

## 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>	Risk factors and between-hospital variation of caesarean section in Denmark: a cohort study
<b>AUTHORS</b>	Wehberg, Sonja; Sørensen, Rikke; Gradel, Kim; Schiøler Kesmodel, Ulrik; Munk, Lis; Andersson, Charlotte; Jølving, Line; Nielsen, Jan; Nørgård, Bente

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Karel Kostev QuintilesIMS, Germany; University Clinic of Marburg, Germany
<b>REVIEW RETURNED</b>	06-Sep-2017

<b>GENERAL COMMENTS</b>	<p>This is well written and very interesting manuscript. I have no major comments. Only some recommendations and thoughts:</p> <p>1) In the introduction "the reasons for the steep rise remain mysterious". I am not sure if the term "mysterious" is appropriate in this case.</p> <p>2) Methods : "The data source was the Danish Medical Birth Register". Could authors please write 1-2 sentences about how such database can be accessed as in many other countries such databases do not exist or cannot be used by scientists.</p> <p>3) Tables 1-3: instead of OR: 1.00 in the reference group I would better include the term "Reference"; I find it more clear, but authors can decide.</p>
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<b>REVIEWER</b>	Alexander Humberg Department of Pediatrics, Neonatology and Pediatric Intensive Care, University Hospital of Schleswig-Holstein, Campus Luebeck, Germany
<b>REVIEW RETURNED</b>	13-Sep-2017

<b>GENERAL COMMENTS</b>	<p>The authors of this paper study the very important question of risk factors leading to CS and ECS. The paper is written in a good and fluent english and the scientific question is clearly mentioned. Unfortunately, to my mind there are some lethal flaws who need profound revision:. Especially, type I error is not tested.</p> <p>Page 4 Line 9: I could not find citation no. 1 on pubmed</p>
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	<p>Line 11: there is no overall risk for subsequent pregnancies, see Acta Obstet Gynecol Scand. 2017 Sep;96(9):1053-1062. doi: 10.1111/aogs.13163. Epub 2017 Jun 26. Mode of first delivery and severe maternal complications in the subsequent pregnancy. Colmorn LB et al</p> <p>Line 11-18: RDS is more often seen in preterm infants &gt; 34 weeks gestation. But CS seems to be a very important factor to reduce complications in preterms &lt; 30 weeks gestation and infants with breech presentation. Reduction could improve neonatal outcome: e.g.: Acta Obstet Gynecol Scand. 2017 Apr;96(4):479-486. doi: 10.1111/aogs.13097. Epub 2017 Mar 9. Neonatal morbidity after spontaneous labor onset prior to intended cesarean delivery at term: a cohort study. Glavind J et al</p> <p>Eur J Obstet Gynecol Reprod Biol. 2017 May;212:144-149. doi: 10.1016/j.ejogrb.2017.03.032. Epub 2017 Mar 22. Delivery mode and intraventricular hemorrhage risk in very-low-birth-weight infants: Observational data of the German Neonatal Network. Humberg A et al</p> <p>J Health Econ. 2015 Jan;39:289-302. doi: 10.1016/j.jhealeco.2014.07.004. Epub 2014 Aug 13. Can Caesarean section improve child and maternal health? The case of breech babies. Jensen VM, Wüst M.</p> <p>BJOG. 2013 Aug;120(9):1123-32. doi: 10.1111/1471-0528.12278. Epub 2013 May 20. Elective caesarean section at 38 weeks versus 39 weeks: neonatal and maternal outcomes in a randomised controlled trial. Glavind J</p> <p>Acta Obstet Gynecol Scand. 2011 Jul;90(7):767-71. doi: 10.1111/j.1600-0412.2011.01143.x. Epub 2011 May 27. Consequences of the Term Breech Trial in Denmark. Hartnack Tharin JE, Rasmussen S, Krebs L.</p> <p>Line 21: citation 6 claims high variation and no increase of CS!</p> <p>Line 32-33: This may also be due to improved neonatal outcomes and the possibility to give preterm infants a better chance to survive today than 1973!</p> <p>Line 54: This is a very good intention, but the authors can not give good explanations why smaller hospitals have lower rates of CS.</p> <p>Page 7 Line 4: unfortunately, no information about the type I error level was given, p-value is missing! a CI with a crossing 1 seems not very significant and sadly this is nowhere mentioned (e.g. Page 7, l 42-43; Page 8. l 38; Table 1-2).</p> <p>Page 8 line 34: the word 'significantly' is not clear, because no data about p-value are mentioned</p>
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	<p>Page 9 Line 33: The first sentence of the discussion is not true: no significancies were tested. A further problem of the study is that some neonatal risk factors are missing. Please discuss, why the risk for ECS in large centers decreased from 2009 to 2010.</p> <p>Page 10 Line 13-33: well discussed!</p> <p>Page 11 Line 4: should we really reduce the CS proportion? For me it is more important to select those infants who benefit from CS, therefore it is important for an analysis like yours to look at neonatal reasons for CS (see citation 3 and 4). Acta Obstet Gynecol Scand. 2017 Jul;96(7):862-867. doi: 10.1111/aogs.13113. Epub 2017 Apr 3. Decline in stillbirths and perinatal mortality after implementation of a more aggressive induction policy in post-date pregnancies: a nationwide register study. Zizzo AR et al</p> <p>Therefore, your paper shows, that Denmark has a good functioning health system, because breech presentation (especially in preterms) has a high risk for perinatal complications.</p> <p>Line 11: please discuss, why in smaller hospitals the rate of CS is less than in larger ones. There are a lot of national differences and for the reader it is easier to understand the local system.</p> <p>Page 16-19: missing p values Page 16 Line 22: wrong values in 95%CI, OR 0.02? Line 49, 51: no significancies</p> <p>Page 18 Line 4: CI doubled</p>
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<b>REVIEWER</b>	Alison Macfarlane City, University of London England
<b>REVIEW RETURNED</b>	22-Sep-2017

