PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Caesarean sections and the prevalence of preterm and early term births in Brazil: secondary analyses of national birth registration
AUTHORS	Barros, Fernando; Rabello Neto, Dacio; Villar, Jose; Kennedy, Stephen; Silveira, Mariangela; Diaz-Rossello, Jose Luis; Victora, C

VERSION 1 – REVIEW

REVIEWER	Alexandre Chiavegatto Filho School of Public Health of the University of São Paulo, Brazil
REVIEW RETURNED	17-Jan-2018

GENERAL COMMENTS	This is a very well-written paper on an important area of research in Brazil. The study aimed to analyze whether the very high rates of caesarean sections (CS) in Brazil have impacted the gestational age. The major issue with the statistical analysis is the use of ecological data. The fact that municipalities in Brazil follow similar trends regarding CS and gestational age does not necessarily mean that one leads to the other. First, there could be important confounding factors (such as maternal age and twin births) influencing the results. Second, the ecological fallacy could also be an issue. The study could benefit from trying a multiple regression controlling for other confounding factors apart from maternal education, which is not self-evident that it is a confounding factor in this case (could the authors elaborate on that?). To improve the quality of the analysis, the authors should use individual data on live births available from the Ministry of Health (http://www2.datasus.gov.br/DATASUS/index.php?area=0901&item=1&acao=28&pad=31655) to test the hypothesis that CS is associated with gestational age in Brazil, after controlling for individual confounding factors. This is an important study for Brazil, but the methodological concerns mentioned above need to be carefully addressed and the remaining issues should be included in a limitations paragraph. Smaller points: - Birth data was attributed to the municipalities based on residence or occurrence? - It would be better if the statistical analyzes were also presented in a table or two, instead of only in text. - Given the important statistical issues mentioned above, the authors should be careful with statements like "Brazil is facing (…) an epidemic of early term births, directly related to the high CS rate", and "our findings indicate that pre-labour CS do play a role in the preterm epidemic".

REVIEWER	K.S. Joseph University of British Columbia, Canada
REVIEW RETURNED	11-Mar-2018

| GENERAL COMMENTS | The authors use information on all hospital births in Brazil in 2015 to describe the gestational age distribution and the frequency of cesarean delivery at different gestational ages. Analyses also address cesarean delivery rates by maternal education status and rates of preterm birth and early term birth among municipalities with low and high rates of caesarean delivery. The study showed an overall cesarean delivery rate of 55.5%, and cesarean delivery rates increased with increasing maternal education. Municipalities with the highest cesarean delivery rates had the highest rates of preterm birth and early term birth. The authors concluded that excess rates of cesarean delivery have distorted the normal gestational age distribution in Brazil.

Comments
1. The study deals with a straightforward issue which is nevertheless clinically and socially critical from a national (Brazillian) standpoint.

2. If the information on maternal characteristics is available, it would provide the context for readers to better appreciate the situation in Brazil in 2015. Could the authors provide a descriptive Table 1 showing the maternal age and parity distributions, the proportion of women with a previous cesarean delivery, multi-fetal pregnancy, etc.

3. One point requiring clarification relates to gestational age estimation. Are pre-labour cesarean deliveries being carried out by obstetricians among women with known gestational ages of 34, 35 or 36 weeks? Or are such preterm cesarean deliveries a consequence of errors in gestational age estimation i.e., deliveries which are thought to be term but which are discovered to be preterm after the baby is delivered (based on a physical exam ination of the baby)? If the latter, is gestational age estimate then changed after birth? This is a confusing issue as most pregnancies seem to have a gestational age at delivery estimated based on menstrual or ultrasound dates.

4. This analysis regarding rates of preterm and early term birth may be more informative if it was restricted to singleton live births.

5. There is a possibility that the municipality-based association in rates of preterm and early term births with rates of cesarean delivery is confounded by maternal characteristics such as age or previous caesarean delivery. One simple analysis the authors may wish to carry out to address this concern is to provide rates of very preterm birth e.g., <34 weeks. Presumably, rates of such preterm birth by municipality will not be associated with caesarean delivery rates.

6. The axis labels of the graphs need some attention. For example, in the last 2 Figures the X-axes are labelled 'Gestational age groups' and 'Gestational age distribution', although the scale of the axis ranges from 0 to 100. |

| REVIEWER | Marie Delnord
INSERM UMR1153, Obstetrical, Perinatal and Pediatric
Epidemiology Research Team- EPOPé, Center for Epidemiology |

	and Statistics Sorbonne Paris Cité- CRESS, Paris Descartes University, France
REVIEW RETURNED	21-Mar-2018

GENERAL COMMENTS	Thank you for inviting me to review this manuscript by Barros et al. entitled " Marked shift in gestational age distribution associated with caesarean sections in Brazil: secondary analyses of national birth registration.
	Importance of the study
	This study investigated associations between rates of caesarean section in Brazil with rates of preterm, early term and full term births in 2010.
	Authors have used routine population-based data to analyze this important topic. Results from this study have implications for practice and for orienting preterm birth, early term and cesarean section prevention programmes.
	Introduction:
	The authors provide sufficient background to illustrate the extent of the CS epidemic in Brazil. It might also be good to remind readers on the latest international recommendations on CS rates (15% according to the WHO some years ago although this has been revised..) + add the CS rate range in countries based on Ref.5
	Lines 4-5: add ref
	Line 25: Although the GA threshold for the definition of preterm birth is debated in the literature (look for ref in pubmed . I would avoid using "slightly preterm babies" and "marginal preterm" as these terms are uncommon in the literature and may lead to confusion.
	Methods: Methods are clear but a bit succinct. I would suggest having a more detailed description of:
	- the categories which were used for each of the variables.
	-a couple lines on why authors have chosen to present prevalence ratios and conduct a poisson regression instead of a more "common" multivariate regression (even if the appropriate ref is provided).
	I would encourage authors to use the ISCED 2011 recommendations for their level of education variable.
	Minor comments: it would be good to explicitly mention the associations which were tested using chi-squared tests and which groups were compared using the t-tests.
	In the abstract, add that only municipalities with +1000 births were included (Setting)
	Results:
	General comments: The results of this study are important but lack a little bit of clarity as only percentages are provided across subgroups and without the denominators.
	I suggest including a summary table that gives the characteristics of the mothers (plus number of women in each category), % preterm births, % early term births overall and by mode of onset of delivery. Without the denominator, it is not currently possible to check the percentages. Please also add results from the Chi2 and t-test analyses.
	Specific comments
	In para 3:
	- Please check % provided and add reference to the Figure

that is used.

