PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Caesarean Section in Uninsured Women in the United States: Systematic Review and Meta-analysis
AUTHORS	Hoxha, Ilir; Braha, Medina; Syrogiannouli, Lamprini; Goodman, David C; Jüni, Peter

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Simone G Diniz Institution and Country: University of São Paulo Brazil Competing interests: None declared
REVIEW RETURNED	07-Aug-2018

GENERAL COMMENTS	This is a very interesting paper about a very relevant issue, using a really large database, and I suggest some modifications for improving its potential impact. (1) As the references 6 and 8 show, the cut-off for suggested caesarean rates by World Health Organization was not 15-19%, but 10-15% in ref 6 (1985 WHO), and in 2016, the suggested rate was that over 10% there is no evidence of maternal or neonatal improvements. The 2016 recognizes that this include inconclusive studies and there are areas of uncertainty, but the 10% or 10-15 % are lower than that used in the paper (15 or 19%) to consider underuse. (2) Because "distribution" of caesarean can be problematic (more for those who don't need, less for those who need), in the last decade the international scientific and policy-making community (WHO etc.) started using the Robson criteria to assess how appropriate or not a CS indication was. As in the large groups 1 and 3, for example, rates under 5 % are very ok, while in babies in transverse/cormic presentation (group 9, very small) the CS rate should 100%. The issue of caesarean underuse or overuse was much resolved with this classification, so I wonder why it was not used, or even mentioned. (3) The Robson criteria could be used for at least a part of the sample, considering the data presented in Appendix 3 (parity, previous caesarean, gestational age, etc). If this is not possible, not using the Robson classification should be stated as a limitation of the study. (4) In the mechanism, the authors point to previous publications that "One likely factor is that financial incentives are stronger with private insurance than in the publicly insured or uninsured". "These incentives result from higher payment for CS by private insurers through reimbursement arrangements that encourage more expensive procedures as means to increase profits, as well as providers' (hospitals and individual physicians) responses to these incentives."

"The responses to incentives by hospitals exist in the form of patient scheduling policies that direct privately insured patients to profit inclined physicians." And so on. But this is not properly in the abstract, where it should be clearly stated.

(5) The study concludes that the OR was lower for uninsured women (compared with privately insured, or to insured in general), and in the last appendix (6) are the rates, classified by possible underuse. Should we consider underuse if women did need it and did not get it? Or also when women did not need it and the woman herself and the baby had only the negative outcomes of an unnecessary surgery, including additional risk of infection, haemorrhage, pain, breastfeeding difficulties, iatrogenic prematurity, poor foetal-to-neonatal transition? The authors stress the negative part of having less caesarean (a possible underuse, but if you consider 10-15%, this is not the case), and a more balanced view is needed here.

REVIEWER	Reviewer name: Ana Pilar Betran Institution and Country: World Health Organization, Geneva, Switzerland Competing interests: None declared
REVIEW RETURNED	09-Aug-2018

GENERAL COMMENTS	This is a well written manuscript presenting the results of a systematic review and meta-analysis of the odds ratio of giving birth by caesarean section of uninsured women vs insured women in United States. This is an interesting analysis in the global context of the continuous increase of caesarean section rates worldwide and the debate on equity of the use of caesarean section since in many settings, overuse and underuse coexist. Some comments for consideration: • Methods: page 7, exclusion/inclusion criteria could be expanded and made more detailed. This includes only data for United States so all other countries were excluded. Were any specific groups of women excluded (e.g. race, adolescents, older women, specific pathologies, HIV, socio-economic status); any minimal sample size required? Any specific indications for CS included/excluded? I think it deserve a sentence in the methods to clarify this criteria and let the reader know that all this was considered at planning stage. Also, since the pre-specified primary outcome was the adjusted OR, did authors consider a priori the desirable variables for adjustment that were looking for? If not, this would be better noted in the methods. • Methods: page 7: data-extraction. Authors provide a summary of the type of information they were looking for. I suggest that for transparency and complete documentation, the full data-extraction form (or in its absence, the complete list of variables extracted) would be placed as an Annex. • In my opinion, Appendix 6 presents very important and relevant information for interpretation (e.g. an aOR of 0.70 if the underlying CS rate is 15% may have a very different interpretation than in the context of CS rates of 40%). Throughout the studies included there are not large variations in CS rates but I would suggest editors and authors consider to include this table in the main text of the manuscript. • Discussion: page 10: in the first paragraph, if CI are not reported along the OR I think it will be important to note to the reader which are statistically significant and which not.