<b>GENERAL COMMENTS</b>	<p>The authors have chosen an important topic and it is informative to see it investigated in a country where the caesarean section rate, although possibly still too high in the authors' opinion, had stopped rising and is well below the rates in many high income countries. The authors have used data from the well-established Danish Medical Birth Registry. They are aware of the limitations of these routinely collected data, but the data are nevertheless of considerably higher quality than routine data in many other countries. A limitation they do not mention is the small size of their country, with fewer than 60,000 births per year and only 29 maternity units, making it statistically more challenging to detect outliers. The authors' risk adjusted analysis confirms associations between elective and emergency caesarean section rates and common risk factors.</p> <p>They subdivide these into maternal related factors, clinical complications and maternity unit related but find strong associations</p>
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	<p>with maternity care related factors, previous caesarean section and breech presentation. It would be useful to see a more structured approach to their second question, to investigate the extent to which differences between maternity units are attributable to differences between the women giving birth and their clinical complications and the extent to which this reflects differences in clinical practice. The authors do this to some extent in their analysis of outcomes for low risk nulliparous women, but they could bring out the implications of this more strongly when interpreting the results of this analysis. In particular:</p> <ol style="list-style-type: none"> <li>1. Given the controversies about mode of delivery for breech presentation, it would be useful to see breech births analysed separately, although I appreciate that numbers may be too small to do this in detail.</li> <li>2. Previous caesarean section is identified as a key risk factor in the analyses. It would be informative to see primary and repeat caesarean section rates analysed separately.</li> <li>3. It would also be informative to see if rates of operative vaginal delivery varied between maternity units and whether there were associations between these and rates of caesarean section, especially emergency caesarean section.</li> <li>4. The authors comment that it is perhaps unexpected to find variations in clinical practice in their well regulated country. It would be useful to know if there are published national clinical guidelines, although as shown in some of the articles they reference from other countries, these do not necessarily prevent variations in clinical practice.</li> </ol> <p>Minor points</p> <ol style="list-style-type: none"> <li>1. To interpret data about night and weekend birth, it would be useful to know when elective caesareans are scheduled to take place in Danish hospitals and the extent to which births as a whole take place on weekdays in the day time.</li> <li>2. While the authors' English is excellent, there are a few points of detail which need correction.             <ol style="list-style-type: none"> <li>a) They tend to use causal language, while what they are investigating in an observational study is associations. So, for example, their objectives should say that they aimed to estimate associations between risk factors and CS rates.</li> <li>b) Data are 'recorded' not 'registered', unless an official process such as birth registration is involved.</li> <li>c) The authors use the term 'stimulation'. I presume what is meant is 'augmentation' of labour. The authors should check for the correct word in English and define it.</li> </ol> </li> </ol>
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Reviewer Name: Karel Kostev

