PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Analysis of non-respondent pregnant women who were registered in the Japan Environment and Children's Study: a longitudinal cohort study
AUTHORS	Kigawa, Mika; Tsuchida, Akiko; Miura, Kayoko; Ito, Mika; Tanaka, Tomomi; Hamazaki, Kei; Adachi, Yuichi; Saito, Shigeru; Origasa, Hideki; Inadera, Hidekuni

VERSION 1 - REVIEW

REVIEWER	jim thornton University of Nottingham
REVIEW RETURNED	20-Aug-2018

GENERAL COMMENTS	This is a nice paper. It is particularly interesting since it reports factors relating to non response in a setting with very high response rates. Overall 97.7% (9432/9649) Issues. Can the authors consider separate out the two groups of non respondents, those in 2nd and 3rd trimesters separately. The reference list is duplicated. The statistics look OK but I'm not strictly qualified to judge this. Jim Thornton

REVIEWER	Anna Rosofsky Health Effects Institute, United States
REVIEW RETURNED	14-Sep-2018

GENERAL COMMENTS	Summary This manuscript assesses differences in demographic, lifestyle, environmental and health characteristics between responders and non-responders in the Japan Environment and Children's Study. The results demonstrate elevated odds of being a non-respondent for those with secondary smoke exposure, and decreased odds of being a non-respondent for those who live with a mother-in-law, whose partners responded to questionnaires, and who had allergic rhinitis, body pain or drank alcohol. The study design and statistical analysis to answer the investigator's research question is simple and straightforward. However, there are several aspects of the manuscript that are unclear and that the investigators should address. Major Comments

The investigators state that the presence and extent of bias (p. 5, line 44) from systematic differences in the characteristics of respondents and non-respondents needs to be investigated, and that authors of previous studies have suggested that "non-response increases the proportion of infants with adverse outcomes in the remaining study population" (p. 6, line 36), suggesting that the authors of this study will address those two research gaps. Instead, the investigators examine differences in baseline characteristics between respondents and non-respondent, rather than examining bias in their estimates or examining differences in proportions of infants with adverse outcomes by baseline characteristics. The investigators should either formulate their study to address these research gaps, or re-define their study objectives.

Minor Comments

Background

Pg 5, line 31: Unclear whether the authors mean that the response rates have decreased over time in different epidemiology studies or that response rates have decreased over multiple sampling periods within the same study.

Pg. 5, line 41: What do the investigators mean by "detract from the outcomes of interest"?

Pg. 6, line 39: Please include a citation for "some authors have suggested that non-response increases…"

Methods

Pages 8-10. Because the focus of this manuscript is to assess differences in baseline characteristics between two study groups, the study investigators should clearly define all variables included in the assessment. The following variables require expanded definitions: health status (on pg. 8, line 38 it is unclear whether the variable was defined as "positive" using information from multiple visit to the obstetrician or from the fact that the participant had multiple visits to the obstetrician), health related behaviour, environmental exposure, and contact status with obstetrician. Please clearly define "non-respondents," the dependent variable, at the beginning of the Methods section.

Statistical analyses:

This section is somewhat difficult to follow. The statistical methods that the investigators use to assess their research question should precede description of the variables considered in the analysis, otherwise, the reader may not know to which "analysis" the investigators are referring (pg. 10).

It seems that the authors first assessed differences in proportions between the two groups, then performed bivariate logistic regression models (to determine multivariable model inclusion), then multivariable logistic regression models. The authors should describe their model building in more detail, clearly stating these steps upfront.

How did the authors deal with missing observations?

Results

Pg 11, line 16: This seems like a very high response rate. How does this response rate compare to previous studies?

Pg 12, line 13: change "actively" to "actively"

Pg. 12, line 31. What do the authors mean by "did not match"?

Tables 2 and 3: Please include the analytical sample size included in the multivariable models.

Discussion

Pg. 12, line 52: I would argue that the authors did not evaluate non-response bias, but instead, evaluated differences in baseline characteristics between respondents and non-respondents, which

	in turn, might bias their results. A formal bias assessment was not performed.
	What is the investigators interpretation of the "secondary smoke" result, and its inconsistency with alcohol consumption and health-related variables?
	Please include an expanded discussion of generalizability of study results and how the investigators can apply these results in the design of future epidemiology studies.