	• Discussion, strengths and limitations: the result of the meta-analysis is driven by the largest study which contains 76% of the population included in this review. Fortunately it includes data from all states. Only 5 studies presented data from after 2000. With the rapid increase of CS rates in the last two decades, I wonder if authors have any hypothesis on the potential evolution. I think these points would be worth mentioning under the limitations. Some suggestions for updated references in the introduction: • Introduction, page 5, line 36: authors cite literature about the 15-19% benchmarks. The latest systematic review on this topic compiles all ecological studies available (some cited by the authors on this line and some not). In the eight studies included in this review, the threshold was at CS rates between 9% and 16%; above this threshold, increases of CS rates were not associated with decreases in mortality outcomes regardless of adjustments. I would suggest to include it as a reference: o Betran AP, Torloni MR, Zhang J, Ye J, Mikolajczyk R, Deneux-Tharaux C, Oladapo OT, Souza JP, Tunçalp Ö, Vogel JP, Gülmezoglu AM. What is the optimal rate of caesarean section at population level? A systematic review of ecologic studies. Reprod Health. 2015;12(1):57. • Introduction, page 5, line 45: An analysis of the variations of CS levels within countries was published in BMJ earlier this year: o Boatin AA, Schlotheuber A, Betran AP, Moller AB, Barros AJD, Boerma T, Torloni MR, Victora CG, Hosseinpoor AR. Within country inequalities in caesarean section rates: observational study of 72 low and middle income countries. BMJ. 2018 Jan 24;360:k55

REVIEWER	Reviewer name: Dr Marrissa Martyn-St James Institution and Country: School for Health and Related Research (ScHARR), University of Sheffield, UK Competing interests: None
REVIEW RETURNED	23-Sep-2018

GENERAL COMMENTS	This is a reasonable systematic review and meta-analysis, but with limitations that need addressing as follow: 1. For transparency and reproducibility of the review it is recommended that the authors register the protocol for their review on PROSPERO 2. In the MS the authors state that they have searched MEDLINE, which implies MEDLINE via a platform such as Ovid. However, the syntax and Boolean logic in the search strategy are appropriate for PubMed. The authors need to be explicit throughout that the searches were in PubMed, stating that PubMed comprises more than 28 million citations for biomedical literature from MEDLINE, life science journals, and online books. 3. The authors need to present definitive inclusion AND exclusion criteria for studies using a structured framework, such as the population, definitions of CS and insured/uninsured/, outcomes, settings, study design types, etc. This could easily be presented in tabulated form as an appendix. This will ensure transparency and reproducibility of the systematic review methods. 4. The inclusion criterion the authors report is that studies must present an odds ratio (OR). It is not clear why this is the case and why studies that report raw data from which the review authors could estimate the OR are not being included.

	5. The authors have used the QUIPS quality assessment instrument. This instrument assesses the risk of bias in studies of prognostic factors. The authors have included observational (cross-sectional and cohort studies) and there is no indication that these are prognostic studies. Indeed, the authors have analysed the odds of a CS in uninsured as compared to publicly insured women. No prognostic factors are extracted or analysed. The authors would be better applying a quality assessment instrument more appropriate for the included studies, e.g., Newcastle-Ottowa. 6. For transparency and reproducibility, systematic reviews should present a table of the studies excluded at the full-text stage, with the reason for exclusion. This should be presented as an appendix in tabular form with author and year in the first column and reason for exclusion in the second. These should be cited and the citations included in the review reference list.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Simone G Diniz

Comment 1: This is a very interesting paper about a very relevant issue, using a really large database, and I suggest some modifications for improving its potential impact.

Response: Thank you for your comments.