- " vaginal deliveries represented 62% of ALL BIRTHS" (based on Fig.1) not "all preterm birth" as currently written in the text. Similarly, " vaginal deliveries accounted for 20% of all birth" (cf. Fig.1) not " all preterm births"

In para 4, I would avoid the wording " increased" or " decreased" as you are not looking at trends, but use relative terms " higher"/ "lower".

In the last paragraph, please check calculations for the number of births. I count 133 571 extra preterm births, and 226490 early terms.. You can provide also number of births over 39 weeks in high-income countries.

Minor comments : Figure titles are missing from the PDF.

Discussion: Authors have done a good job bringing out the importance of this study for prevention p9-10, and especially on the importance of creating synergies across prevention efforts to maximize potential gains for perinatal health practice and outcomes.

There is also evidence in the literature that preterm and early term birth (overall and by mode of onset of delivery) may have a common etiology: http://bmjopen.bmj.com/content/8/1/e018745
Delnord M, Blondel B, Prunet C, et al. Are risk factors for preterm and early-term live singleton birth the same? A population-based study in France. BMJ Open 2018;8:e018745. doi: 10.1136/bmjopen-2017-018745

However, the paper would benefit from a standalone strengths and limitation section. As of now, this information is dispersed in the discussion. I would encourage the authors to be more explicit about the representativeness of their results based on the municipalities and hospitals which were selected (520 municipalities with more than 1000 births). Is there information in the literature on CS and preterm rates in some of the hospital and/or municipalities not included in the study? (even if data quality may be poorer..)

Minor comments: p9 para 2 is a bit redundant with the results section. Pleas add ref for this sentence " In addition to the well known poor outcomes for preterm babies, we documented that …gestation" (documented where???)

REVIEWER	Maria Graciela Freyermuth Enciso Centro de Investigaciones y Estudios Superiores en Antropología Social - Unidad Sureste. México
REVIEW RETURNED	23-Mar-2018

GENERAL COMMENTS	I think that the paper should be of interest to the readers of the journal. However, I believe that the paper requires a minor revision before publication. General comments by section are provided below. Methods The authors performed a test of proportion differences but the results are not reported in any table. They just mentioned in the text that all results are significant to 0.001% (P>0.001) but is not clear if they referred to the proportion differences. They also mentioned in the methods the use of a Poisson's model. However, they neither described nor discuss the related results. Thus, I recommend to either exclude the model from the methods section or include related material in the discussion and results

sections.

The first paragraph in the discussion section is about the data source. Therefore, this material should be relocated to the methods section.

The authors do not clarify the relationship between socio-economic aspects and education. They argue that education and poverty are correlated. Thus, I think they need to justify such statement and support with references such as association. Previous studies show a tendency but not the magnitude with respect to the CS. Therefore, further discussion about this aspect is needed.

The data does not demonstrate the epidemic presence in premature babies. They need to provide some historical statistics to be able to support the epidemic statement. Furthermore, it is worth to provide their definition for epidemic since it is not medical sound.

RESULTS
The differential risk of delivering premature babies described in the abstract while comparing communities with 30% of caesarean sections versus those with 80% is neither described nor analyzed in the results sections. The information must be included in the results together with the confidence intervals mentioned in the abstract.
Please include a Conclusions section at the end of the manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Alexandre Chiavegatto Filho
Institution and Country: School of Public Health of the University of São Paulo, Brazil
Competing Interests: None declared.

This is a very well-written paper on an important area of research in Brazil. The study aimed to analyze whether the very high rates of caesarean sections (CS) in Brazil have impacted the gestational age.

The major issue with the statistical analysis is the use of ecological data. The fact that municipalities in Brazil follow similar trends regarding CS and gestational age does not necessarily mean that one leads to the other. First, there could be important confounding factors (such as maternal age and twin births) influencing the results. Second, the ecological fallacy could also be an issue.

Answer: *We realize that our explanation of the study design was not sufficiently clear, as both reviewers #1 and # 3, assumed that this is an ecological study, which is not the case.*

Because of this, we now substantially improved the Methods and Results, and the initial part of Discussion, to make clear how the study was conducted.

In summary, this is a cross-sectional analysis of 2.9 million births– this is presented in Table 1 (new), and Figures 1, 2, and 3. We used the SINASC Ministry of Health database of individual singleton births, as you suggested below.

Within our cross-sectional design of individual births, we resorted to one set of what may have been interpreted as "ecological analyses", for reasons that are explained below (and in the revised paper). In fact, these were individual-level analyses in which the explanatory variable was the CS rate in the municipalities where the women gave birth.

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After almost 40 years of studying Caesarean sections and preterm deliveries in Brazil, we are convinced that residual confounding leads to paradoxical results. This is due to the extremely strong positive association between socioeconomic position and CS jointly with the negative association between socioeconomic position and preterm births (as demonstrated in Figures 1 and 2). We argue that residual confounding persists, in spite of adjustment for measured confounders such as education and others.

You suggest (below) that we should use individual data to test the hypothesis that CS is associated with gestational age, in particular with preterm births, after controlling for individual confounding factors. We carried out such analyses using Poisson regression. The unadjusted prevalence ratio of preterm birth in CS births compared to vaginal deliveries is 0.907 (0.900-091), while the prevalence ratio after adjusting for maternal education, age, parity and marital status is 0.957 (0.950-0.964). Such a "protective" effect of CS on preterm births is the rule in individual studies, due to the strong residual confounding mentioned above, in spite of adjustment for a number of potential confounders.

Another limitation of individual level analyses is that a certain proportion of CS are medically indicated, including some CS that will lead to preterm deliveries, as is the case for early termination of pregnancy due to maternal or fetal conditions.