Institution and Country: QuintilesIMS, Germany; University Clinic of Marburg, Germany Please state any competing interests: None declared

Please leave your comments for the authors below

This is well written and very interesting manuscript. I have no major comments. Only some recommendations and thoughts:

- 1) In the introduction "the reasons for the steep rise remain mysterious". I am not sure if the term "mysterious" is appropriate in this case.
- 2) Methods: "The data source was the Danish Medical Birth Register". Could authors please write 1-2 sentences about how such database can be accessed as in many other countries such databases do not exist or cannot be used by scientists.
- 3) Tables 1-3: instead of OR: 1.00 in the reference group I would better include the term "Reference"; I find it more clear, but authors can decide.

Response: The manuscript has been revised according to all the above recommendations.

Reviewer: 2

Reviewer Name: Alexander Humberg

Institution and Country: Department of Pediatrics, Neonatology and Pediatric Intensive Care, University Hospital of Schleswig-Holstein, Campus Luebeck, Germany Please state any competing interests: None declared

Please leave your comments for the authors below

Comment: The authors of this paper study the very important question of risk factors leading to CS and ECS. The paper is written in a good and fluent english and the scientific question is clearly mentioned.

Response: Unfortunately, to my mind there are some lethal flaws who need profound revision: Especially, type I error is not tested.

Before we address your points individually, we would like to make two more general comments. First, we agree, that the ultimate goal of research should focus on the question of how to optimize the decision for or against CS, that is, how to select fetuses – and mothers - who benefit from CS, or not. To be able to do so would imply quantifying short and long term consequences for both infants and mothers, and ultimately, assigning costs. This is far beyond the scope of our study. As a very first step, we simply wanted to see whether there was more-than-random variation between risk-adjusted CS rates of different maternity units in the rather small country of Denmark. A systematic variation would indicate different practices, which in turn indicate a potential for optimization – however optimization may be defined.

Second, we would like to apologize for the sloppiness regarding p-values. A sentence regarding the general statistical significance level is added in section statistical analysis. We chose to present odds ratios without the corresponding p-values because (1) with our rather large sample sizes, almost any effect would turn out to be statistically – but not necessarily clinically – significant, (2) as you point out, there is a correspondence between confidence intervals and p-values, and p-values do not add extra information beyond the CIs, and (3) our risk models for elective and non-elective CS were essentially just the means to produce risk-adjusted rates to investigate inter-hospital variation. Therefore, we went for a full-model approach without any model selection procedures, that is, without taking into

account the statistical significance of single factors. But since we are discussing the results of the risk models, we should have defined statistical significance properly, which is now done. P-values have not been added in the tables as yet. Of course, these will be added, should the editor take your view.

Page 4

Line 9: I could not find citation no. 1 on pubmed

Response: This citation is from an expert review on Medscape.com, which is featuring peer-reviewed original medical articles. We believe the article relevant, although it is not in PubMed.

Line 11: there is no overall risk for subsequent pregnancies, see Acta Obstet Gynecol Scand. 2017 Sep;96(9):1053-1062. doi: 10.1111/aogs.13163. Epub 2017 Jun 26. Mode of first delivery and severe maternal complications in the subsequent pregnancy.

Colmorn LB et al

Response: Thank you for drawing our attention to this recently published article. We substituted our original reference with this one. However, we believe that this article provides evidence that there is a risk in subsequent pregnancies after CS. Table 2 shows the rates and risk of complications after a first CS compared to a first vaginal delivery (adjusted relative risk of 5.5 for abnormally invasive placenta and adjusted relative risk of 160 for uterine rupture). Therefore, the sentence in the manuscript is unchanged.

