Maternal factors associated with smoking during gestation and consequences in newborns: results of an 18-year study

Jose Miguel Sequí-Canet, Jose Miguel Sequí-Sabater, Ana Marco-Sabater, Francisca Corpas-Burgos, Jose Ignacio Collar del Castillo, Nelson Orta-Sibú

Corresponding author
Jose Miguel Sequí-Canet
Department of Paediatrics, University Hospital "Francisco de Borja", Av. de la Medicina 646702-Gandia, Spain.

Handling editor:
Michal Heger
Department of Pharmaceutics, Utrecht University, the Netherlands
Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

Review timeline:

Received: 10 May, 2021
Editorial decision: 28 July, 2021
Revision received: 3 August, 2021
Editorial decision: 31 August, 2021
Revision received: 16 October, 2021
Editorial decision: 26 November, 2021
Published online: 3 January, 2022

1st Editorial decision
28-Jul-2021

Ref.: Ms. No. JCTRes-D-21-00067
Maternal factors associated with smoking during gestation: results of an 18 year study.
Journal of Clinical and Translational Research

Dear Dr. SEQUI CANET,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Aug 27, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Authors have admirably conducted a research in tobacco use and breastfeeding. However, there are a lot of scope for improvement and is advised to thoroughly revise the manuscript prior to consideration. I have suggested few importation points below despite a gross revision on self is advised.
Abstract:
Advised to be revised as per comments below in each section.
Introduction:
The introduction is very brief and lacks basic background information to the readers.
My advice would be to include following detail: importance of abstinence of smoking during gestation and perinatal period overall, impact of tobacco use with child health outcomes including congenital and risks of health outcomes to child in future (need to conduct an extensive literature review), factors related to tobacco use which has major impact, global contextuality of the topic, risks associated to mothers, income and social standing as factor etc.
The research aims need to be mentioned clearly as per the research conducted. As authors mentioned "evolution of smoking", the study is an audit rather than cohort so please clearly structure your aim as per the research.
Rationale for research, what novel information does this research generate for global research community? A lot of study has previously conducted in relation to tobacco use, how is the given study novel?
Again, the literature review is very superficial, as only 17 literature in total has been cited and some of those are not recent. So would strongly advice to conduct a thorough literature review and provide evidence based concise background for readers.

Method:
Method are mixed up and advised to structure it with subheadings. Details on inclusion and exclusion criteria is advised.
The regression model should be mentioned in a bit detail, how was analysis conducted, how was the variable selected from one model to other? How was it excluded?
Usually alcohol consumption is associated with smoking, may possess confounding effect, why was the variable not included in the model?
Were the biases based on confounding, exposure measurement, selection of participants, measurement of outcomes, missing data etc. how was it taken into consideration. Infant birth weight might be another important factor.
As authors mentioned on limitation of the study that the selected mothers were only who had a healthy outcomes (healthy new born), and often tobacco use has acute outcomes that, I wonder the prevalence itself would be lower on your group of population? Selection bias?

How was that taken into consideration? The factors identified may potentially not reflect the scenario.
Wholly, the method doesn't provide detail overview to the readers.

Results:
As per earlier advise, trend and prevalence of smoking in gestation in timepoint would be a better terminology rather in evolution itself.
Usually alcohol consumption is associate with smoking, may possess confounding effect, why was the variable not included in the model?

Discussion
Authors should discuss why there was fluctuation on prevalence as it was high in 2002 and down in 2004 again high in 2008 and sown in 2012 and higher in 2018. Is it a random chance or has some explanation?
Again, the literature review is very superficial, as only 17 literature in total has been cited and some of those are not recent. So would strongly advice to conduct a thorough literature review and correlate and discuss the findings based on literature review.
Advised for a gross revision.

Limitation:
How is generalisable across the country of data collection or globally?

Authors' response

Jctres 521: Reviewers comments

Reviewer #1: Authors have admirably conducted a research in tobacco use and breastfeeding. However, there are a lot of scope for improvement and is advised to thoroughly revise the manuscript prior to consideration. I have suggested few importation points below despite a gross revision on self is advised.
THANK YOU VERY MUCH FOR YOUR INTEREST AND REALLY GOOD RECOMMENDATIONS. A VERY GOOD REVIEW.
I WILL ANSWER EACH POINT IN CAPTIAL LETTER IN ORDER YOU TO SEE MY COMMENTS.