For these reasons, we believe that examining preterm and early term rates in groups of municipalities is a better alternative. These are still individual-level analyses, but the main explanatory variable is the CS rate in a municipality, not whether or not each pregnancy resulted in a CS. If a municipality has CS rates say of 60% or higher, most of these operations will not have medical indications. Therefore we can assess the role of CS in changing gestational age distribution in a more reliable way than analyzing individual pregnancies. This is why we carried out the analyses including the 520 municipalities with more than 1,000 births in 2015, for which the results are presented in Figure 4, and in the Poisson regression analyses using preterm and early term births as outcomes (Table 2, new). All other results in the paper refer to strictly individual level analyses.

We have revised the paper to explain these issues to the readers.

The study could benefit from trying a multiple regression controlling for other confounding factors apart from maternal education, which is not self-evident that it is a confounding factor in this case (could the authors elaborate on that?). To improve the quality of the analysis, the authors should use individual data on live births available from the Ministry of Health (http://www2.datasus.gov.br/DATASUS/index.php?area=0901&item=1&acao=28&pad=31655) to test the hypothesis that CS is associated with gestational age in Brazil, after controlling for individual confounding factors.

Answer: *We have answered this above. As stated in Methods and in other parts of the paper, the database used in this paper is the individual database of live births from the Ministry of Health – SINASC.*

Maternal education was treated as a confounder because it was associated with both the exposure (CS) and the outcome (gestational age distribution), not being part of the causal chain leading to the outcome. The same applies to the other variables – age, parity and marital status.

This is an important study for Brazil, but the methodological concerns mentioned above need to be carefully addressed and the remaining issues should be included in a limitations paragraph.

Answer: *We thank the reviewer, and we believe that our previous answers clarified this point. Nevertheless, we now mention (in the limitations section) the possible bias associated with the municipality-based variable, and we explain the adjustment for confounders in greater detail.*

Smaller points:

- Birth data was attributed to the municipalities based on residence or occurrence?

Answer: *Occurrence. This is now specified in the Methods (page 6).*

- It would be better if the statistical analyzes were also presented in a table or two, instead of only in text.

Answer: *We have now added Table 1 with a description of the population, and Table 2 with the results of the multivariable analyses assessing the association of preterm and early term births and municipalities grouped by CS rates.*

- Given the important statistical issues mentioned above, the authors should be careful with statements like "Brazil is facing (…) an epidemic of early term births, directly related to the high CS rate", and "our findings indicate that pre-labour CS do play a role in the preterm epidemic".

Answer: *We hope that we have settled the reviewer's concerns about the statistical issues. Therefore, in conjunction with the results of earlier studies on the rising trends in CS and preterm deliveries (which are cited in our paper), we believe that our analyses allow us to refer to the three epidemics. Nevertheless, we have replaced "our findings indicate" by "our results suggest", on Discussion, on page 12.*

Reviewer: 2
Reviewer Name: K.S. Joseph
Institution and Country: University of British Columbia, Canada
Competing Interests: None declared.

The authors use information on all hospital births in Brazil in 2015 to describe the gestational age distribution and the frequency of cesarean delivery at different gestational ages. Analyses also address cesarean delivery rates by maternal education status and rates of preterm birth and early term birth among municipalities with low and high rates of caesarean delivery. The study showed an overall cesarean delivery rate of 55.5%, and cesarean delivery rates increased with increasing maternal education. Municipalities with the highest cesarean delivery rates had the highest rates of preterm birth and early term birth. The authors concluded that excess rates of cesarean delivery have distorted the normal gestational age distribution in Brazil.

Comments
1. The study deals with a straightforward issue which is nevertheless clinically and socially critical from a national (Brazillian) standpoint.

2. If the information on maternal characteristics is available, it would provide the context for readers to better appreciate the situation in Brazil in 2015. Could the authors provide a descriptive Table 1 showing the maternal age and parity distributions, the proportion of women with a previous cesarean delivery, multi-fetal pregnancy, etc.

Answer: *Thanks for the suggestion. We have now included Table 1 with information on maternal age, parity, schooling, marital status, caesarean section rates, previous caesarean sections, gestational age and birth weight distribution. The Methods and Results sections were changed accordingly.*

3. One point requiring clarification relates to gestational age estimation. Are pre-labour cesarean deliveries being carried out by obstetricians among women with known gestational ages of 34, 35 or

36 weeks? Or are such preterm cesarean deliveries a consequence of errors in gestational age estimation i.e., deliveries which are thought to be term but which are discovered to be preterm after the baby is delivered (based on a physical examination of the baby)? If the latter, is gestational age estimate then changed after birth? This is a confusing issue as most pregnancies seem to have a gestational age at delivery estimated based on menstrual or ultrasound dates.

Answer: *Obstetricians, as a rule, do not perform cesarean sections at 34, 35, or 36 weeks without medical reasons. Nevertheless, due to inaccurate estimation of gestational age, elective CS (often schedules for 38 exact weeks) may eventually lead to preterm deliveries.*

Gestational age estimates are based on LMP or ultrasound and are not usually changed after birth, but this information on possible change after birth is not available in the database.

4. This analysis regarding rates of preterm and early term birth may be more informative if it was restricted to singleton live births.

Answer: *All analyses were conducted in singletons only, but we failed to mention it in the original draft. This has been corrected in Methods and Abstract.*

5. There is a possibility that the municipality-based association in rates of preterm and early term births with rates of cesarean delivery is confounded by maternal characteristics such as age or previous caesarean delivery. One simple analysis the authors may wish to carry out to address this concern is to provide rates of very preterm birth e.g., <34 weeks. Presumably, rates of such preterm birth by municipality will not be associated with caesarean delivery rates.