Line 11-18: RDS is more often seen in preterm infants > 34 weeks gestation. But CS seems to be a very important factor to reduce complications in preterms < 30 weeks gestation and infants with breech presentation. Reduction could improve neonatal outcome:

e.g.:

Acta Obstet Gynecol Scand. 2017 Apr;96(4):479-486. doi: 10.1111/aogs.13097. Epub 2017 Mar 9. Neonatal morbidity after spontaneous labor onset prior to intended cesarean delivery at term: a cohort study.

Glavind J et al

Response: This is an interesting article on neonatal comorbidity. The study focuses on CS for gestational ages 37-40 weeks and on labor-onset prior to CS compared to non-labor CS. It does not add information on prematurity or on the risk of Respiratory Distress Syndrome after CS compared to vaginal delivery, and has therefore not been included in our reference list.

Eur J Obstet Gynecol Reprod Biol. 2017 May;212:144-149. doi: 10.1016/j.ejogrb.2017.03.032. Epub 2017 Mar 22. Delivery mode and intraventricular hemorrhage risk in very-low-birth-weight infants: Observational data of the German Neonatal Network. Humberg A et al

Response: Thank you for drawing our attention to this article, which we have included in our reference list. We also added a sentence in the introduction that CS in preterm infants is associated with a better outcome and reduced neonatal morbidity and mortality.

J Health Econ. 2015 Jan;39:289-302. doi: 10.1016/j.jhealeco.2014.07.004. Epub 2014 Aug 13. Can Caesarean section improve child and maternal health? The case of breech babies. Jensen VM, Wüst M.

Response: The discussion on the mode of delivery in breech presentation (CS versus vaginal delivery) is a very interesting topic, but not the focus of our study. There are many articles on this, and a thorough discussion of CS versus vaginal delivery in case of breech presentation (which accounts for up to 5% of our study population) in our introduction is beyond the scope of our study. Since this

one article cannot act as a representative of this topic, we chose to not include it. See also our reply to reviewer 3 below.

BJOG. 2013 Aug;120(9):1123-32. doi: 10.1111/1471-0528.12278. Epub 2013 May 20.  
Elective caesarean section at 38 weeks versus 39 weeks: neonatal and maternal outcomes in a randomised controlled trial. Glavind J

Response: This study was comparing elective CS scheduled at 39 weeks compared to 38 weeks of gestation in uncomplicated pregnancies, and they found no increased risk of adverse neonatal or maternal outcomes between the two groups. This study has not been included in our reference list.

Acta Obstet Gynecol Scand. 2011 Jul;90(7):767-71. doi: 10.1111/j.1600-0412.2011.01143.x. Epub 2011 May 27. Consequences of the Term Breech Trial in Denmark. Hartnack Tharin JE, Rasmussen S, Krebs L.

Response: This is another interesting study on breech presentation, but as mentioned earlier the discussion on this specific topic is beyond the scope of this article, and the study is therefore not included.

Line 21: citation 6 claims high variation and no increase of CS!

Response: We agree that the data in that study were on high variation and not on increase of CS. However, the authors state in their introduction: "Overall rates of cesarean delivery in the United States have increased in the past 3 decades without a corresponding positive impact on perinatal or maternal outcomes". Therefore, it was retained as reference.

Line 32-33: This may also be due to improved neonatal outcomes and the possibility to give preterm infants a better chance to survive today than 1973!

Response: You are right. This has been added to the sentence.

Line 54: This is a very good intention, but the authors can not give good explanations why smaller hospitals have lower rates of CS.

Response: In the discussion section on page 9 the centralization of risk births is mentioned and we have added a further description of the smaller hospitals (criteria for delivery: expected normal delivery by health women at term).

Page 7

Line 4: unfortunately, no information about the type I error level was given, p-value is missing! a CI with a crossing 1 seems not very significant and sadly this is nowhere mentioned (e.g. Page 7, I 42-43; Page 8. I 38; Table 1-2).