REVIEWER	Dr Maria K Wolters
	School of Informatics, University of Edinburgh, United Kingdom
REVIEW RETURNED	24-Nov-2018

GENERAL COMMENTS	This paper is a much needed and highly interesting complement to an extremely valuable epidemiological data set.
	Below, I will detail my concerns regarding the discussion of study limitations, and the overall interpretation of the findings. I hope that the authors will find these of value.
	1. Limitations of the study
	First of all, you state on p. 5 that „in recent years, the response rates have decreased in several epidemiological studies, which may lead to selection bias." Selection bias has always been present in epidemiological studies, which is why papers such as yours are important, and should be published for each major epidemiological survey. Therefore, I would rephrase this sentence.
	In this context, you should also highlight that you studied people who had already consented to taking part in a study, and were then lost to follow up. This is very different from a population that does not respond to initial questionnaires, initial contact, or declines to be recruited into a trial. Therefore, it would be good to get more information about the representativeness of the sample that was recruited into the main study with respect to the general population of Japanese mothers
	2. Discussion and Conclusions
	The indicators of non-response may have been affected by common latent variables related to personality or socioeconomic status. In the UK, I would expect people from higher socioeconomic strata to be more healthy (in less pain, less likely to have a family member who smokes), and more likely to be in a relationship. I would like to see you discuss these possible explanations in a Japanese context, just as you discuss the reasons for the „mother-in-law" effect, which I find very illuminating.
	On the subject of the „mother-in-law" effect, I wonder whether this might also reflect a latent variable of „conscientiousness", part of the OCEAN model of personality. If a woman is conscientious enough to have her mother in law live with her and her partner, even though it is potentially stressful, she might also be conscientious enough to return a questionnaire.
	I conclude with some minor editorial suggestions:
	* Specify the number of mothers in the abstract

	* On p. 8, you need a formal reference for the SF-8 questionnaire * What exactly is a positive health status in pregnancy? Does it mean that the woman is healthy? * You state on page 16 that you were unable to "confirm participant's medical or obstetric history" - does that mean that you have no medical records linkage?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Jim Thornton

Institution and Country: University of Nottingham

Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below

This is a nice paper. It is particularly interesting since it reports factors relating to non-response in a setting with very high response rates. Overall 97.7% (9432/9649) Issues. Can the authors consider separate out the two groups of non-respondents, those in 2nd and 3rd trimesters separately.

Thank you for your comments.

The reasons for response rate being extremely high are: a) the sample included people who agreed to participate in JECS, and b) data were collected through face-to-face surveys. In the MT2 questionnaire survey, which was the focus of this study, JECS coordinators distributed questionnaires directly to the participants at the JECS collaborative obstetric hospital when they visited during the 2nd or 3rd trimesters as the second baseline survey, and later, at the hospital, the JECS coordinators collected it. In Japan, when pregnancy is detected, pregnant women would visit obstetric hospitals because they can undergo medical check-up and consult several times during pregnancy free of charge. Therefore, JECS researchers could meet JECS participants (pregnant women) at an obstetric hospital that recruited them, and could also collect questionnaires.

The administration of the MT2 questionnaire survey was planned for when a JECS participant visited the collaborative obstetric hospital in either the 2nd or 3rd trimester; data were not available regarding the trimester at the time of collection, so unfortunately, we could not divide the data into two groups according to trimester.

The reference list is duplicated.

Thank you for pointing this out.

In the revised document, there is only one reference list.

The statistics look OK but I'm not strictly qualified to judge this.

Jim Thornton

Reviewer: 2

Reviewer Name: Anna Rosofsky

Institution and Country: Health Effects Institute, United States

Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below

Please see attached file

Summary

This manuscript assesses differences in demographic, lifestyle, environmental and health characteristics between responders and non-responders in the Japan Environment and Children's Study. The results demonstrate elevated odds of being a non-respondent for those with secondary smoke exposure, and decreased odds of being a non-respondent for those who live with a mother-in-law, whose partners responded to questionnaires, and who had allergic rhinitis, body pain or drank alcohol. The study design and statistical analysis to answer the investigator's research question is simple and straightforward.

However, there are several aspects of the manuscript that are unclear and that the investigators should address.

Major Comments

The investigators state that the presence and extent of bias (p. 5, line 44) from systematic differences in the characteristics of respondents and non-respondents needs to be investigated, and that authors of previous studies have suggested that "non-response increases the proportion of infants with adverse outcomes in the remaining study population" (p. 6, line 36), suggesting that the authors of this study will address those two research gaps. Instead, the investigators examine differences in baseline characteristics between respondents and non-respondent, rather than examining bias in their estimates or examining differences in proportions of infants with adverse outcomes by baseline characteristics. The investigators should either formulate their study to address these research gaps, or re-define their study objectives.

Thank you for your comments and suggestion.

In the questionnaire survey, we collected data based on the research hypothesis. Therefore, if the baseline data of the group that responded differs from that of the non-responded group, it indicates a bias. As a previous study reported that there are differences in the characteristics of the response and non-response groups, it is important to find ways to reduce the number of non-responses. Thus, in this study, factors related to response/non-response were investigated.

Minor Comments

Background

Pg 5, line 31: Unclear whether the authors mean that the response rates have decreased over time in different epidemiology studies or that response rates have decreased over multiple sampling periods within the same study.

