

## 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

<b>TITLE (PROVISIONAL)</b>	Long-term mortality in mothers with perinatal losses and risk modification by surviving children and attained education: a population-based cohort study.
<b>AUTHORS</b>	Halland, Frode; Morken, Nils-Halvdan; DeRoo, Lisa; Klungsoyr, Kari; Wilcox, Allen; Skjaerven, Rolv

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Marie-Helene BOUVIER-COLLE Inserm UMR1153, EPOPé, Paris, France
<b>REVIEW RETURNED</b>	15-Jun-2016

<b>GENERAL COMMENTS</b>	<p>Since several years by a long serie of papers already published, the authors are pursuing their research on association between cardio vascular mortality of the women and their reproductive story. Here the precise aim is to decorticate the association between perinatal losses and the women mortality, in particular by cardio vascular diseases, taking number of surviving children and education into account.</p> <p>A cohort study is of great value for such question. The present cohort includes women who delivered in Norway from 1967 to 2003 which unique national identification number served for linking Medical birth registry to the population based Cause of death registry.</p> <p>This cohort was used yet and two papers (nos 24 and 26 ) cited in the list of references showed interesting results. One of these previous papers studied the association of women's reproductive history with long term mortality (24) and the other assessed that women with pre eclampsia in their 1st pregnancy had higher rates of cardiovascular death than those who did not have the condition mainly if they have no additionnal birth (26).</p> <p>The present paper with impeccable and rather similar methodology brings new original features.</p> <p>Nevertheless, I have some remarks</p> <p>A weakness of the present analysis lies in the fact that perinatal loss has been considered as a whole although the possible association with cardiovascular causes of death for women probably depend on the etiologies (pre-eclampsia eclampsia versus other obstetric pathologies) of perinatal losses.</p> <p>Secondly, Considering the high level of life expectancy in Norway, as in other</p>
-------------------------	---

	<p>European Countries such as Sweden, France ; Considering that the general mortality of women at 52 years (median age of the present cohort) is very low (dying probability from 50 to 54 is about 0,015) and that cardio vascular diseases are not the main cause of death at this age, I think a more adequate period of women mortality to be studied would be after their fifty.</p> <p>Considering that the life expectancy at 52 years old is about 35 years, in Norway ;</p> <p>My opinion is that the demonstration may be more efficient by analysing the causes of death of women around eighty.</p> <p>Lastly this study shows that the educational level is the most important factor as the past papers did (references 24 and 26). May be at the end of life (around eighty ) the mortality differentials would result from characteristics of perinatal losses more than from education</p>
--	---

<b>REVIEWER</b>	Olof Stephansson Karolinska Institutet Sweden
<b>REVIEW RETURNED</b>	21-Jun-2016

<b>GENERAL COMMENTS</b>	<p>This is a study on the association between perinatal losses and mother's long-term mortality and modification by surviving children and attained education. The study is based on the Norwegian Medical Birth Register. In general the study data and methods is of high quality.</p> <p>General comments</p> <ol style="list-style-type: none"> <li>1. The main question is on the conclusion one can make of the study given the lack of important life-style factors and information on maternal morbidity before and during pregnancy. Was it not possible to include information about maternal morbidity before and during pregnancy in the analysis? What do you mean with the conclusion of the Discussion: "Our study suggests that life-style factors and subfertility outweighs perinatal loss as a risk factor for later life maternal mortality." The present study did not include life-style factors like smoking, BMI, stress or alcohol consumption.</li> <li>2. The definition of perinatal loss includes stillbirth from 16 weeks of gestation and onwards and neonatal mortality. Is it possible to study whether gestational age at stillbirth influences risk? One would assume that earlier fetal loss would be less likely to have an influence on later mortality. This would be interesting to have more information about.</li> <li>3. Why did the study focus on cardiovascular mortality? Was it because of the findings by Hvidtjorn et al., in the Danish study? What does it mean that the Danish study "should be interpreted with caution" in the last section of the first paragraph in the Discussion?</li> </ol> <p>Specific comments</p> <ol style="list-style-type: none"> <li>1. Why did the authors exclude plural pregnancies – could early fetal losses have been plural?</li> <li>2. Women born outside of Norway were excluded, how large was this proportion? Could this influence the generalizability of the study? What about women emigrating from Norway and loss of follow-up?</li> <li>3. There was a significant interaction between perinatal loss and educational level for cardiovascular mortality. How about overall mortality and non-cardiovascular mortality? Please report these</li> </ol>
-------------------------	---