Comment 2: As the references 6 and 8 show, the cut-off for suggested caesarean rates by World Health Organization was not 15-19%, but 10-15% in ref 6 (1985 WHO), and in 2016, the suggested rate was that over 10% there is no evidence of maternal or neonatal improvements. The 2016 recognizes that this include inconclusive studies and there are areas of uncertainty, but the 10% or 10-15 % are lower than that used in the paper (15 or 19%) to consider underuse.

Response: Thank you for your comments. We have revised the sentence to "Presently, many countries have long exceeded the 9 to 16 percent or 10 to 15 percent thresholds or 19 percent benchmark for CS out of total deliveries, argued to be the ideal rates of CS in terms of improving the health of women and newborns.6-9" (page 5, paragraph 2, of the manuscript). Please note that the 9-16 percent threshold was suggested by reviewer Betran based on a published paper in 2015. We have also revised Appendix 6 (now Table 2) to address these comments.

We have also revised a sentence in the discussion section to "Most studies included in our meta-analysis, including the most recent studies from California49 and Florida,50 show that rates for CS among uninsured women are below or close to the 10 and 19 percent benchmarks previously reported.6-8 Even in instances where the average state rates are slightly above the 19 percent benchmark, some hospitals service areas are likely to have CS rates lower than 19 percent or even 9 percent for uninsured women because of the well-established within state variation in CS rates.5 54" (page 13, paragraph 2, of the manuscript)

Comment 3: Because "distribution" of caesarean can be problematic (more for those who don't need, less for those who need), in the last decade the international scientific and policy-making community (WHO etc.) started using the Robson criteria to assess how appropriate or not a CS indication was. As in the large groups 1 and 3, for example, rates under 5 % are very ok, while in babies in transverse/cormic presentation (group 9, very small) the CS rate should 100%. The issue of caesarean underuse or overuse was much resolved with this classification, so I wonder why it was not used, or even mentioned.

Response: This is very good idea. But unfortunately, studies have not reported data according to Robson criteria and only two studies could be classified according to the Robson criteria. See answer bellow for more details.

Comment 4: The Robson criteria could be used for at least a part of the sample, considering the data presented in Appendix 3 (parity, previous caesarean, gestational age, etc). If this is not possible, not using the Robson classification should be stated as a limitation of the study.

Response: We immediately reviewed studies through the Robson criteria's lens. Only two out of sixteen studies could be classified using Robson criteria. Coonrod (2008) could be classified under group 2 and Sebastião et al. (2016) could be classified under group 1, of groups defined by Robson criteria. Other studies could not fit in any of 10 groups defined by Robson.

To address your comment, we have added the sentence "We considered but could not make use of the Robson criteria to classify studies and analyze CS rates among the studies reviewed. Only two out of sixteen studies could be classified using the Robson criteria." (page 12, paragraph 1, of the manuscript)

Comment 5: In the mechanism, the authors point to previous publications that "One likely factor is that financial incentives are stronger with private insurance than in the publicly insured or uninsured." "These incentives result from higher payment for CS by private insurers through reimbursement arrangements that encourage more expensive procedures as means to increase profits, as well as providers' (hospitals and individual physicians) responses to these incentives." "The responses to incentives by hospitals exist in the form of patient scheduling policies that direct privately insured patients to profit inclined physicians." And so on. But this is not properly in the abstract, where it should be clearly stated.

Response: To address this comment we have added the sentence in abstract: "While the higher rates for CS among privately insured women can be explained with financial incentives associated with private insurance, the lower odds among uninsured women draw attention at barriers to access for delivery care." (page 2, last paragraph, of the manuscript)

We have also added a sentence in conclusion: "While the higher rates for CS among privately insured women can be explained with financial incentives associated with private insurance, the lower odds among uninsured women draw attention at barriers to access for delivery care." (page 14, paragraph 1, of the manuscript)

Comment 6: The study concludes that the OR was lower for uninsured women (compared with privately insured, or to insured in general), and in the last appendix (6) are the rates, classified by possible underuse. Should we consider underuse if women did need it and did not get it? Or also when women did not need it and the woman herself and the baby had only the negative outcomes of an unnecessary surgery, including additional risk of infection, haemorrhage, pain, breastfeeding difficulties, iatrogenic prematurity, poor foetal-to-neonatal transition? The authors stress the negative part of having less caesarean (a possible underuse, but if you consider 10-15%, this is not the case), and a more balanced view is needed here.