Answer: *We thank you for this excellent suggestion. Rates of very preterm births are presented in a table and a simple graph below. There are no clear patterns between municipalities with different CS rates, although the p-value is 0.0001 due to the large numbers. We have added this information to the Results (page 10) and if the Editor so wishes, we can add a supplementary table or figure.*

Municipalities by rates of CS	N municipalities	N births	% <34 weeks
<30%	38	75,798	2.4%
30-39	53	138,893	2.7%
40-49	91	377.575	2.8%
50-59	109	889,175	2.9%
60-69	112	558,709	3.1%
70-79	73	242,430	2.7%
80+	26	56,250	2.6%
All	502	2.337,830	2.9%
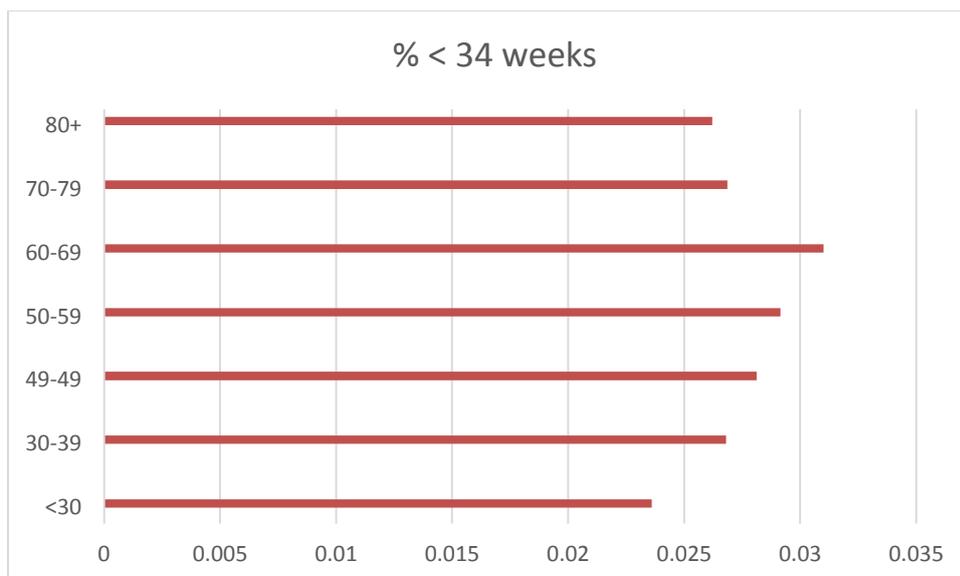
% < 34 weeks

6. The axis labels of the graphs need some attention. For example, in the last 2 Figures the X-axes are labelled 'Gestational age groups' and 'Gestational age distribution', although the scale of the axis ranges from 0 to 100.

Answer: *the x-axes of the Figures 3 and 4 have been corrected. They now read "% distribution of gestational age groups", in both Figures.*

Reviewer: 3
Reviewer Name: Marie Delnord
Institution and Country: INSERM UMR1153 Obstetrical, Perinatal and Pediatric Epidemiology Research Team- EPOPé Center for Epidemiology and Statistics Sorbonne Paris Cité- CRESS, Paris Descartes University, France
Competing Interests: None declared

Thank you for inviting me to review this manuscript by Barros et al. entitled " Marked shift in gestational age distribution associated with caesarean sections in Brazil: secondary analyses of national birth registration.

Importance of the study
This study investigated associations between rates of caesarean section in Brazil with rates of preterm, early term and full term births in 2010.
Authors have used routine population-based data to analyze this important topic. Results from this study have implications for practice and for orienting preterm birth, early term and cesarean section prevention programmes.

Introduction:
The authors provide sufficient background to illustrate the extent of the CS epidemic in Brazil. It might also be good to remind readers on the latest international recommendations on CS rates (15% according to the WHO some years ago although this has been revised..) + add the CS rate range in countries based on Ref.5

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Lines 4-5: add ref

Answer: *The revised WHO recommendations (2015) are now mentioned at the very beginning of Introduction. We have reviewed the paper by Betrán and colleagues (ref 5), including supplemental files, but could not find ranges for CS rates for countries, but only for regions and sub-regions. We added a sentence in the first paragraph of the Introduction mentioning the range of regional CS rates.*

Line 25: Although the GA threshold for the definition of preterm birth is debated in the literature (look for ref in pubmed . I would avoid using "slightly preterm babies" and "marginal preterm" as these terms are uncommon in the literature and may lead to confusion.

Answer: *We had used such terms in accordance with Lindstrom et al in Pediatrics, 2007, but following your request we have dropped this sentence.*

Methods: Methods are clear but a bit succinct. I would suggest having a more detailed description of: - the categories which were used for each of the variables.

Answer: *The Methods section was been expanded and we include the categories used for all variables that were used in the analyses.*

-a couple lines on why authors have chosen to present prevalence ratios and conduct a Poisson regression instead of a more "common" multivariate regression (even if the appropriate ref is provided).

Answer: *We have added a sentence as requested: Poisson regression was chosen, instead of logistic regression, because it provides estimates of prevalence ratios, which are more interpretable and easier to communicate to non-specialists than odds ratios. (Methods page 7)*

I would encourage authors to use the ISCED 2011 recommendations for their level of education variable.

Answer: *Although we agree that the ISCED "levels" of education would be preferable, the women who gave birth in 2015 attended school during a period in which the Brazilian education system underwent changes in the number of years required for attaining primary and secondary levels. For this reason, we opted to report years of schooling as grouped in the current paper.*

Minor comments: it would be good to explicitly mention the associations which were tested using chi-squared tests and which groups were compared using the t-tests.

Answer: *we deleted references to t-tests, as these are no longer used in the analyses. We mention in the text the chi-squared results when appropriate. As these tests refer to values in the Figures (and this was added to Methods), we could provide the actual values as Supplemental materials, but this would depend on a decision from the Editors.*

In the abstract, add that only municipalities with +1000 births were included (Setting)

Answer: *We realize that the study design had not been properly described, as reviewer #1 noted. We revised the Methods, Results and the initial part of the Discussion.*

In summary, this is a cross-sectional study with 2.9 million births analyzed – this is presented in Table 1 (new), and Figures 1, 2, and 3. These include all municipalities in the country, regardless of population.

The creation of a variable with 520 municipalities with more than 1,000 births was done with the single purpose of analysing the association between CS rates and gestational age distribution, using municipalities with different levels of CS rates, instead of individuals. The results of these analyses are presented in Figure 4 and the new Table 2 (Poisson regression analyses using preterm and early term births as outcomes).

