

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Effects of maternal smoking on body size and proportions at birth: A register-based cohort study of 1.4 million births
<b>AUTHORS</b>	Rumrich, Isabell; Vähäkangas, Kirsi; Viluksela, Matti; Gissler, Mika; de Ruyter, Hanna; Hänninen, Otto

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Christa L. Lilly West Virginia University, School of Public Health USA
<b>REVIEW RETURNED</b>	29-Aug-2019

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review this manuscript. It tackles the timely issue of maternal smoking on fetal growth, specifically focusing on body proportions at birth and related birth outcomes. I provide the statistical review but am also interested in the topic area. The statistical analysis are appropriately conducted using traditional methodology. I have some minor suggestions to improve the clarity of these results.</p> <p>Study design: The figure S1 is missing the percentages on the bottom rows. The sub-population should be explained at this point in text along with some description of what it was used for in the figure S1 (I think an outcome perhaps was only available post 2004).</p> <p>Statistical analysis: Table 1 should not be referenced here, as the covariates are mentioned in the paragraph previous. Why were some covariates excluded for some analyses, was the decision based on a combination of available data and bivariate associations or literature/theoretical confounding?</p> <p>I could be wrong about this, but table 1 column "No of mother-child pairs..." leads me to think the logistic regressions were stratified by exposure (Continued/Quitted) with both exposure being in referent to No smoke exposure? Was there a reason this (possible) stratification occurred rather than an ordinal exposure grouping? Some clarification here in the analysis section would be helpful for both understanding the decisions behind the analysis and being used for replication.</p> <p>Results: Table 1, given it's primary focus, needs some work to be publication worthy. It is really only interpretable in conjunction with tables S2 and S3. For example, the Column "Smoking" should include the referent for all models, the Column "OR" should note that it is Adjusted.</p> <p>Figure 1 also needs some work to be publication worthy; for example, the X-axis legend is upside down!</p> <p>More pertinently, Table S3 should be referenced in text in the results section.</p> <p>Discussion: Please use consistent citing for the supplemental tables (should be Table S4, not table 4).</p>
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	<p>I think it not appropriate for the analysis given this data set, but a great next steps would be to separate out newer forms of smoke exposure and non-tobacco smoke (e.g. vaping, cannabis).</p> <p>Thank you again for the opportunity to review this important work.</p>
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<b>REVIEWER</b>	Anne Eskild Akershus University Hospital and Univeristy of Oslo, Norway
<b>REVIEW RETURNED</b>	06-Sep-2019

<b>GENERAL COMMENTS</b>	<p>This study aims at studying the impact of maternal smoking in pregnancy on birthweight and body composition of the newborn. This is an interesting and important aim. I believe, however, that the reading of the paper is difficult. I have started many times. The main limitation of manuscript, I believe, is that the aim of the study is difficult to understand. The aim of the study is stated differently in different part of the manuscript (see examples below). Hence, the exposure (categories of maternal smoking) is not presented accurately or consistently throughout the manuscript. Also, the outcomes in the study are not consistently presented.</p> <p><b>Aim</b> In the Abstract: to study the effect of growth restriction on body proportions at birth in newborns exposed to maternal smoking at different time points during pregnancy.</p> <p><b>In the Introduction:</b> to compare the effect of early or continued smoking during pregnancy on body proportions at birth associated with growth restriction induced by smoking. Additionally, we investigated the possibility of mechanistic interpretations of possible alterations in body proportions in newborns of smoking mothers.</p> <p><b>In the Materials and methods</b> We analysed the effect of maternal smoking on four groups of outcomes: (i) preterm birth (PTB); (ii) low birth weight (LBW); (iii) small anthropometric indices for gestational age, and (iv) body proportions. We analysed the effect of smoking during the 1st trimester only and smoking during later pregnancy separately with no smoking during pregnancy as a reference. In the abstract the outcomes listed are: Outcomes included reduced body size (birth weight, body length, and head circumference) and altered body proportions (indicated by high ponderal index (PI), low brain-to-body ratio (BBR), and high head-to- length ratio (HLR)) at birth</p> <p><b>In the Discussion</b> This work indicated a difference in susceptibility for growth restriction between the anthropometric indices.</p> <p><b>Suggestions to improve the manuscript.</b> Make the text simpler and thereby easier to read. Be consistent throughout the manuscript while describing the exposures and the outcomes. May be there at to many outcomes in this study? Add a table of the composition of the study sample according to smoking status. Too much information in Table 1. Better to make two?</p>
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	<p>Be consistent in the wording; maternal smoking ... offspring birthweight. In my opinion, too many abbreviations are used.</p> <p>Maternal body composition and body mass index, many be important confounder, and could be discussed.</p>
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### VERSION 1 – AUTHOR RESPONSE

**Reviewer: 1**

**Reviewer Name: Christa L. Lilly**

**Institution and Country: West Virginia University, School of Public Health, USA Please state any competing interests or state 'None declared': None declared**

Please leave your comments for the authors below

Thank you for the opportunity to review this manuscript. It tackles the timely issue of maternal smoking on fetal growth, specifically focusing on body proportions at birth and related birth outcomes. I provide the statistical review but am also interested in the topic area.

