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.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Educational disparities in perinatal health in Denmark in the first decade of the 21st century: A register-based cohort study
AUTHORS	Bilsteen, Josephine Funck; Andresen, Josefine Bernhard; Mortensen, Laust Hvas; Hansen, Anne; Andersen, Anne-Marie Nybo

VERSION 1 – REVIEW

REVIEWER	Jennifer Zeitlin Inserm U1153, Paris France
REVIEW RETURNED	10-May-2018

GENERAL COMMENTS	This manuscript explores differences in perinatal health outcomes linked to maternal educational level in Denmark from 2000 to 2009. Following up on previous research, the authors seek to measure whether these inequalities persist and to provide updated estimates of the impact of social factors on perinatal health outcomes. The topic of social inequalities in perinatal health is a major public health issue as this is a mechanism for perpetuating health and social inequality across generations. The fact that these exist in egalitarian societies with strong social safety nets is an important message for researchers, clinicians and policy makers. The study uses high quality data on a very large number of births from Danish birth register. The authors do a good job of underscoring the strengths of their analysis. The manuscript is clear and well written. I have several comments about the analyses. The authors use several outcomes – stillbirth, neonatal mortality, post-neonatal mortality, preterm birth, small for gestational age and congenital anomalies. These are all linked – in particular, preterm and SGA infants face higher risks of death. It would be interesting for this study if the authors could go further and assess whether the mortality differences are explained by the higher rates of preterm birth and fetal growth restriction. Could the authors consider undertaking a mediation analysis to explore what proportion of the impact of maternal education on mortality is due to higher risks of preterm birth and growth restriction? The investigation of all congenital anomalies as one group, ascertained on live births without consideration of stillbirths and TOP, is a weakness of this study. Many pregnancies complicated by severe anomalies are terminated. Furthermore, previous research

has shown that the association of social factors differs by type of anomaly– the risk of T21 is not associated with social factors after adjustment for age, for instance. This group is highly heterogeneous (the list of reportable Eurocat anomalies includes both serious and not very serious defects) which limits its relevance. More thought based on this previous work would make the analysis of this outcome more relevant. In the discussion, the authors state that their results differ from previous studies (perhaps even on the same data source?) – more careful investigation of this previous research and why they find something different is needed. Another option would not be to include this outcome and explore the others in more depth as suggested above.

The authors do not consider multiples in their analysis, but this may be related to education (via age and income) and multiples are at higher risks of all these outcomes. This should be discussed.

This study also raises question about how maternal age should be managed: if longer education (and more focus on career) leads to later childbearing, may that not also be one of the effects of educational level, similar to other lifestyle factors that the authors choose not to include? Some discussion of this point would be welcome.

Finally, the authors introduce their study by providing research results from other disciplines showing that trends in inequality increased in the beginning of the 21st century. In the discussion, it would be good to spend some more time on this point. It seems that inequalities in perinatal health have stayed constant in Denmark over time, but this message should be justified more clearly with respect to the results of previous studies.

More minor comments

The authors use odds ratios to describe risks associated with maternal education. However, this is a cohort study and risk ratios (or risk différences) would be more appropriate.

I didn't understand the sentence: Maternal year of birth was considered implausible after year 1999?

It wasn't intuitive why the authors included the mother's year of birth as opposed to actual year of birth. The results shouldn't change, but this seems more in line with previous analyses which take into consideration secular changes. At least the authors should explain why they chose one instead of the other for their model.

I did not see any information about ethics/IRB. The manuscript should include an explanation about how ethics approvals and access to confidential personal data are managed in the Danish registries.

REVIEWER	Maria M. Morales Suárez-Varela
	Valencia University, CIBERESP, Spain
REVIEW RETURNED	24-May-2018

| GENERAL COMMENTS | Thank you very much for allowing me to review the original article "Educational disparities in perinatal health in Denmark in the first decade of the 21st century: A register study of 649,905 children" (bmjopen-2018-023531) |

	The work is based on the health condition of the mother's perinatal outcomes, thus transferring socioeconomic inequality in health from one generation to the next.
	The aim of this study was to describe the associations between maternal educational level and risk of adverse perinatal outcomes in Denmark during the first decade of the 21 st century. The adverse perinatal outcomes of interest in this study were stillbirth, preterm birth, small-for-gestational age (SGA), congenital anomalies, neonatal mortality and post-neonatal mortality.
	They present the approval of the ethical committee.
	To carry it out they did a longitudinal register linkage study of all live births and stillbirths in Denmark from 2000 through 2009, as recorded in the Danish Medical Birth Register. Information on maternal education level from the Population's Education register of the Danish Medical Birth Register, the Danish National Patient Register, and the Danish Register of Causes of Death. The Danish system of unique person identifiers (CPR-number) was used to link individuals across the different registers in an anonymised data set in Statistics Denmark, which could be assessed via VPN connection from the Department of Public Health, University of Copenhagen.
	A classification of the education of the mother is made. And the characteristics of children at birth are collected. The age of the mother at the time of delivery is used as potential confounders.
	The variable maternal age at birth and birth year of birth was used. Unadjusted and adjusted odds ratios (OR) were presented with a 95% confidence interval.
	The results are well structured according to the objectives. The results tables are clear and contain all the required information. The importance of mother's education is clearly described.
	The discussion is well structured is clear, compare with other works. Justify not including other confusing variables.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Jennifer Zeitlin