Results:
General comments: The results of this study are important but lack a little bit of clarity as only percentages are provided across subgroups and without the denominators.
I suggest including a summary table that gives the characteristics of the mothers (plus number of women in each category), % preterm births, % early term births overall and by mode of onset of delivery. Without the denominator, it is not currently possible to check the percentages. Please also add results from the Chi2 and t-test analyses.

Answer*: We added Table 1 with the denominators – numbers and proportions – of all variables used in the analyses. In relation to the Figures, we could present the numerical results as supplementary tables, if the Editors are agreeable*

Specific comments
In para 3:
-    Please check % provided and add reference to the Figure that is used.

Answer*: Done*
-

  " vaginal deliveries represented 62% of ALL BIRTHS" (based on Fig.1) not "all preterm birth" as currently written in the text. Similarly, " vaginal deliveries accounted for 20% of all birth" (cf. Fig.1) not " all preterm births"

Answer*: Thanks, it is now correct.*

In para 4, I would avoid the wording " increased" or " decreased" as you are not looking at trends, but use relative terms " higher"/ "lower".

Answer*: Done*

In the last paragraph, please check calculations for the number of births. I count 133 571 extra preterm births, and 226490 early terms.. You can provide also number of births over 39 weeks in high-income countries.

Answer*: Using as denominator the total number of singleton births – 2,903,716, and the high-income country prevalence of 5.5% preterm and 22.2% early term births, compared to 10.1% and 29.8%, respectively, in Brazil, we arrived at estimates of 133,571 extra preterm births and 220,682 extra early term births. We have changed the text accordingly.*

Minor comments : Figure titles are missing from the PDF.

Answer*: Figure legends, by instruction of the journal, are placed at the end of the paper, on page 16*

Discussion: Authors have done a good job bringing out the importance of this study for prevention p9-10, and especially on the importance of creating synergies across prevention efforts to maximize potential gains for perinatal health practice and outcomes.

There is also evidence in the literature that preterm and early term birth (overall and by mode of onset of delivery) may have a common etiology: http://bmjopen.bmj.com/content/8/1/e018745
Delnord M, Blondel B, Prunet C, et al. Are risk factors for preterm and early-term live singleton birth the same? A population-based study in France. BMJ Open 2018;8:e018745. doi: 10.1136/bmjopen-2017-018745

Answer: thanks, we have added the reference to Discussion (now ref number 30)

However, the paper would benefit from a standalone strengths and limitation section. As of now, this information is dispersed in the discussion. I would encourage the authors to be more explicit about the representativeness of their results based on the municipalities and hospitals which were selected (520 municipalities with more than 1000 births). Is there information in the literature on CS and preterm rates in some of the hospital and/or municipalities not included in the study? (even if data quality may be poorer..)

Answer: Again, we apologize for failing to convey the fact that all births in the country were studied, not only those in the 520 municipalities. We added text in the Methods section (page 6) comparing these 520 municipalities with the remaining municipalities in the country. A sub-section on strengths and limitations has been added at the beginning of Discussion.

Minor comments: p9 para 2 is a bit redundant with the results section. Pleas add ref for this sentence " In addition to the well known poor outcomes for preterm babies, we documented that …gestation" (documented where???)

Answer: reference was added

Reviewer: 4
Reviewer Name: Maria Graciela Freyermuth Enciso
Institution and Country: Centro de Investigaciones y Estudios Superiores en Antropología Social - Unidad Sureste. México
Competing Interests: None declared

I think that the paper should be of interest to the readers of the journal. However, I believe that the paper requires a minor revision before publication. General comments by section are provided below. Methods

The authors performed a test of proportion differences but the results are not reported in any table. They just mentioned in the text that all results are significant to 0.001% (P>0.001) but is not clear if they referred to the proportion differences.

Answer: The chi-squared tests refer to the differences in proportions displayed in the Figures. This is now made clear in the text (Methods, page 7). We have also included Table 1 with numbers and proportions of all variables analyzed in the paper. This may enable the calculation of denominators by readers, if they find it necessary. Another possibility, already mentioned above, would be to present the results of Figures 1, 2, and 3 as Supplemental tables, but this would depend on a decision from the Editors

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They also mentioned in the methods the use of a Poisson's model. However, they neither described nor discuss the related results. Thus, I recommend to either exclude the model from the methods section or include related material in the discussion and results sections.

Answer: *Poisson regression analyses are now well described in Methods, fully described in Results, and shown in the new Table 2.*

The first paragraph in the discussion section is about the data source. Therefore, this material should be relocated to the methods section.

Answer: *We have now fully expanded the Methods section to provide a more detailed description of the study population. The Discussion section has also been modified, and now starts with strengths and limitations of the study, and then addresses some of the positive aspects of the database under analysis.*

The authors do not clarify the relationship between socio-economic aspects and education. They argue that education and poverty are correlated. Thus, I think they need to justify such statement and support with references such as association. Previous studies show a tendency but not the magnitude with respect to the CS. Therefore, further discussion about this aspect is needed.

Answer: *Education is often used as a proxy for socioeconomic position in epidemiological studies. In our particular analyses, this was the only such proxy available in the database. Education has several advantages, including its high reliability and validity, its stability after early adulthood, and the fact that it can be collected as a continuous variable. We added a sentence in the Discussion and inserted a reference on the association between education and other markers of social class (REF Liberatos et al (1988) The measurement of social class in epidemiology. Epidemiol Rev 10:87-121) (page 11)*

Previous Brazilian studies have also shown important differences in CS rates among different socioeconomic groups. (see Barros AJ et (2011) Patterns of deliveries in a Brazilian birth cohort: almost universal cesarean sections for the better-off. Revista de Saude Publica 45 (4):635-643) We added this reference to Discussion (page 12)

The data does not demonstrate the epidemic presence in premature babies. They need to provide some historical statistics to be able to support the epidemic statement. Furthermore, it is worth to provide their definition for epidemic since it is not medical sound.