Abstract:
Advised to be revised as per comments below in each section.
Introduction:
The introduction is very brief and lacks basic background information to the readers.
My advice would be to include following detail: importance of abstinence of smoking during gestation and perinatal period overall, impact of tobacco use with child health outcomes including congenital and risks of health outcomes to child in future (need to conduct an extensive literature review), factors related to tobacco use which has major impact, global contextuality of the topic, risks associated to mothers, income and social standing as factor etc.
IT IS ALL MENTIONED BUT IN A BRIEF MODE IN ORDER NOT TO EXTEND TOO MUCH THE TEXT. I PREFER TO INTRODUCE BRIEFLY AND TO DISCUSS LATER WITH MORE TEXT.

The research aims need to be mentioned clearly as per the research
conducted. As authors mentioned "evolution of smoking", the study is an
audit rather than cohort so please clearly structure your aim as per the research.
CORRECTED

Rationale for research, what novel information does this research generate for global research
community? A lot of study has previously conducted in relation to tobacco use, how is the
given study novel?
I HAVE ADDED SOME NEW ITEMS IN NEONATES NOT USUALLY DESCRIBED, I
HOPE THIS WILL ADD SOME INTEREST.

Again, the literature review is very superficial, as only 17 literature in total has been cited and
some of those are not recent. So would strongly advice to conduct a thorough literature review
and provide evidence based concise background for readers.
NOW THERE ARE 33 STUDIES ANS SOME IN THIS YEAR, I HOPE THIS WILL
AMELIORATE THE QUESTION

Method:
Method are mixed up and advised to structure it with subheadings. Details on inclusion and
exclusion criteria is advised.
DONE

The regression model should be mentioned in a bit detail, how was analysis conducted, how
was the variable selected from one model to other? How was it excluded?
 I THINK IT IS ALREADY DONE IN TEXT

Usually alcohol consumption is associated with smoking, may possess confounding effect,
why was the variable not included in the model?
NO RECORDED IN A WAY TO BE ANALYSED

Were the biases based on confounding, exposure measurement, selection of participants,
measurement of outcomes, missing data etc. how was it taken into consideration. Infant birth
weight might be another important factor.
I THINK NEONATAL FACTORS SOLVE THIS QUESTION

As authors mentioned on limitation of the study that the selected mothers were only who had
a healthy outcomes (healthy new born), and often tobacco use has acute outcomes that, I
wonder the prevalence itself would be lower on your group of population? Selection bias?
How was that taken into consideration? The factors identified may potentially not reflect the
scenario.
Wholly, the method doesn't provide detail overview to the readers.
DATA WERE REGISTERED FROM MATERNITY WARD, SO FROM HEALTHY
NEWBORNS. THIS IS A HANDICAP DISCUSSED IN LIMITATIONS PARAGRAPH. IN
SPITE OF THIS I THINK THE STUDY HAS A REAL VALUE BECAUSE IT REFLECTS
AVERAGE POPULATION WITHOUT OTHER CONFOUNDING FACTORS.

Results:
As per earlier advise, trend and prevalence of smoking in gestation in timepoint would be a
better terminology rather in evolution itself. CORRECTED

Usually alcohol consumption is associate with smoking, may possess confounding effect, why was the variable not included in the model? NOT RECORDED

Discussion
Authors should discuss why there was fluctuation on prevalence as it was high in 2002 and down in 2004 again high in 2008 and sown in 2012 and higher in 2018. Is it a random chance or has some explanation?
THERE WERE LIMITED INFORMATION CAMPAIGNS THAT THEN STOPPED

Again, the literature review is very superficial, as only 17 literature in total has been cited and some of those are not recent. So would strongly advice to conduct a thorough literature review and correlate and discuss the findings based on literature review.
NOW YOU HAVE MORE BIBLIOGRAPHY

Advised for a gross revision.

Limitation:
How is generalisable across the country of data collection or globally? I PUT A SENTENCE SAYING THAT I THINK IT IS USEFUL FOR SIMILAR COUNTRIES BAUT NOT FOR ALL WORLD

THANK YOU VERY MUCH AGAIN FOR YOU EXCELENT REVIEW, NOW I THINK THE PAPER IS BETTER AND I HOPE THIS MUST MEET YOUR EXPECTATIONS.