The statistical analysis are appropriately conducted using traditional methodology. I have some minor suggestions to improve the clarity of these results.

**Comment:**

Study design: The figure S1 is missing the percentages on the bottom rows.

**Response:**

The figure has been corrected (Supplemental Material p.2).

**Comment:**

The sub-population should be explained at this point in text along with some description of what it was used for in the figure S1 (I think an outcome perhaps was only available post 2004).

**Response:**

Yes, some of the outcomes were only available 2004 onwards. This has been explained more clearly in the text (Manuscript p. 5; Supplemental Material p.2).

**Comment:**

Statistical analysis: Table 1 should not be referenced here, as the covariates are mentioned in the paragraph previous. Why were some covariates excluded for some analyses, was the decision based on a combination of available data and bivariate associations or literature/theoretical confounding?

**Response:**

Some covariates were excluded due to availability of data. A sensitivity analyses has been conducted to test the robustness of the results for confounder inclusion/exclusion (Supplemental Material p.8, 11). The confounder selection has been described in more detail (Manuscript p. 8).

**Comment:**

I could be wrong about this, but table 1 column "No of mother-child pairs..." leads me to think the logistic regressions were stratified by exposure (Continued/Quitted) with both exposure being in referent to No smoke exposure? Was there a reason this (possible) stratification occurred rather than an ordinal exposure grouping? Some clarification here in the analysis section would be helpful for both understanding the decisions behind the analysis and being used for replication.

**Response:**

Yes, the logistic regression was stratified by exposure (continued/quitted smoking) with both exposures being in referent to no smoking exposure. This has been clarified in the main manuscript, p. 8. We stratified the logistic regression as we aimed to be able to validate our analysis with previously published.

**Comment:**

Results: Table 1, given it's primary focus, needs some work to be publication worthy. It is really only interpretable in conjunction with tables S2 and S3. For example, the Column "Smoking" should include the referent for all models, the Column "OR" should note that it is Adjusted.

**Response:**

The table has been updated, taking into account also Reviewer 2's comments (Manuscript p. 8).

**Comment:**

Figure 1 also needs some work to be publication worthy; for example, the X-axis legend is upside down!

**Response:**

The figure has been updated.

**Comment:**

More pertinently, Table S3 should be referenced in text in the results section.

**Response:**

A reference has been added on p. 10 of the manuscript.

**Comment:**

Discussion: Please use consistent citing for the supplemental tables (should be Table S4, not table 4).

**Response:**

The manuscript has been revised accordingly.

**Comment:**

I think it not appropriate for the analysis given this data set, but a great next steps would be to separate out newer forms of smoke exposure and non-tobacco smoke (e.g. vaping, cannabis).

**Response:**

We highly agree that other forms of nicotine, tobacco and non-tobacco exposure (nicotine replacement products, e-cigarettes, cannabis) would be highly interesting. Unfortunately, in the dataset analysed in this article, only information explicitly on cigarette (tobacco) smoking is available.

Thank you again for the opportunity to review this important work.

**Reviewer: 2**

**Reviewer Name: Anne Eskild**

**Institution and Country: Akershus University Hospital and University of Oslo, Norway Please state any competing interests or state 'None declared': None declared**

Please leave your comments for the authors below

Title: Maternal smoking alters body proportions at birth: A register-based cohort study of 1.4 million births

This study aims at studying the impact of maternal smoking in pregnancy on birthweight and body composition of the newborn. This is an interesting and important aim. I believe, however, that the reading of the paper is difficult. I have started many times.

**Comment:**

The main limitation of manuscript, I believe, is that the aim of the study is difficult to understand. The aim of the study is stated differently in different part of the manuscript (see examples below). Hence, the exposure (categories of maternal smoking) is not presented accurately or consistently throughout the manuscript. Also, the outcomes in the study are not consistently presented.

Aim

In the Abstract:

to study the effect of growth restriction on body proportions at birth in newborns exposed to maternal smoking at different time points during pregnancy.