Answer: *The reviewer is correct in pointing out that our cross-sectional data, per se, do not demonstrate the presence of an epidemic. We added a reference to a systematic review that shows that preterm births are increasing over time in Brazil (Silveira et al, ref 6 in the current paper). We believe that our results – compared to a prevalence of 5.5% in high-income countries (Delnorde et al, ref 26 in the current paper) – configure an epidemic, and we have added text to justify our statement. Discussion, page 12.*

RESULTS
The differential risk of delivering premature babies described in the abstract while comparing communities with 30% of caesarean sections versus those with 80% is neither described nor analyzed in the results sections. The information must be included in the results together with the confidence intervals mentioned in the abstract.

Answer: *The risks described in the Abstract were now corrected, according to the new Poisson*

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regressions adjusted for a series of confounders. It now reads: The adjusted prevalence ratios of preterm and early term birth were, respectively, 1.215 (1.174-1.257) and 1.643 (1.616-1.671) higher in municipalities with >=80% CS compared to those <30%. This information is included in Results (page 11), and in Table 2 (new).

Please include a Conclusions section at the end of the manuscript.

Answer: *The BMJ Open format for original research papers does not include a section on Conclusions. The Abstract, however, includes a short sub-section with the main conclusions. We summarize the main conclusions in the body of the Discussion section.*

VERSION 2 – REVIEW

REVIEWER	María Graciela Freyermuth Enciso Centro de Investigaciones y Estudios Superiores en Antropología Social (CIESAS), San Cristóbal de Las Casas, Chiapas, México
REVIEW RETURNED	11-May-2018

GENERAL COMMENTS	1. The authors must include a conclusions section at the end of the document. That will help the reader to identify the main outcomes of the current work. 2. The authors must discuss the implication while excluding the number of deliveries, that most likely are vaginal, in their analysis of the preterm births and early births. It is important to clarify what are the characteristics of such excluded births to more clearly identify possible biases in the analysis. 3. The authors argued that their analysis "lead to paradoxical finding in the individual analysis, showing apparently protective effect of CS on preterm births". However, I differ with such impression. Women undergoing C-section usually go through a process of more intensive medicalization that women who are not medicalized. Women under threat of premature born get more medical treatment to ensure that they reach 37 weeks. This is the effect of medicalization on preterm infants. 4. I suggest that in page 11, Line 6 the authors refer to Table 2 in order to improve readability

REVIEWER	Alexandre Chiavegatto Filho School of Public Health of the University of São Paulo, Brazil.
REVIEW RETURNED	14-May-2018

GENERAL COMMENTS	The authors have adequately addressed my concerns.

REVIEWER	Marie Delnord INSERM UMR1153 Obstetrical, Perinatal and Pediatric Epidemiology Research Team- EPOPé Center for Epidemiology and Statistics Sorbonne Paris Cité- CRESS, Paris Descartes University; INSERM UMR1153 Maternité de Port Royal 53 Avenue de l'Observatoire 75014 Paris, France
REVIEW RETURNED	17-May-2018

GENERAL COMMENTS	Congratulations on a much improved paper. Thank you for this revison and for taking into account the points I raised in the first round.

I recommend this paper for publication, after taking into account some additional minor changes.

Recommended changes:
• I understand that one of the reviewers asked you to redo analyses for very preterm births. While I agree this is an interesting subanalysis, the GA threshold is not correct and should be 32 weeks; This could also explain why the results are inconclusive…as you have mixed some of the moderate preterm babies in at 33-34 weeks + should also add ref. as to why the etiology/practices for very preterm (babies born at or before 32) vs (late and moderate preterm births 33-36 weeks) may be different.
ALternatively leave as is but still provide reference for etiologies by GA subgroups.
• In Table 1, add a category for CS rate groupings and the number of municipalities in each category.
• Methods are still a little unclear. Try to explain more simply that you conducted population based analyses overall, and also that you conducted a sensitivity analyses based on municipalities with more than 1000 births.
I would recommend moving the lines below to the methods section as this is your rationale for the sensitivy analyses:
"For these reasons, we propose that examining the gestational age distribution in groups of municipalities is a better alternative. These are still individual-level analyses, but the main explanatory variable is the CS rate in a municipality, not whether or not each pregnancy resulted in a CS. If a municipality has CS rates say of 60% or higher, most of these operations will not have medical indications.1
Therefore we can assess the role of CS in affecting gestational age in a more reliable way than analysing individual pregnancies. This is the rationale for our analyses including the 520 municipalities with more than 1,000 births in 2015 (Figure 4)." P.10
In the results section indicate in the text and for each table/figure when you are presenting overall data vs sensitivity analysis data.
• This should be in methods not results: P.8 "Because these variables were also associated with the prevalence of preterm and early term births, we used Poisson regression to produce unadjusted and adjusted analyses of the association between preterm and early term births and municipalities with different CS rates, taking into account the possible confounding effect of maternal education, age, parity, and marital status. The units of analyses were individual women, according to municipal rates of CS"

• Add 2-3 lines in your discussion that links back more explicitly to your original hypothesis : "In this paper it was hypothesized that, from a public health perspective, the most important consequence of scheduled CS deliveries - in terms of the number of births affected - would not be the increase in pretem deliveries, but the shift of term (39-41 weeks' gestation) births to the early term (37-38 weeks' gestation) period."

Minor edits:
• Use the same number of decimal points in abstract, text and tables.
• Add the abbreviation for cesarean section (CS) when you use the term for the first time (ie. in abstract)
• P7-8: In your results, refrain from using terms such as: "increased"/"diminished"/"dropped" when comparing preterm vs. early term birth prevalence rates. These terms imply trends whereas

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	you are looking at data from one year only. Replace by relative terms such as "higher"/"greater"/"lower"
	• P.9 I think this should read "excess of 354,253 babies born preterm or early term" instead of " excess of 354,253 babies born at 39 or more weeks".
	• P.12: "Data from 34 high-income countries show that preterm births represent 5.5% of births while early term births represent 22.2% of the total." Add "of the total number of births"
	• P. 12 Therefore, in addition to "a" short-term increase (word missing)

VERSION 2 – AUTHOR RESPONSE

We are resubmitting our paper Caesarean sections and gestational age distribution in Brazil: secondary analyses of national birth registration, after the second round of reviews.
We have tried to satisfy all Editorial requests, and carefully answered all comments, suggestions and queries from the Reviewers. The paper has been slightly modified to satisfy some of the reviewers' demands, and a Conclusions section was included. Abstract has now 256 words and the text has 4,403 words. We kept the same number of tables (2) and figures (4).
All changes in the paper were marked with track changes, and a clean copy is also included.