Response: We have tried to be very careful in the interpretation, hence, we have stated within limitations of the study section: "While a population level caesarean section rate of less than 9 or 19 percent suggests underuse, we cannot determine the mix of under, over, and appropriate use in a specific population." (page 4, paragraph 5, of the manuscript). We also tried to reflect this in conclusions implying that it is important to look at outcomes before we can come to more firm conclusions for underuse:

"In many regions, the rates for uninsured women are close or below the benchmarks for appropriate CS rates, therefore efforts to assess the delivery outcomes as well as policy options that could improve insurance coverage for women giving birth are important." (page 14, paragraph 1, of the manuscript)

We have considered your feedback and have revised the last sentence of the conclusion section to "In many regions the rates for uninsured women are above, close or below the benchmarks for appropriate CS rates and could imply both, underuse and overuse. Therefore, efforts to assess the delivery outcomes as well as policy options that could improve insurance coverage for women giving birth are important." (page 14, last paragraph, of the manuscript)

Reviewer: 2

Reviewer Name: Ana Pilar Betran

Comment 1: This is a well written manuscript presenting the results of a systematic review and meta-analysis of the odds ratio of giving birth by caesarean section of uninsured women vs insured women in United States. This is an interesting analysis in the global context of the continuous increase of caesarean section rates worldwide and the debate on equity of the use of caesarean section since in many settings, overuse and underuse coexist.

Response: Thank you for your comments.

Comment 2: Methods: page 7, exclusion/inclusion criteria could be expanded and made more detailed. This includes only data for United States so all other countries were excluded. Were any specific groups of women excluded (e.g. race, adolescents, older women, specific pathologies, HIV, socio-economic status); any minimal sample size required? Any specific indications for CS included/excluded? I think it deserve a sentence in the methods to clarify this criteria and let the reader know that all this was considered at planning stage. Also, since the pre-specified primary outcome was the adjusted OR, did authors consider a priori the desirable variables for adjustment that were looking for? If not, this would be better noted in the methods.

Response: To address this we have added following sentence "More specifically, we didn't exclude studies based on any population characteristic. Studies had to report normal (vaginal) and CS deliveries with uninsured and privately and/or publicly insured comparisons. In an ideal situation, studies would report adjusted OR of uninsured as compared to privately and/or publicly insured women, but in cases ORs were not calculated by the authors, we would extract data (rates and regression coefficients) and perform calculations that would allow for the derivation of OR. We didn't exclude studies by type of study design, variables used for adjustment or any other study characteristic." (page 7, paragraph 1, of the manuscript)

Comment 3: Methods: page 7: data-extraction. Authors provide a summary of the type of information they were looking for. I suggest that for transparency and complete documentation, the full data-extraction form (or in its absence, the complete list of variables extracted) would be placed as an Annex.

Response: Table 1 and Appendices 2-6 were used as data extraction sheets, almost in the exact form as they were organized into the annexes of the manuscript. In addition, we extracted data on effect estimate. Annex 6 provides a list of all variables extracted.

Comment 4: In my opinion, Appendix 6 presents very important and relevant information for interpretation (e.g. an aOR of 0.70 if the underlying CS rate is 15% may have a very different interpretation than in the context of CS rates of 40%). Throughout the studies included there are not large variations in CS rates but I would suggest editors and authors consider to include this table in the main text of the manuscript.

Response: Thank you for your suggestion. We have integrated Appendix 6 into main body of manuscript. Now, Table 2 of the manuscript. (page 29, of the manuscript)

Comment 5: Discussion: page 10: in the first paragraph, if CI are not reported along the OR I think it will be important to note to the reader which are statistically significant and which not.