Best regards.

PD. I send the text in a clean review for editorial manager but also in track changes to M. Heger for your convenience.

2nd Editorial decision
31-Aug-2021

Ref.: Ms. No. JCTRes-D-21-00067R1
Maternal factors associated with smoking during gestation and its consequences in newborns: results of an 18 year study.
Journal of Clinical and Translational Research

Dear Dr. SEQUI CANET,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

Although the editorial board acknowledges that some effort has been made to improve the manuscript, we have to side with the reviewer in the assessment that the change implementation is grossly insufficient to warrant publication of the revised draft. Accordingly, the reviewer recommended a rejection. However, we would like to extend one more chance to

you to CONSIDERABLY improve your paper along the lines of the new set
of recommendations (below). Please note that the board will look critically at
the depth of revisions implemented.

If you decide to revise the work, please submit a list of changes or a rebuttal against each
point which is being raised when you submit the revised manuscript. Also, please ensure that
the track changes function is switched on when implementing the revisions. This enables the
reviewers to rapidly verify all changes made.

Your revision is due by Sep 30, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author.
You will see a menu item call Submission Needing Revision. You will find your submission
record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: I would like to thank the authors for resubmitting the revised version. Most of
the comments are not resolved despite being clearly pointed out. The rebuttals are also
unjustifiable. Some examples are listed below.

The authors mentioned the preference of a brief introduction. Acknowledging that, I would
recommend in-depth literature review to be reflected in the introduction. The introduction still
sounds very superficial to the topic, and the readers would not able to get acclimatised to the
study with the introduction provided. Please be mindful Journal of Clinical and Translational
Research is not a women health specific journal, so a reflection of in-depth literature review is
expected, not just by the reviewer but also by the readers. Additionally, smoking in pregnancy
is a well established research area without limitation to available literatures.

As your study is titled "Maternal factors associated with smoking during gestation and
consequences in newborns", including neonatal factors in consideration comes under the
"consequences" part as suggested by the title itself. A lot of studies do include neonatal
factors, for example, https://doi.org/10.1093/ntr/ntr117. How is the study novel? Has the
knowledge gap been identified? How would this study fill the existing knowledge gap?

The response provided by the authors doesn't resolve this query "The regression model should
be mentioned in detail, how was analysis conducted, how was the variable selected from one
model to other? How was it excluded?". Please suggest the line number, a lot of people with
statistical background would find the statistical analysis unreliable with the amount of
information provided in the manuscript.

In response to query "Were the biases based on confounding, exposure measurement,
selection of participants, measurement of outcomes, missing data etc. How was it taken into

consideration. Infant birth weight might be another important factor".
Authors replied "I THINK NEONATAL FACTORS SOLVE THIS
QUESTION". How?

To query "Again, the literature review is very superficial, as only 17 literature in total has
been cited and some of those are not recent. So would strongly advice to conduct a thorough
literature review and correlate and discuss the findings based on literature review." authors
replied "NOW YOU HAVE MORE BIBLIOGRAPHY". It is not clear what the authors
meant by the statement.

Authors' response
Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

*We are very grateful for the reviewer's comments because they can ameliorate the paper and
we recognize the time and effort that this implies.*

Reviewers' comments:

Reviewer #1: I would like to thank the authors for resubmitting the revised version. Most of
the comments are not resolved despite being clearly pointed out. The rebuttals are also
unjustifiable. Some examples are listed below.

The authors mentioned the preference of a brief introduction. Acknowledging that, I would
recommend in-depth literature review to be reflected in the introduction. The introduction still
sounds very superficial to the topic, and the readers would not able to get acclimatised to the
study with the introduction provided. Please be mindful Journal of Clinical and Translational
Research is not a women health specific journal, so a reflection of in-depth literature review is
expected, not just by the reviewer but also by the readers. Additionally, smoking in pregnancy
is a well established research area without limitation to available literatures.

*We are aware of the long paper that it results and that is why we make a brief introduction
but perhaps you are right and there are many more aspects of the question to be mentioned.
We have done now a better review that we hope fits the requirements. We also focus in long
term consequences as you can read.*

As your study is titled "Maternal factors associated with smoking during gestation and
consequences in newborns", including neonatal factors in consideration comes under the
"consequences" part as suggested by the title itself. A lot of studies do include neonatal
factors, for example, https://doi.org/10.1093/ntr/ntr117. How is the study novel? Has the
knowledge gap been identified? How would this study fill the existing knowledge gap?