VERSION 3 – REVIEW

REVIEWER	Marie Delnord INSERM UMR1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team- EPOPé, Center for Epidemiology and Statistics Sorbonne Paris Cité- CRESS, Paris Descartes University, INSERM UMR1153, Maternité de Port Royal, 53 Avenue de l'Observatoire, 75014 Paris, France, Tel : +33 1 71 72 29 91
REVIEW RETURNED	04-Jul-2018

GENERAL COMMENTS	Thank you for inviting me to review this paper which I find criticial in order to push for the prevention of high cesarean section use in Brazil, and for the development of new prevention strategies for preterm and early term delivery. I still have some comments though that I would like the authors to address. I have attached them here, reading linearly through the text. - The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 3 – AUTHOR RESPONSE

Answers to the Editors and Reviewer #3
Editorial Comments:

Thank you for resubmitting your manuscript to BMJ Open and I am very sorry that your revision has been under review for a long period of time. Reviewer 3 was unable to submit her report within the 14 day deadline set, hence the delay. Please note that your next revision will not be sent to any peer reviewers. It will be reviewed in-house by our editorial team only.

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Before submitting your next revision, please remember to review the paper for spelling and grammar one more time. For example, on page 6, please amend "..with CS that are, frequently decided by the patients themselves." to "..with CS that are frequently decided by the patients themselves."
Answer: text on page 6 was corrected.
Reviewer #3
Title: I am not sure the title is specific enough since in the end you only analyze preterm and early term, and not the entire gestational age distribution.
Answer: We have changed the title, according to your suggestion. It is now: "Caesarean sections and the prevalence of preterm and early term births in Brazil: secondary analyses of national birth registration".

Abstract: Conclusions: Brazil faces three interrelated epidemics: a CS epidemic, an epidemic of early term births, directly related to the high CS rates; and an epidemic of preterm. "Associated with" instead of "directly related to".
Answer: We have modified the text that now reads: "Brazil faces three interrelated epidemics: a CS epidemic, an epidemic of early term births, associated with the high CS rates; and an epidemic of preterm birth, also associated with CS but mostly linked to poverty related risk factors."

Strengths and limitations of this study. Analysis of a national database of 2.9 million singleton births, representing >96% of all births occurring in Brazil in 2015, a country where <2% of births occur at home. Add "live" births.
Answer: we have added live births, as requested. The text now reads: "Analysis of a national database of 2.9 million singleton live births, representing >96% of all births occurring in Brazil in 2015, a country where <2% of births occur at home."
Strengths and limitations of this study. Gestational ages are assessed routinely, according to recommendations of the Ministry of Health, and available for 97.5% of the births. What are the rules? You could be more explicit here since the method of pregnancy dating can affect gestational age subgroup estimates.
Answer: We did not describe the methods of gestational age estimation adopted by the Ministry of Health in "Strenghts and limitations of this study" because this section should be succinct and formatted in bullets. But we did describe these methods in details in the Methods section (page 5): "Gestational age is assessed following the Ministry of Health recommendations, by the date of the last menstrual period (LMP).21 In cases where the LMP is unknown or inconsistent, the best obstetric estimate is then utilized, comprising either ultrasonographic evaluation or physical examination of the newborn."

Introduction. General comment: In the introduction, you are missing information on why there can be indicated preterm deliveries in the first place (this will be tied to CS rates), and also on the adverse health outcomes of preterm birth. This will strenghten your point that it is necessary from a public health perspective to explore combined prevention initiatives that will lower iatrogenic interventions as well as reduce preterm and early term birth.
Answer: We have changed the Introduction section to address the two points raised by the reviewer. Regarding indicated preterm deliveries, the text now reads (page 4): "Brazil is also undergoing an epidemic of preterm births, 4 and although some of these births could represent medically indicated preterm deliveries (e.g. to avoid maternal or fetal mortality), part of this epidemic has been attributed to scheduled CS, frequently due to doctor and/or maternal convenience. 5-9
Regarding the adverse health outcomes of preterm deliveries, the text now reads (page 4): "It is well known that preterm babies are at increased risk of mortality and long-term sequelae14. Early term infants are also at higher risk of mortality12 15-17, including post-neonatal sudden unexpected infant deaths18

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Also see comments on this sentence: "In this paper it was hypothesized that, from a public health perspective, the most important consequence of scheduled CS deliveries - in terms of the number of births affected - would not be the increase in pretem deliveries, but the shift of full term (39-41 weeks' gestation) births to the early term (37-38 weeks' gestation) period.
Please add ref. To the definition of term pregnancy. And explain why 39-41 weeks is a more desirable outcomes. Lots of refs on this from ACOG and US literature..
Answer: We have now added a phrase (and reference) in Introduction (page 4) defining term pregnancy and explaining that this is the gestational age group with the lowest morbidity and mortality. The text reads: " Babies born between 39 0/7 weeks and 41 6/7 weeks are considered full term and late term11, and this is the gestational age group with the lowest levels of morbidity and mortality. 12 13 "

I am not sure that with your results you can justify a "shift" from full term to early term birth since you have not tested associations between the rates of full term and early term birth by mode of onset over time.
Answer: We could not test associations over time, due to the cross-sectional design of our study. However, we have shown important (and statistically significant) differences between the prevalence of early term and term births in municipalities with different levels of CS. Early births were markedly less frequent (21.7%) In municipalities with less than 30% of CS in comparison with 40.4% in those municipalities with >=80% of CS - a difference of 18.7 percent points.
We have changed the text on page 12 to "Our results suggest that the main impact of the high CS rates has been a shift from term to early term births."