Response: See general comment above. Since p-values add no new information beyond the CIs we have not included p-values as yet.

Page 8

line 34: the word 'significantly' is not clear, because no data about p-value are mentioned

Response: See general comment above.

Page 9



Line 33: The first sentence of the discussion is not true: no significancies were tested.

Response: See general comment above regarding significance.

A further problem of the study is that some neonatal risk factors are missing. Unfortunately, our dataset does not include further neonatal risk factors. This is now mentioned as a limitation.

Response: Please discuss, why the risk for ECS in large centers decreased from 2009 to 2010. We would very much like to do so, but we do not even have a good hypothesis to propose. We could only state, that we do not have an explanation for the decrease. Again, since this is not the primary focus of our study, we decided against to (not) discuss this further. As a consequence, the corresponding results should maybe be removed?

Page 10

Response: Line 13-33: well discussed!

Page 11

Line 4: should we really reduce the CS proportion? For me it is more important to select those infants who benefit from CS, therefore it is important for an analysis like yours to look at neonatal reasons for CS (see citation 3 and 4).

Acta Obstet Gynecol Scand. 2017 Jul;96(7):862-867. doi: 10.1111/aogs.13113. Epub 2017 Apr 3. Decline in stillbirths and perinatal mortality after implementation of a more aggressive induction policy in post-date pregnancies: a nationwide register study.

Zizzo AR et al

Response: You are, of course, right in the sense that CS should not be reduced, if the neonatal morbidity/mortality increases due to the reduction in rate of CS. This has been added to the sentence. Our dataset does not include further neonatal risk factors.

Zizzo AR et al studied the changed in induction guidelines in Denmark, and the more aggressive induction policy did not increase the risk of CS. The article is not included in our reference list.

Comment: Therefore, your paper shows, that Denmark has a good functioning health system, because breech presentation (especially in preterms) has a high risk for perinatal complications.

Line 11: please discuss, why in smaller hospitals the rate of CS is less than in larger ones. There are a lot of national differences and for the reader it is easier to understand the local system.

Response: This has been added on page 9 (there are specific criteria for delivery in smaller hospitals such as expected normal delivery at term), whereas larger hospitals have more complicated deliveries with e.g. sick foetus, maternal comorbidities, preterm delivery, high maternal BMI leading to a higher rate of CS.

Page 16-19: missing p values

Since p-values add no new information beyond the CIs we have not included p-values as yet.

Page 16

Line 22: wrong values in 95%CI, OR 0.02?

Response: No, this is correct, since almost no elective procedures are performed at night-time.

Line 49, 51: no significancies



Response: Correct, these confidence intervals include the null hypothesis of 1. . This is mentioned on page 7 line 26.

Page 18

Line 4: CI doubled

Response: Thank you, we missed that in our proofreading.

Reviewer: 3

Reviewer Name: Alison Macfarlane

Institution and Country: City, University of London, England

Please state any competing interests: None declared.

Please leave your comments for the authors below

Comment: The authors have chosen an important topic and it is informative to see it investigated in a country where the caesarean section rate, although possibly still too high in the authors' opinion, had stopped rising and is well below the rates in many high income countries.

The authors have used data from the well-established Danish Medical Birth Registry. They are aware of the limitations of these routinely collected data, but the data are nevertheless of considerably higher quality than routine data in many other countries. A limitation they do not mention is the small size of their country, with fewer than 60,000 births per year and only 29 maternity units, making it statistically more challenging to detect outliers.

Response: This has been added to the discussion. As shown in Figure 1, we actually did find outliers despite the small size (few units).

Comment: The authors' risk adjusted analysis confirms associations between elective and emergency caesarean section rates and common risk factors. They subdivide these into maternal related factors, clinical complications and maternity unit related but find strong associations with maternity care related factors, previous caesarean section and breech presentation. It would be useful to see a more structured approach to their second question, to investigate the extent to which differences between maternity units are attributable to differences between the women giving birth and their clinical complications and the extent to which this reflects differences in clinical practice. The authors do this to some extent in their analysis of outcomes for low risk nulliparous women, but they could bring out the implications of this more strongly when interpreting the results of this analysis.