	<p>estimates as well.</p> <p>4. In the tables, please use one or two decimals throughout.</p> <p>5. It would be informative to provide the reader with a table on causes of death in the mothers in an appendix.</p>
--	--

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Marie-Helene BOUVIER-COLLE

Institution and Country: Inserm UMR1153, EPOPé, Paris, France

Competing Interests: none

Since several years by a long serie of papers already published, the authors are pursuing their research on association between cardio vascular mortality of the women and their reproductive story. Here the precise aim is to decorticate the association between perinatal losses and the women mortality, in particular by cardio vascular diseases, taking number of surviving children and education into account.

A cohort study is of great value for such question. The present cohort includes women who delivered in Norway from 1967 to 2003 which unique national identification number served for linking Medical birth registry to the population based Cause of death registry.

This cohort was used yet and two papers (nos 24 and 26 ) cited in the list of references showed interesting results. One of these previous papers studied the association of women's reproductive history with long term mortality (24) and the other assessed that women with pre eclampsia in their 1st pregnancy had higher rates of cardiovascular death than those who did not have the condition mainly if they have no additionnal birth (26).

The present paper with impeccable and rather similar methodology brings new original features.

Nevertheless, I have some remarks

A weakness of the present analysis lies in the fact that perinatal loss has been considered as a whole although the possible association with cardiovascular causes of death for women probably depend on the etiologies (pre-eclampsia eclampsia versus other obstetric pathologies) of perinatal losses.

-We considered this, therefore we redid the analysis excluding mothers with preeclampsia and the results did not change. There is an obvious association between perinatal loss and preterm birth. A preterm birth will, if the gestational age is low, end in a perinatal loss. We therefore divided the cohort in mothers with term and preterm losses to see whether this influenced the outcome. We did not find significant differences between the two groups. See sensitivity analyses Page 10 Lines 231-234.

Secondly,

Considering the high level of life expectancy in Norway, as in other European Countries such as Sweden, France ; Considering that the general mortality of women at 52 years (median age of the present cohort) is very low (dying probability from 50 to 54 is about 0,015) and that cardio vascular diseases are not the main cause of death at this age, I think a more adequate period of women mortality to be studied would be after their fifty.

Considering that the life expectancy at 52 years old is about 35 years, in Norway ;

My opinion is that the demonstration may be more efficient by analysing the causes of death of women around eighty.

-This is an important point, and we agree that the age-specific mortality we are focusing is not the age at death that most women in Norway would expect. However, this is the very reason why we want to focus it. Since everyone will die at some point, we believe that the interesting focus is to find causes of deaths that occur BEFORE the expected age (premature deaths), with an overall aim of finding ways to prevent such premature deaths.

Lastly this study shows that the educational level is the most important factor as the past papers did (references 24 and 26). May be at the end of life (around eighty ) the mortality differentials would result from characteristics of perinatal losses more than from education

-In this paper we show that the most important factor predicting premature maternal death is having a perinatal loss without additional surviving children. This was the case for mothers in both educational strata. However, we also demonstrate that additional surviving children do not eliminate the excess risk completely in mothers with low education as opposed to what it does in mothers with high education. In our data set we do not have enough women dying at the age of 80 years to adequately evaluate the associations between perinatal losses and causes of maternal death at this age. However, we believe that it is likely that these associations will be weaker as the age at death increases, rather than stronger. In the previous study focusing preeclampsia and maternal death, the strongest associations were found for deaths occurring before 50 years, and weakened as the age at death increased (Skjaerven et al., BMJ 2012). On the other hand, we believe that the links between low education and maternal death will be more related to life style factors unlikely to disappear as age increases.