You clearly show that high rates of CS are associated with greater risk of preterm and early term delivery in Brazil, and that high rates of CS seems to have a greater impact on early term deliveries. General comments : It would really strengthen the paper if you could explain why you have decided to look at births < 34 weeks. I don't think it's enough to say "presumably, these rates should not be associated with CS rates."
Answer: the rationale of analyzing the distribution of births <34 weeks in municipalities with different CS rates was exactly because the prevalence of births in this gestational age group should not be affected by non-medically indicated CS. This was a suggestion from a BMJ Open reviewer in a previous iteration. This is known as a surrogate outcome, that is, one that should not be affected by CS due to bias. Since there was no association between births <34 weeks and CS, it is more plausible that the association between early term birth and CS is a causal one.
We have explained in detail this analysis in Methods (page 7): "However, as presumably such births should not be affected by elective, non-medically indicated CS (as obstetricians would not err by several weeks when estimating gestational age), we also examined <34 weeks births in the analyses of municipalities. If municipal CS rates are not associated with the prevalence of <34 weeks births, this finding will support the hypothesis that CS without medical indication are solely affecting the prevalence of preterm (34-36 weeks) and early term births."

It would really strengthen the paper to have a reference here for this about rates of indicated very preterm (<32 weeks) and moderate preterm births (32-33 weeks).
Answer: We have added a reference about rates of indicated CS <34 weeks of gestation. The text now reads (page 7): "The proportion of medically-indicated CS births <34 weeks is high, having increased 36% between 1996 and 2006 in the United States27. However, as presumably such births should not be affected by elective, non-medically indicated CS (as obstetricians would not err by several weeks when estimating gestational age), we also examined <34 weeks births in the analyses of municipalities."

"We adopted this second approach to account for the fact that a certain proportion of CS are medically indicated, including some procedures that will result in preterm deliveries, as is the case for

early termination of pregnancy due to maternal or fetal conditions.22 The main explanatory variable is the CS rate in a municipality, not whether or not each pregnancy resulted in a CS. If a municipality has CS rates say of 60% or higher, most of these operations will not have medical indications.1 Therefore we can assess the role of CS in affecting gestational age in a more reliable way than analysing individual pregnancies for which a medical indication may or may not be present. This is the rationale for conducting analyses based on data from 520 municipalities with more than 1,000 births in 2015 out of the 3157 municipalities overall in the study."

Ok but this statement is confusing because you studied live births so I am not sure this is the best example for what you are trying to say.

A bit colloquial "say of"

Answer: We do not understand the reviewer's comments on live births, as all our analyses included live-born children. Perhaps the reviewer was confused by the term "early termination of pregnancy", that we have now replaced with "early interruption of pregnancy". (page 6.)

We have replaced the colloquial "say of" by "For example, if a municipality has CS rates of 60% or higher, most likely a high proportion of these operations will not be medically indicated." (page 6)

Better to say " Most likely a high proportion of non medically indicated deliveries contribute to the higher rates of CS in some of the municipalities we studied"

English not clear – please rephrase

Answer: we have changed the text according to your suggestion, as we commented before. It now reads (page 6): "For example, if a municipality has CS rates of 60% or higher, most likely a high proportion of these operations will not be medically indicated.1 Therefore we can assess the role of CS in affecting gestational age in a more reliable way than analysing individual pregnancies for which a medical indication may or may not be present. This is the rationale for our analyses including the 520 municipalities with more than 1,000 births in 2015."

Minor edits: In results, perhaps use only up to the tenth decimal only, or centiles if you wish.

Discussion: • Please discuss how the method of estimating GA may affect your results. There are inherent biases to using LMP vs. Ultrasound. Add refs to explain and justify.

Answer: we have included text on the different methods of gestational age estimation in the limitations section of Discussion (page 14). It now reads: "The system has some limitations, including the lack of information on indications for CS and reliance on routine assessment of gestational age, with date of LMP being the first option, with ultrasonography and physical examination being used in cases when LMP is not known. It is recognized that LMP assessed after birth produces slightly higher prevalence estimates of preterm birth than early ultrasound exams.37 These limitations, however, are unlikely to have affected the present results as they should apply to all municipalities under study."

Add confidence intervals to table with results of individual analyses.

Answer: we have added 95% confidence intervals to Table 1. As confidence intervals were very narrow, due to big numbers, we used two decimal points for the prevalence of individual variables.

However, the remarkably strong positive association between socioeconomic position and CS (Figure 1) jointly with the negative association of socioeconomic position and preterm vaginal births (Figure 2) leads to a paradoxical finding in the individual analyses, showing an apparently protective effect of CS on preterm births. In fact, in our individual analyses the prevalence ratio of preterm birth associated with CS was 0.957, indicating a protective effect of 4.3%. Conceivably, women subjected to more intense medicalization might be protected from preterm delivery, which would explain a protective effect of CS on preterm births in the individual-level analyses.

I wouldn t conclude on any protective effect of CS given that results are borderline signifcant and all of the confidence intervals overlap. If anything where CS rates are higher, risk of preterm birth is greater based on results... 1.1-1.2 95% CI for +80% is greater than 95%CI for the lower categories of CS.

Answer: we agree with you. We state on page 12 that the inverse associations between maternal education and CS as well as with preterm births result in a paradoxical finding of an apparent small protective effect of CS on preterm births. We now mention that these results could be due to residual confounding, and we finish the sentence by stating: "However, these findings might be due to residual confounding and were not confirmed by our municipality-based analyses, where preterm and early term births was more prevalent in municipalities with higher CS rates."

I am not sure this is the right interpretation..your results show that higher educated women are more at risk for cesarean section, but these women are also less at risk of preterm birth in general...to me this finding looks like there is residual confounding due to socioeconomic status instead of a protective effect of CS.
Answer: We agree, we are conveying that individual-based analyses lead to findings that are not confirmed by the municipal level analyses. As mentioned earlier, we state that the individual-level findings could be due to residual confounding. The text now reads: "Conceivably, women subjected to more intense medicalization might be protected from preterm delivery, which would explain a protective effect of CS on preterm births in the individual-level analyses. However, these findings might be due to residual confounding and were not confirmed by our municipality-based analyses, where preterm and early term births was more prevalent in municipalities with higher CS rates. (page 12)

I would avoid saying CS has a role in protecting from preterm birth, this could be misinterpreted. Also there is evidence that the more CS you have the higher your rate of late preterm birth which is a main driver of overall preterm birth rates in the US.
Answer: we agree, and we have changed the sentence, as shown in our previous answer.