In particular:

1. Given the controversies about mode of delivery for breech presentation, it would be useful to see breech births analysed separately, although I appreciate that numbers may be too small to do this in detail.
2. Previous caesarean section is identified as a key risk factor in the analyses. It would be informative to see primary and repeat caesarean section rates analysed separately.
3. It would also be informative to see if rates of operative vaginal delivery varied between maternity units and whether there were associations between these and rates of caesarean section, especially emergency caesarean section.

Response: We agree that more subgroup analyses could have contributed to valuable insights. We even discussed, at an earlier stage, to split the analyses into the 10 Robson subgroups, but subsequently decided against it, mostly to keep a strict focus. We made sure to include as many relevant factors as possible, so even though we opted for an adjustment approach instead of a stratification (subgroup analysis) approach, these factors have been considered.

In view of the lively, ongoing discussion about the handling of breech presentations, we feel that the inclusion of a specific breech subgroup would go beyond the scope of our article. In particular, because in Denmark, CS rates for breech and for previous CS are rather low compared to other published rates, and we would need to discuss in length these Danish “peculiarities” [In Denmark, care during pregnancy and childbirth is primarily provided by midwives. In pathological and risk pregnancies or births there is, of course, a close cooperation with an obstetrician. Vaginal birth is the primary choice for mode of delivery. For previous CS, the common approach is a confidence in VBAC (vaginal birth after CS), if the right precautions and recommendations for the care are met. Obstetricians make the final decision for mode of delivery in cooperation with the pregnant woman. Since almost all births take place in a public hospital, and labor care is organized suitably, it is regarded as possible and safe to try a vaginal birth, even with previous CS or breech presentation - it is rather uncomplicated to change to CS at short notice.]

With respect to other outcome measures (primary versus repeat CS, operative vaginal delivery), we explored several possibilities during our analysis (for example, whether the combined rates of CS and instrumental delivery were constant). Again, we decided against to include them in this manuscript to retain focus of our paper.

4. The authors comment that it is perhaps unexpected to find variations in clinical practice in their well regulated country. It would be useful to know if there are published national clinical guidelines, although as shown in some of the articles they reference from other countries, these do not necessarily prevent variations in clinical practice.

Response: In Denmark, there are currently four national guidelines regarding CS organized through the Danish Society for Obstetrics and Gynecology (DSOG), which consists of Danish specialists in obstetrics and gynecology and younger doctors in training: Guideline for acute CS classification and organization (2009), Guideline for handling women with previous CS (2013), Guideline for CS at term – surgical technique and practical handling (2016), and Guideline for handling maternal request (2017). In general, such a guideline is developed by a working group of 10-12 people and mainly based on a review of the current scientific literature. The proposed guideline is then presented at an annual meeting among Danish obstetricians and discussed until consensus is reached.

There is no DSOG guideline covering decision making for CS in general (this has been added to the introduction). Furthermore, the existing guidelines are only indicative, since each clinical situation (condition of the patient and other relevant current clinical information) must be individually evaluated. The physician must then act according to his/hers experience, knowledge and judgement.

#### Minor points

The manuscript has been revised according to your following minor points.

1. To interpret data about night and weekend birth, it would be useful to know when elective caesareans are scheduled to take place in Danish hospitals and the extent to which births as a whole take place on weekdays in the day time.

2. While the authors’ English is excellent, there are a few points of detail which need correction.

- a) They tend to use causal language, while what they are investigating in an observational study is associations. So, for example, their objectives should say that they aimed to estimate associations between risk factors and CS rates.
- b) Data are 'recorded' not 'registered', unless an official process such as birth registration is involved.
- c) The authors use the term 'stimulation'. I presume what is meant is 'augmentation' of labour. The authors should check for the correct word in English and define it.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Karel Kostev QuintilesIMS, Frankfurt am Main, Germany University Clinic of Marburg, Germany
<b>REVIEW RETURNED</b>	31-Oct-2017
<b>GENERAL COMMENTS</b>	The manuscript has been revised according to all recommendations. I have no further comments.