Response: We revised the sentence include confidence intervals "Our systematic review and meta-analyses estimated that the overall odds of receiving a caesarean section are on average 0.70 times lower for uninsured women as compared with privately insured women (95%CI 0.63 to 0.78), 0.92 times lower for uninsured women as compared with publicly insured women (95%CI 0.80 to 1.07) and 0.70 times lower for uninsured women as compared to privately and publicly insured women (95%CI 0.69 to 0.72). The lower odds were noticed across all subgroups of studies in subgroup analyses as well as in crude analyses.". (page 11, paragraph 1, of the manuscript)

Comment 6: Discussion, strengths and limitations: the result of the meta-analysis is driven by the largest study which contains 76% of the population included in this review. Fortunately it includes data from all states. Only 5 studies presented data from after 2000. With the rapid increase of CS rates in the last two decades, I wonder if authors have any hypothesis on the potential evolution. I think these points would be worth mentioning under the limitations.

Response: We added a sentence "The results of this study are driven by the largest study which contains over two thirds of the population included in this review. Only five out of 16 studies included in the review report data after year 2000." (Page 4, paragraph 4 and page 11, paragraph 2, of the manuscript)

The subgroup analysis (Figure 3) in uninsured vs privately insured comparison shows that the odds for CS have lowered in post 2001 period (OR=0.51, 95CI 0.42 to 0.61), with only one study reporting the data from 2001 period subgroup and with no positive trend in the period of data collection subgroup. The subgroup analysis (Figure 3) in uninsured vs publicly insured comparison shows that the odds for CS have increased in post 2001 period (OR=1.07, 95CI 0.97 to 1.18), with only one study reporting the data from 2001 period subgroup (p for interaction=0.03). We could conclude that from 2001, the odds for CS have lowered among uninsured (as compared to privately insured) and that odds for CS have increased (as compared to publicly insured) and attempt to explain that considering changes of incentive structures with time. But, given constraints in these results (negative p for trend and the fact that subgroups contain results from only one study in each comparison) we refrained from interpreting these findings.

Comment 7: Some suggestions for updated references in the introduction:

Introduction, page 5, line 36: authors cite literature about the 15-19% benchmarks. The latest systematic review on this topic compiles all ecological studies available (some cited by the authors on this line and some not). In the eight studies included in this review, the threshold was at CS rates between 9% and 16%; above this threshold, increases of CS rates were not associated with decreases in mortality outcomes regardless of adjustments. I would suggest to include it as a reference:

Betran AP, Torloni MR, Zhang J, Ye J, Mikolajczyk R, Deneux-Tharaux C, Oladapo OT, Souza JP, Tunçalp Ö, Vogel JP, Gülmezoglu AM. What is the optimal rate of caesarean section at population level? A systematic review of ecologic studies. Reprod Health. 2015;12(1):57.

Response: Many thanks for the recommendation. We have included the reference in the list as well as made corrections in the manuscript to accommodate information from this article.

Comment 8 Introduction, page 5, line 45: An analysis of the variations of CS levels within countries was published in BMJ earlier this year:

Boatin AA, Schlotheuber A, Betran AP, Moller AB, Barros AJD, Boerma T, Torloni MR, Victora CG, Hosseinpoor AR. Within country inequalities in caesarean section rates: observational study of 72 low and middle income countries. BMJ. 2018 Jan 24;360:k55

Response: Many thanks. We have added this reference.

Reviewer: 3

Reviewer Name: Dr Marrissa Martyn-St James

Comment 1: This is a reasonable systematic review and meta-analysis, but with limitations that need addressing as follow: 1. For transparency and reproducibility of the review it is recommended that the authors register the protocol for their review on PROSPERO

Response: Thank you for your suggestion. We considered registering it with Prospero but will not be able to do so within this deadline for re-submission of manuscript. We will adopt this practice in future reviews we are or will perform.

Comment 2: In the MS the authors state that they have searched MEDLINE, which implies MEDLINE via a platform such as Ovid. However, the syntax and Boolean logic in the search strategy are appropriate for PubMed. The authors need to be explicit throughout that the searches were in PubMed, stating that PubMed comprises more than 28 million citations for biomedical literature from MEDLINE, life science journals, and online books.