In the Introduction:

to compare the effect of early or continued smoking during pregnancy on body proportions at birth associated with growth restriction induced by smoking. Additionally, we investigated the possibility of

mechanistic interpretations of possible alterations in body proportions in newborns of smoking mothers.

In the Materials and methods

We analysed the effect of maternal smoking on four groups of outcomes: (i) preterm birth (PTB); (ii) low birth weight (LBW); (iii) small anthropometric indices for gestational age, and (iv) body proportions. We analysed the effect of smoking during the 1st trimester only and smoking during later pregnancy separately with no smoking during pregnancy as a reference.

In the abstract the outcomes listed are: Outcomes included reduced body size (birth weight, body length, and head circumference) and altered body proportions (indicated by high ponderal index (PI), low brain-to-body ratio (BBR), and high head-to-length ratio (HLR)) at birth

In the Discussion

This work indicated a difference in susceptibility for growth restriction between the anthropometric indices.

**Response:**

The aims have been clarified and harmonized throughout the manuscript (Abstract, Introduction (p.4)). Additionally, the manuscript has been revised for clarity, taking care to use consistent phrasing of the exposure categories and all outcomes (Abstract, Material and methods (p. 5)).

Suggestions to improve the manuscript.

**Comment:**

Make the text simpler and thereby easier to read. Be consistent throughout the manuscript while describing the exposures and the outcomes. May be there at to many outcomes in this study?

**Response:**

The description of the exposure and outcomes has been revised for consistency and clarity.

**Comment:**

Add a table of the composition of the study sample according to smoking status.

**Response:**

Table S2, showing the composition of the study sample by smoking status, has been partly brought from the Supplemental Material to the manuscript. Table 2 (manuscript p. 9) describes the composition of the study population for the main variables, while Table S2 (Supplemental Material p. 4) describes the composition of the study population in more detail.

**Comment:**

Too much information in Table 1. Better to make two?

**Response:**

Table 1 has been revised, taking also into account Reviewer 1's comments. The numerical results of the logistic regression have been moved to Figure 1 and Table S3 (Supplemental Material p. 6).

**Comment:**

Be consistent in the wording; maternal smoking ... offspring birthweight. In my opinion, too many abbreviations are used.

**Response:**

The language has been revised for consistency. The number of abbreviations used has been reduced to the most commonly used ones.

**Comment:**

Maternal body composition and body mass index, may be important confounder, and could be discussed.

**Response:**

Maternal body mass index has been included as a confounder in the sensitivity analysis (Figure S4) and it did not change the results presented in the manuscript (Supplemental Material p8, 11).

<b>REVIEWER</b>	Christa L Lilly West Virginia University, USA
<b>REVIEW RETURNED</b>	16-Oct-2019

<b>GENERAL COMMENTS</b>	Thank you for your thorough response to previous review, I have no further suggestions.
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<b>REVIEWER</b>	Anne Eskild Akershus Univeristy Hopsital, Norway
<b>REVIEW RETURNED</b>	02-Nov-2019

<b>GENERAL COMMENTS</b>	<p>The manuscript s improved, but in my opinion there are still potentials for improvements. I have made some comments below. I have also included some comments in the manuscript (enclosed). May be those could be of help.</p> <p>Still I am not sure if I understand the Abstract: “The aim of our work was, using a register-based approach, to compare the effect of smoking quitted during the 1st trimester or continued after the 1st trimester on body size and body proportions at birth, and preterm birth associated with smoking”</p> <p>Would it be better to write: We aimed to study the effect of maternal smoking during the 1st trimester only, and maternal smoking during the whole pregnancy on offspring body size and offspring body proportions at birth. We also studied the effects of maternal smoking on the risk of preterm delivery.</p> <p>Other comments To me, it remains unclear: Which pregnancies constitute the study sample in the different analyses. Is the 1.4 mill birth in the headline misleading? Are the percentiles calculated in the MATEX-cohort? in the sub-samples included in each sub-analyses, or in a different Finish population of births? There are many outcomes and many tables. Different samples and different set of potentially confounding factors are included. Also, different measures for low birthweight are included. Additionally several analyses within strata of birth year and socioeconomic groups are performed. I think that this manuscript is very difficult to review properly. The study’s main message is not easy to grasp. Still, I believe that this manuscript would benefit from reducing the number of outcomes, and using the same study sample for all (most) of the analyses.</p>
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## VERSION 2 – AUTHOR RESPONSE

### Reviewer: 1

Reviewer Name: Christa L Lilly

Institution and Country: West Virginia University, USA Please state any competing interests or state

‘None declared’: None declared

Please leave your comments for the authors below Thank you for your thorough response to previous review, I have no further suggestions.