Institution and Country: Inserm U1153, Paris, France

Competing Interests: None declared

This manuscript explores differences in perinatal health outcomes linked to maternal educational level in Denmark from 2000 to 2009. Following up on previous research, the authors seek to measure whether these inequalities persist and to provide updated estimates of the impact of social factors on perinatal health outcomes. The topic of social inequalities in perinatal health is a major public health issue as this is a mechanism for perpetuating health and social inequality across generations. The fact that these exist in egalitarian societies with strong social safety nets is an important message for researchers, clinicians and policy makers. The study uses high quality data on a very large number of births from Danish birth register. The authors do a good job of underscoring the strengths of their analysis. The manuscript is clear and well written.

I have several comments about the analyses.

The authors use several outcomes – stillbirth, neonatal mortality, post-neonatal mortality, preterm birth, small for gestational age and congenital anomalies. These are all linked – in particular, preterm and SGA infants face higher risks of death. It would be interesting for this study if the authors could go further and assess whether the mortality differences are explained by the higher rates of preterm birth and fetal growth restriction. Could the authors consider undertaking a mediation analysis to explore what proportion of the impact of maternal education on mortality is due to higher risks of preterm birth and growth restriction?

The investigation of all congenital anomalies as one group, ascertained on live births without consideration of stillbirths and TOP, is a weakness of this study. Many pregnancies complicated by severe anomalies are terminated. Furthermore, previous research has shown that the association of social factors differs by type of anomaly– the risk of T21 is not associated with social factors after adjustment for age, for instance. This group is highly heterogeneous (the list of reportable Eurocat anomalies includes both serious and not very serious defects) which limits its relevance. More thought based on this previous work would make the analysis of this outcome more relevant. In the discussion, the authors state that their results differ from previous studies (perhaps even on the same data source?) – more careful investigation of this previous research and why they find something different is needed. Another option would not be to include this outcome and explore the others in more depth as suggested above.

Authors reply:

Thank you for these very valid comments. We acknowledge that it is important address the mechanisms of socioeconomic inequality and that socioeconomic differences in preterm birth and SGA are likely to contribute to the socioeconomic inequality in perinatal mortality. We think that the mechanisms of socioeconomic inequality should be examined for each of the six perinatal outcomes and that this will require different investigations as the mechanisms are likely to differ.

We also agree that the group all congenital anomalies (excluding minor) is a highly heterogeneous group and that investigation of socioeconomic inequality in specific groups of congenital anomalies would provide greater insights to this association. We have elaborated on the inconsistency in findings from previous studies and this study in section three in the discussion.

However, the aim of this article was to give an overview of socioeconomic inequality in six perinatal outcomes. While we fully acknowledge the validity of the reviewer's comments, we consider her suggestions to be beyond the scope of this article and it would be impossible to encompass in a single article.

The authors do not consider multiples in their analysis, but this may be related to education (via age and income) and multiples are at higher risks of all these outcomes. This should be discussed.

Authors reply:

We have now included a discussion on multiple births in the analyses in section five in the discussion. Based on our assumptions (Please see DAG below) it was not necessary to adjust for multiple births. We assumed that multiple births did not have an independent effect on maternal level of education and that maternal age affects the level of education that a woman can have obtained.
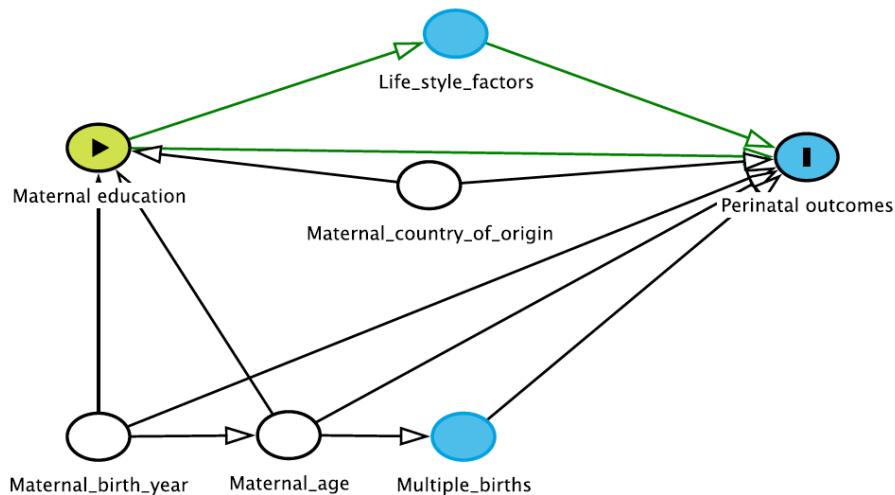
This study also raises question about how maternal age should be managed: if longer education (and more focus on career) leads to later childbearing, may that not also be one of the effects of educational level, similar to other lifestyle factors that the authors choose not to include? Some discussion of this point would be welcome.