*This study points at some factors already known (like birth weight) but have some other new
(such as hearing screening results, apgar at minute 1) and some discordant ones (such as
differences in gestational age not significant up from 34 weeks) to be considered. As each*

population is different we think very important to know what is the status quo of our pregnant mothers. In our country is one of the greatest studies done and their conclusion can serve to compare with other countries or regions.

The response provided by the authors doesn't resolve this query "The regression model should be mentioned in detail, how was analysis conducted, how was the variable selected from one model to other? How was it excluded?". Please suggest the line number, a lot of people with statistical background would find the statistical analysis unreliable with the amount of information provided in the manuscript.

Regression analysis is detailed in the Materials and methods section (please see pages of the manuscript). As indicated, we performed a multiple logistic regression analysis to assess maternal factors that may be related to smoking during pregnancy. The maternal factors considered as possible explanatory variables of the smoking habit were the mother's age, origin, level of education, performance of paid work, parity and occurrence of previous abortions. The model was constructed following a backward stepwise variable selection procedure based on p-value criterion and considering a significance level of 0.05. This procedure begins fitting a model that contains all explanatory variables under consideration and then stars removing the least significant variables (with the highest p-value in the model), one after the other, until the stopping rule is reached (all remaining variables in the model have a p-value smaller than 0.05). Furthermore, the forward and bidirectional procedure, and other criterio to add or subtract each variable in the model, such as Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), were also considered. All procedures and criteria led to the same model. As a consequence of the large data set analyzed, we obtain robust results and accurate estimates (small standard errors).

We have added some additional details about the regression analysis performed (please see Material and methods section of the manuscript). The variable selection procedure in the model is detailed on lines 110-115 of the manuscript.

In response to query "Were the biases based on confounding, exposure measurement, selection of participants, measurement of outcomes, missing data etc. How was it taken into consideration. Infant birth weight might be another important factor". Authors replied "I THINK NEONATAL FACTORS SOLVE THIS QUESTION". How?

We consider as explanatory variables in the regression model all maternal factors that could be related to smoking during pregnancy (according to other studies, our knowledge and common sense) and for which we have information, trying to minimize effects of confusion.

Missing values withing each variable are specified in Table 2. Participants with missing data in any of the variables of the final regression model (6% of the total) were excluded from the analysis. We only consider participants with information on all the variables of the regression model since we have a sufficient sample size to examine the relationships of interest. Additionally, associations between the loss of data in the response variable (smoking during pregnancy) and the explanatory variables were studied. We did not find any relationship between missingness of data in smoking and the maternal factors considered.

In relation to the baby weight at birth, we did not consider this variable in the regression model since we studied possible factors that influence smoking during pregnancy. Smoking could influence the weight of the baby, but not the other way around. In a separate analysis (Table 3), we studied the association between smoking during pregnancy and the newborns weight. We found a significant association between mothers who smoke and low newborns weight (OR: 2.177 [1.854 – 2.551]).

To query "Again, the literature review is very superficial, as only 17 literature in total has been cited and some of those are not recent. So would strongly advice to conduct a thorough literature review and correlate and discuss the findings based on literature review." authors replied "NOW YOU HAVE MORE BIBLIOGRAPHY". It is not clear what the authors meant by the statement.

Sorry for the inconvenience but the former "NOW YOU HAVE MORE BIBLIOGRAPHY" was referred to the increase in references from 17 to 33 with some very recent but in this new paper we have again increase them in order to accomplish the query and to include the amount of new references to written paragraphs.

Thank you very much. We acknowledge your efforts and hope this new submission will be ok.

3rd Editorial decision
26-Nov-2021

Ref.: Ms. No. JCTRes-D-21-00067R2

Maternal factors associated with smoking during gestation and its consequences in newborns: results of an 18 year study.

Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger

Editor-in-Chief

Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #1: Dear Authors,

Most of the advised co.mments are well revised, the manuscripts is scientifically sound compared to the initial submission. I would like to acknowledge the authors for their effort in revising the manuscript. I would recommend the paper to accepted in the current forms