**Reviewer: 2**

Reviewer Name: Anne Eskild

Institution and Country: Akershus Univeristy Hopsital, Norway Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below The manuscript s improved, but in my opinion there are still potentials for improvements.

I have made some comments below. I have also included some comments in the manuscript (enclosed). May be those could be of help.

We appreciate the detailed and constructive feedback provided here and as comments in the manuscript. We are grateful for the great amount of time and work the Reviewer invested to help us improve the manuscript. It certainly helped to clarify which parts of the manuscript remained unclear.

Still I am not sure if I understand the Abstract:

“The aim of our work was, using a register-based approach, to compare the effect of smoking quitted during the 1st trimester or continued after the 1st trimester on body size and body proportions at birth, and preterm birth associated with smoking”

Would it be better to write:

We aimed to study the effect of maternal smoking during the 1st trimester only, and maternal smoking during the whole pregnancy on offspring body size and offspring body proportions at birth. We also studied the effects of maternal smoking on the risk of preterm delivery.

We appreciate the very clear suggestion on how to clarify the aims presented in the abstract. We revised it accordingly. [p2, lines 36ff]

Other comments

To me, it remains unclear:

Which pregnancies constitute the study sample in the different analyses. Is the 1.4 mill birth in the headline misleading?

The study population is indeed conducted in a study population of roughly 1.38 million mother-child pairs. The stratification if the analyses, i.e. separately analyzing smoking during the first trimester only vs no smoking, and smoking continued after the first trimester vs no smoking leads to a bit smaller study population in each analyses (max 1.21 million and 1.33 million mother-child pairs respectively, see Table 1). This has been clarified in the Material and Methods section. [p2, line 52; p6, lines 170ff; p10, Table 1 footnote]

Are the percentiles calculated in the MATEX-cohort? in the sub-samples included in each sub-analyses, or in a different Finish population of births?

The percentiles are calculated based on the Finnish references for body weight, body length and head circumference published by Sankilampi et al 2013. These references are also used in clinical setting in Finland. The references are based on population based data different from the MATEX cohort. For body proportions no Finnish references are available for newborns, thus we calculated the percentiles in the MATEX cohort. This was clarified in the Material and Method section. [p7, lines 202ff and p8, lines 209ff]

Reference: Sankilampi U, Hannila ML, Saari A, et al. New Population-Based References for Birth Weight, Length, and Head Circumference in Singletons and Twins from 23 to 43 Gestation Weeks. *Annals of Medicine* 2013;45(5-6):446-454.

There are many outcomes and many tables. Different samples and different set of potentially confounding factors are included. Also, different measures for low birthweight are included. Additionally several analyses within strata of birth year and socioeconomic groups are performed.

I think that this manuscript is very difficult to review properly. The study's main message is not easy to grasp.

Still, I believe that this manuscript would benefit from reducing the number of outcomes, and using the same study sample for all (most) of the analyses.

We agree that the manuscript includes many outcomes (8 outcomes in 3 groups) and that the different study populations add confusion. After careful consideration of splitting the manuscript or moving outcomes to the supplemental material to reduce the number of outcomes presented in the manuscript, we opted to remove the subcategories of preterm birth and low birth weight (<1,000g) from the main manuscript. After further careful consideration, we decided to keep all remaining endpoints in the manuscript. The interpretation of the effect of maternal smoking on prenatal growth requires the presentation of both, small body size and body proportions. We don't feel that removing preterm birth and low birth weight (<2,500g) from the manuscript would add clarity. [p7, lines 194f and 198f; p15 Table 2; Figure 1]

Currently, the manuscript includes two tables and one figure. We considered each of them and think all have their place in the manuscript supporting clarity. Table 1 describes the included endpoints and statistical analyses (sample size, factors included in the multivariate regression). We hope that this table can guide the reader through the different outcomes and analyses included in the manuscript. The study population is described in Table 2. This table was initially in the supplementary material and was moved upon request during the previous revision round into the main manuscript. We agree that it is useful for the reader to be able to gain a quick overview over the baseline characteristics of the study population. Finally, there is Figure 1, which presents an overview of the numerical results of the analysis. We argue that a figure is initially easier to read than a table listing the numerical results. Thus, such a table is only presented in the supplementary material.

