal morbidity’ as a whole, and the inherent challenges of this approach. Please inform us if you would like the wording changed or further clarification of this paragraph.

20. Page 15, line 5: I do not believe the findings can be interpreted as evidence of a causal pathway.
We agree with the reviewer and have removed reference to this.

21. Page 15, conclusion: I suggest to state that the findings were not statistically significant. Likewise, I suggest to add this in the abstract conclusion.
We have revised our phrasing and interpretation extensively in the light of this comment and those of reviewer 1.

VERSION 2 – REVIEW

REVIEWER	Laust H Mortensen University of Copenhagen
REVIEW RETURNED	14-May-2013

GENERAL COMMENTS	I agree with most of the responses. There are a few places where I fail to follow the authors' arguments, but whether this is of substantial importance for the manuscript is an editorial decision. 1) In my previous review I suggested that multiple imputation (MI) might appropriate. The authors argue against my suggestion to use MI by stating that they think that MI might be inappropriate as the authors observe "systematic differences between the women with complete data and those with missing data, in particular for socioeconomic position". I agree that their observations suggest that data is not missing completely at random, but I want to point out that the assumption in MI not that data is missing completely at random (MCAR), but that it is missing at random conditional on the observed covariates (MAR). This is exactly why I recommended the use of MI. Related to this point, I do think the category of 'missing' for education really lends itself to any straightforward interpretation. 2) I my previous review I suggested that the authors might be adjusting for non-confounders. I think that this may still be the case. For example, I think it that it is unclear how multiple pregnancy is causally related education in a way that would make it appropriate to adjust for it. The authors state that they "included multiple pregnancy in the analysis as a potential confounder on the basis that the two strongest predictors of multiple pregnancy (maternal age at conception and IVF conception) are both strongly socially patterned in the UK and thus multiple pregnancy is socially patterned. Multiple pregnancy is a known risk factor for pregnancy complications and severe maternal morbidity". Let me for the sake of the argument assume that maternal education causes women to postpone pregnancies, which causes an increased age at a given pregnancy and an increased risk of needing/seeking IVF treatment. If this causal scenario is correct then the authors should not adjust for multiple pregnancy (and perhaps not even age at conception or IVF conception) because it is an intermediary variable. If the authors assume that the reason for the association between education and multiple pregnancy is that both are caused by age at conception and IVF conception, then I think it is sufficient to adjust for maternal age at conception and IVF conception. In general, I think that the approached favored by the authors might result in overadjustment of the estimates.

Correction

Lindquist A, Knight M, Kurinczuk JJ. Variation in severe maternal morbidity according to socioeconomic position: a UK national case–control study. *BMJ Open* 2013;**3**:e002742. The order of author names is incorrect. It should be Lindquist A, Kurinczuk JJ, Knight M.

BMJ Open 2013;**3**:e002742corr1. doi:10.1136/bmjopen-2013-002742corr1