Reviewer: 2

Reviewer Name: Olof Stephansson

Institution and Country: Karolinska Institutet, Sweden

Competing Interests: None declared

This is a study on the association between perinatal losses and mother's long-term mortality and modification by surviving children and attained education. The study is based on the Norwegian Medical Birth Register. In general the study data and methods is of high quality.

General comments

1. The main question is on the conclusion one can make of the study given the lack of important life-style factors and information on maternal morbidity before and during pregnancy. Was it not possible to include information about maternal morbidity before and during pregnancy in the analysis?

-See comment to reviewer 1's first remark.

It is correct that we lack information on life-style factors. However, we argue that we can use education as a proxy. It is established in the literature that low education is associated with low income, smoking, obesity and other negative life-style factors. By grouping the mothers in two levels of education we compare mothers with a low socioeconomic position (and more negative life style factors) to mothers with a more favourable position.

-Maternal morbidity before pregnancy is more difficult to address. Reproducing mothers are relatively young, and low educated mothers tend to be the youngest mothers (in our dataset median age at first birth was 22 years among mothers with low education versus 25 in mothers with high education; Table 1). Manifest chronic disease is rare at this age. As we mention on Page 11 Lines 254-255, nearly to thirds of the women who suddenly die of cardiovascular disease have no previously recognized symptoms (Mosca L et al., 2004). Adjusting or stratifying on manifest maternal disease would therefore probably not be adequate to adjust for predisposing biological risk factors.

What do you mean with the conclusion of the Discussion: “Our study suggests that life-style factors and subfertility outweighs perinatal loss as a risk factor for later life maternal mortality.” The present study did not include life-style factors like smoking, BMI, stress or alcohol consumption.

-In mothers with high education (not low) and additional surviving children, having a perinatal loss was not associated with increased mortality risk. In mothers with low education and perinatal loss we found an attenuation of the risk by surviving children. As already mentioned, it is established in the literature that low education is associated with low income, smoking, obesity and other negative life-style factors. The difference in mortality risk in the two educational groups therefore suggests that negative life-style factors are the more plausible explanation for the difference between the two groups. Further, mothers with low education (low SES) have almost a two-fold (1.7) risk of experiencing a perinatal loss compared to mothers with high education, so a perinatal loss is likely to be an intermediate factor when maternal mortality is the outcome.

The normal response to a perinatal loss is to have another pregnancy and eventually a surviving child (replacement). We find that mothers who fail to have additional children have increased mortality independent of educational level. This indicates that subfertility/ infertility is associated with mortality and is a stronger exposure than a perinatal loss.

2. The definition of perinatal loss includes stillbirth from 16 weeks of gestation and onwards and neonatal mortality. Is it possible to study whether gestational age at stillbirth influences risk? One would assume that earlier fetal loss would be less likely to have an influence on later mortality. This would be interesting to have more information about.

-See comment to reviewer 1's first remark and sensitivity analyses Page 10 Lines 231-234.

3. Why did the study focus on cardiovascular mortality? Was it because of the findings by Hvidtjorn et al., in the Danish study?

-There is a general focus in the literature on reproductive factors and later cardiovascular maternal disease. In accordance with previous studies we feel that this is an appropriate focus.

What does it mean that the Danish study “should be interpreted with caution” in the last section of the first paragraph in the Discussion?

-We question that they can control for predisposing disease and isolate the effect of bereavement (see response to your first comment). We also question the way they have handled social confounding: They adjusted for educational level at the time of the first pregnancy and neglected that many mothers will complete their education after giving birth to their first child. Also: our results show that educational level is an effect modifier, and thus should NOT be adjusted for.