We take the suggestion that the manuscript is confusing due to the many outcomes and analyses very serious. Thus we tried to improve clarity by structuring the manuscript in a very clear manner. Materials & Methods, Results, Tables 1 & 2 and Figure 1 present the outcomes in a similar grouping: general traditional outcomes (preterm birth, low birth weight (<2,500g)), followed by small body size and then lastly body proportions. Additionally, we explained the use of the different study populations in more detail. The use of two different study populations is due to the register-based design of the study. Information on head circumference are only available for the later years of the study forcing us to use only a sub-sample of the MATEX cohort for any analyses requiring information of head circumference (small head circumference, low brain-to-body ratio, high head-to-length ratio). We added explanation of this throughout the manuscript for clarity. [p6 lines 170ff; Table 1 Footnote]

#### Annotations in the manuscript

1. Definitions of the outcomes have been added. [p2, lines 54ff]
2. We changed the language throughout the manuscript from altered body proportions to abnormal body proportions.
3. We revised the sentence for clarity. [p2, lines 63ff]
4. We agree that it is not possible to present all outcomes and results in the abstract. We try to find a balance between completeness, understandability and conciseness. It seems reasonable to only present the main results in the abstract and thus we decided to present the numerical results only for abnormal body proportions. We agree that ponderal index may not be self-explanatory to all readers; however, it should become clear that it is an indicator for body proportions.
5. We revised the conclusions and aims in the abstract for clarity and consistency with the aims presented at the end of the introduction. The aims in the abstract presents now the main aim of the work and the aims at the end of the introduction also list the specific aims [p2, lines 36ff; p3, lines 71ff; p6, lines 145ff]



6. We updated the strengths and limitations section for clarity. [p4, lines 94ff]
7. We revised the aims for clarity and consistency with the aims presented in the abstract. The aims section at the end of the introduction is more detailed while the abstract presents the main aim. [p2, lines 36ff; p3, lines 71ff; p6, lines 145ff]
8. The smaller sub-population was also used for any analyses requiring information on head circumference (small head circumference, low brain-to-body ratio, high head-to-length ratio) since information on head circumference are only available for the later years of the study (2004-2016). This has been clarified in the manuscript (Material and Method Section and footnote of Table 1). [p6, lines 170ff; p10, Table 1 footnote]
9. To aid clarity we added the reference group definition for each outcome in Table 1 and revised the text for clarity. [p7, lines 203; p8, lines 2010ff and 208ff; p10, Table 1]
10. After consideration, we decided not to mention the units in the text since they are given in the equations, which are referenced clearly. We hope that the reduction of wordiness aids the clarity. [p8, lines 215 and 221f and 230f]
11. For the outcomes of body proportions we excluded the opposite tail of the distribution because both ends of the distribution can be considered "abnormal", i.e. and indicator for some problems in the prenatal growths. Of course, our cut-off at 10% at each ends is arbitrary, but we decided for this relatively high cutoff since a lower cut-off would shift the odds ratio artificially also towards higher odds. The definition of reference groups has been clarified in the Materials and Method Section and Table 1. The exclusion of high birth weight and the opposite ends of the distribution for body proportions can be assumed indirectly from that. [p7, lines 203; p8, lines 2010ff and 208ff; p10, Table 1]
12. Correct, the percentiles were calculated based on the MATEX cohort (the study population) since no Finnish standard references for the indicators of body proportions were available. We revised the paragraph for clarity. As described above, we clarified the definition of reference groups and exclusion of mother-child pairs throughout the manuscript. [p8, lines 2010ff; p10 Table 1]
13. There was a typo in the manuscript, which was corrected. Furthermore, we clarified the definition of reference groups and exclusion of mother-child pairs throughout the manuscript (as described in the responses to comments 8 and 11). [p8, lines 217f and 223f and p9, lines 230f]
14. This was clarified (see response to comment 13).
15. The sentence was deleted because it was obsolete after revision of the paragraph on p8 lines 209ff.
16. The definition has been revised for clarity. [p10 Table 1]
17. The definition has been revised for clarity [p10 Table 1]
18. We stratified our analyses, i.e. in the statistical analyses we compared smoking quitted during the 1<sup>st</sup> trimester with no smoking and separately smoking continued after the 1<sup>st</sup> trimester with no smoking. The paragraph has been revised for clarity. [p14, lines 261ff]
19. The wording has been changed according to the proposal. [p14, lines 264f]
20. The wording has been changed according to the proposal. [p14, lines 266f]
21. The sentence has been revised for clarity. [p14f, lines 267ff]
22. We changed the decimal accuracy in the table so that the given percentages sum to 100. [p 15 Table 2]
23. Please see our response to comment 22.
24. Preterm birth and small for gestational age were spelled out. [p16, line 264f]
25. The paragraph has been revised for clarity. [p17, lines 306ff]
26. Please see our response to comment 25.
27. Please see our response to comment 25.
28. Please see our response to comment 25.
29. Please see our response to comment 25.
30. Please see our response to comment 25.