Response: Thanks for feedback. We have revised this in abstract, methods and result section. (Page 2, 6, and 9 of the manuscript)

Comment 3: The authors need to present definitive inclusion AND exclusion criteria for studies using a structured framework, such as the population, definitions of CS and insured/uninsured/, outcomes, settings, study design types, etc. This could easily be presented in tabulated form as an appendix. This will ensure transparency and reproducibility of the systematic review methods.

Response: To address this we have added the following sentence "More specifically, we didn't exclude studies based on any population characteristic. Studies had to report normal (vaginal) and CS deliveries with uninsured and privately and/or publicly insured comparisons. In an ideal situation, studies would report adjusted OR of uninsured as compared to privately and/or publicly insured women, but in cases ORs were not calculated by the authors, we would extract data (rates and regression coefficients) and perform calculations that would allow for the derivation of OR. We didn't exclude studies by type of study design, variables used for adjustment or any other study characteristic." (page 7, paragraph 1, of the manuscript)

Comment 4: The inclusion criterion the authors report is that studies must present an odds ratio (OR). It is not clear why this is the case and why studies that report raw data from which the review authors could estimate the OR are not being included.

Response: We revised the sentence "To be included in the analysis, studies had to report odds ratio (OR) of CS comparing uninsured against privately and/or publicly insured women.

" to "To be included in the analysis, studies had to report odds ratio (OR) or data that enabled the calculation of OR of CS comparing uninsured against privately and/or publicly insured women." (page 7, paragraph 1, of the manuscript)

Comment 5: The authors have used the QUIPS quality assessment instrument. This instrument assesses the risk of bias in studies of prognostic factors.

The authors have included observational (cross-sectional and cohort studies) and there is no indication that these are prognostic studies.

Indeed, the authors have analysed the odds of a CS in uninsured as compared to publicly insured women. No prognostic factors are extracted or analysed. The authors would be better applying a quality assessment instrument more appropriate for the included studies, e.g., Newcastle-Ottowa.

Response: This is the third meta-analysis of this kind. Two have already been published (https://bmjopen.bmj.com/content/7/2/e013670; https://bmjopen.bmj.com/content/7/8/e016600). In the first meta-analysis we didn't use any quality assessment tool.

In the second meta-analysis, we used QUIPS after it was suggested by BMJ Open editors (https://bmjopen.bmj.com/content/7/8/e016600).

We accepted this suggestion as we found the tool very much appropriate for the studies we included in the review, although, we agree with your comment, our studies are not prognostic studies. The only consideration we had to make during the use of the QUIPS tools was, that we considered the prognostic section of QUIPS assessment tool as exposure section, i.e. if women were insured or not.We appreciate your suggestion for the Newcastle-Ottowa Scale (NOS).

We reviewed it in light of the studies we have included in the review. We believe that QUIPS is still more appropriate than NOS for the types of studies that we have included in the analysis. Firstly, the structure of QUIPS tool (with some rare exceptions) is fully applicable to the studies we included in the review. Secondly, we think that the QUIPS tool provides an opportunity to assess studies in more detail than NOS does.

Comment 6: For transparency and reproducibility, systematic reviews should present a table of the studies excluded at the full-text stage, with the reason for exclusion. This should be presented as an appendix in tabular form with author and year in the first column and reason for exclusion in the second. These should be cited and the citations included in the review reference list.

Response: Thank you for suggestion. Please see Appendix 7 for the list of all excluded articles during full text review. We have also included them in reference list of the manuscript. Hope this is acceptable to BMJ Open as there are many articles that we have reviewed as full text. If not acceptable, then they can simply delete these additional references in the main body of manuscript. In MS Word document of the manuscript the references are Endnote formatted. So once you remove citations from the manuscript and update citations and bibliography, the citations will be removed from reference list.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Ana Pilar Betran
	Institution and Country: World Health Organization, Switzerland
	Competing interests: None declared
REVIEW RETURNED	28-Nov-2018

| GENERAL COMMENTS | I have no further comments |

REVIEWER	Reviewer name: Dr Marrissa Martyn-St James
	Institution and Country: School for Health and Related Research (ScHARR), University of Sheffield, UK
	Competing interests: None declared
REVIEW RETURNED	15-Nov-2018

GENERAL COMMENTS	None