We have rephrased the section and the phrase “should be interpreted with caution” has been removed. See Page 11 Lines 243-259.

#### Specific comments

1. Why did the authors exclude plural pregnancies – could early fetal losses have been plural?

-Mothers with plural pregnancies are much more at risk for experiencing perinatal losses than singleton mothers. Also, a plural pregnancy is a bigger burden on the mother's biology than a singleton pregnancy is, and therefore may show other causal relations with later maternal mortality than a singleton pregnancy. We believe that this should rather be focused in a separate paper, and in the present study, we chose to exclude them to avoid bias. In the Medical Birth Registry of Norway, a birth with one live child in addition to one stillbirth/fetal loss or a birth with two fetal losses/stillbirths would still be listed as twin pregnancies, except for situations where one fetus is lost very, very early

in pregnancy and is not present as a fetus at birth.

2. Women born outside of Norway were excluded, how large was this proportion?

-7.9%.

Could this influence the generalizability of the study?

-We excluded mothers born outside Norway in order to handle social confounding. There is a high proportion of mothers born outside Norway without educational level registered in the National Education Database and the diversity in backgrounds could affect both perinatal losses and long-term mortality. The way we see it, the generalizability is not compromised, but, as we also state in strengths and weaknesses, the study applies best to developed countries where selective fertility is strong.

What about women emigrating from Norway and loss of follow-up?

-In the STROBE-statement we commented on emigration:

“WE HAVE NOT COMMENTED ON EMIGRATION. WE FOUND, FOR THE MOST IMPORTANT YEARS OF OUR STUDY (1967-1980) THAT EMIGRATION OF MOTHERS WAS LESS THAN 1%. CONFINED TO WOMEN BORN IN NORWAY (OUR INCLUSION CRITERIA), THIS NUMBER IS LESS THAN 0.5%.”

3. There was a significant interaction between perinatal loss and educational level for cardiovascular mortality. How about overall mortality and non-cardiovascular mortality? Please report these estimates as well.

-Overall mortality: 0.084 (NS).

Non-CVD mortality: 0.40 (NS).

Included in the revision. See Page 8 Lines 185-186.

4. In the tables, please use one or two decimals throughout.

-The tables now use one decimal throughout where appropriate.

5. It would be informative to provide the reader with a table on causes of death in the mothers in an appendix.

-Thank you for this important comment. We absolutely agree that causes of maternal death outside cardiovascular death would be interesting. We have provided some data on causes of death in mothers with low versus high education on pages 12-13, lines 278-286. However, in our view this is outside the scope of the present paper and we plan to focus other causes of death in a separate paper. We therefore hope that the referee agrees that we do not include it here (the present paper already has quite a lot of tables and information, and we would like to keep it focused).

## Correction

Halland F, Morken N-H, DeRoo LA, *et al.* Long-term mortality in mothers with perinatal losses and risk modification by surviving children and attained education: a population-based cohort study. *BMJ Open* 2016;6:e012894

The author affiliations were listed incorrectly. The correct author affiliations should be:

Frode Halland,<sup>1,2</sup> Nils-Halvdan Morken,<sup>1,2,3</sup> Lisa A DeRoo,<sup>1,4</sup> Kari Klungsoyr,<sup>1,5</sup> Allen J Wilcox,<sup>4</sup> Rolv Skjaerven<sup>1,5</sup>

<sup>1</sup>Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway,

<sup>2</sup>Department of Obstetrics & Gynecology, Haukeland University Hospital, Bergen, Norway,

<sup>3</sup>Department of Clinical Science, University of Bergen,

<sup>4</sup>Epidemiology Branch, NIEHS/NIH, Durham, North Carolina, USA,

<sup>5</sup>Medical Birth Registry of Norway, Norwegian Institute of Public Health, Bergen, Norway

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

*BMJ Open* 2016;6:e012894corr1. doi:10.1136/bmjopen-2016-012894corr1



CrossMark