Authors reply:

We agree that it could be debated whether maternal age is a confounder or a mediator in the association between maternal education and the perinatal outcomes. We included a discussion on this in section five in the discussion.

Finally, the authors introduce their study by providing research results from other disciplines showing that trends in inequality increased in the beginning of the 21st century. In the discussion, it would be good to spend some more time on this point. It seems that inequalities in perinatal health have stayed constant in Denmark over time, but this message should be justified more clearly with respect to the results of previous studies.

Authors reply:

We agree that it is very interesting to compare development in economic inequality with development in socioeconomic inequality in perinatal health. Based on findings from this study it is not possible to describe how the increased economic inequality in the 21st century affected the socioeconomic inequality in perinatal outcomes.

In addition, it is difficult to conclude whether the gradients we find in this study are stronger or weaker than gradients from previous studies as the studies as use different measures of socioeconomic position, different relative measures and included different potential confounders. What we wrote would be a 'safe' conclusion without exaggerating the findings. We conclude that the educational inequality is still present in the 21st century.

More minor comments
The authors use odds ratios to describe risks associated with maternal education. However, this is a cohort study and risk ratios (or risk différences) would be more appropriate.

Authors reply:
We have estimated and provided risk ratios instead of odds ratios.

I didn't understand the sentence: Maternal year of birth was considered implausible after year 1999?

Authors reply:
We changed this sentence.

It wasn't intuitive why the authors included the mother's year of birth as opposed to actual year of birth. The results shouldn't change, but this seems more in line with previous analyses which take into consideration secular changes. At least the authors should explain why they chose one instead of the other for their model.

Authors reply:
We included maternal birth year as a confounder as the pattern in education changes substantially over the decades (See section six in the discussion). However, as the reviewer also states this should not change the results notably.

I did not see any information about ethics/IRB. The manuscript should include an explanation about how ethics approvals and access to confidential personal data are managed in the Danish registries.

Authors reply:
We included information about ethics in the first section in methods.

Reviewer: 2
Reviewer Name: Maria M. Morales Suárez-Varela
Institution and Country: Valencia University, CIBERESP, Spain
Competing Interests: None declared.

Thank you very much for allowing me to review the original article "Educational disparities in perinatal health in Denmark in the first decade of the 21st century: A register study of 649,905 children" (bmjopen-2018-023531)

The work is based on the health condition of the mother's perinatal outcomes, thus transferring socioeconomic inequality in health from one generation to the next.

The aim of this study was to describe the associations between maternal educational level and risk of adverse perinatal outcomes in Denmark during the first decade of the 21 st century. The adverse perinatal outcomes of interest in this study were stillbirth, preterm birth, small-for-gestational age (SGA), congenital anomalies, neonatal mortality and post-neonatal mortality.

They present the approval of the ethical committee.

To carry it out they did a longitudinal register linkage study of all live births and stillbirths in Denmark from 2000 through 2009, as recorded in the Danish Medical Birth Register. Information on maternal education level from the Population's Education register of the Danish Medical Birth Register, the Danish National Patient Register, and the Danish Register of Causes of Death. The Danish system of unique person identifiers (CPR-number) was used to link individuals across the different registers in an anonymised data set in Statistics Denmark, which could be assessed via VPN connection from the Department of Public Health, University of Copenhagen.

A classification of the education of the mother is made. And the characteristics of children at birth are collected. The age of the mother at the time of delivery is used as potential confounders.

The variable maternal age at birth and birth year of birth was used. Unadjusted and adjusted odds ratios (OR) were presented with a 95% confidence interval.

The results are well structured according to the objectives. The results tables are clear and contain all the required information. The importance of mother's education is clearly described.

The discussion is well structured is clear, compare with other works.

Justify not including other confusing variables.

Authors reply:

Thank you for your kind comments. We included potential confounder variables based on the DAG presented above. We did not include life style factors as we were interested in the overall effect of maternal educational level on adverse perinatal outcome and we believed that life style factors mediate this association (We have addressed this in section five in the discussion)