Thank you for your comment. I added the word as follows;

"In recent years, the response rates have decreased in several epidemiological studies over time, which may lead to selection biases."

Pg. 5, line 41: What do the investigators mean by "detract from the outcomes of interest"?

It may affect the outcomes due to biases.

Pg. 6, line 39: Please include a citation for "some authors have suggested that non-response increases…"

Please see the citation No.13.

Methods

Pages 8-10. Because the focus of this manuscript is to assess differences in baseline characteristics between two study groups, the study investigators should clearly define all variables included in the assessment. The following variables require expanded definitions: health status (on pg. 8, line 38 it is unclear whether the variable was defined as "positive" using information from multiple visit to the obstetrician or from the fact that the participant had multiple visits to the obstetrician), health related behaviour, environmental exposure, and contact status with obstetrician.

In Japan, there is a free service that allows you to consult an obstetrician at least three times during pregnancy, and the data of health condition of pregnant women at that time are maintained by the obstetricians. In the JECS study, we posted: "Health status data during pregnancy" to transcription sheet and confirmed from this sheet that obstetrician has been consulted these times.

For data on health-related behaviors and environmental exposures, the procedures are described in the method, so please check.

Please clearly define "non-respondents," the dependent variable, at the beginning of the Methods section.

Thank you for your comment. I added the sentence as follows.

"In this study, we defined "non-respondents" as JECS participants who did not return the questionnaire of 2nd/3rd trimesters MT2)."

Statistical analyses:

This section is somewhat difficult to follow. The statistical methods that the investigators use to assess their research question should precede description of the variables considered in the analysis, otherwise, the reader may not know to which "analysis" the investigators are referring (pg. 10).

It seems that the authors first assessed differences in proportions between the two groups, then performed bivariate logistic regression models (to determine multivariable model inclusion), then multivariable logistic regression models. The authors should describe their model building in more detail, clearly stating these steps upfront.

Thank you for your suggestion. We have increased the information in the "Statistical analysis" section to provide more details.

How did the authors deal with missing observations?

In the logistic regression analysis, data with missing observations were deleted on a case-by-case basis. I have included the numbers used for analysis in Table 2 and Table 3.

Results

Pg 11, line 16: This seems like a very high response rate. How does this response rate compare to previous studies?

In the paper, I did not compare the response rate in this study with those in previous studies. The comment is correct; the response rate is much higher than other questionnaire surveys in Japan. There are several reasons for this: a) the sample included people who agreed to participate in JECS, and b) data were collected through face-to-face surveys. In the MT2 questionnaire survey, which was the focus of this study, JECS coordinators distributed questionnaires directly to the participants at the JECS collaborative obstetric hospital when they visited during the 2nd or 3rd trimesters as the second baseline survey, and later, at the hospital, the JECS coordinators collected it. In Japan, when pregnancy is detected, pregnant women regularly visit obstetric hospitals because they can undergo medical check-ups and consultations several times during pregnancy free of charge. Therefore, JECS researchers were able to meet JECS participants (pregnant women) at the obstetric hospital that recruited them, and they could also collect the questionnaires, so the response rate was high.

Pg 12, line 13: change "actively" to "actively"

Thank you for your comment. I corrected it.

Pg. 12, line 31. What do the authors mean by "did not match"?

It means that these variables did not show significance in the multiple logistic regression. We deleted those variables and proceeded with the analysis.

Tables 2 and 3: Please include the analytical sample size included in the multivariable models.

I wrote the numbers that we used for analysis. Please find them in Table 2 and 3.

Discussion

Pg. 12, line 52: I would argue that the authors did not evaluate non-response bias, but instead, evaluated differences in baseline characteristics between respondents and non-respondents, which in turn, might bias their results. A formal bias assessment was not performed.

What is the investigators interpretation of the "secondary smoke" result, and its inconsistency with alcohol consumption and health-related variables?

Thank you for your comment. In this paper, I examined how the characteristics of non-respondents differ from those of respondents as variables that may be connected to non-response bias.

These data were based on responses by all of the participants (pregnant women) to self-administered questionnaires. Therefore, such inconsistencies may be subjective. Additionally, the inconsistencies could be related to information bias or participants' socioeconomic and education status. This is not clear, however, because we do not have data on these variables.

Regarding secondary smoke, I added the following "limitation of this study":

"In particular, it seems that the investigators' interpretation of 'secondary smoke' was inconsistent with their results regarding alcohol consumption or health-related variables. These variables were related to socioeconomic and education status." (p. 16, line 9)

Please include an expanded discussion of generalizability of study results and how the investigators can apply these results in the design of future epidemiology studies.

Thank you for your comment. I added the sentence as follows.

"Because the data collected from pregnant women participating in JECS were used in this study, it means the participants may have been influenced by the Japanese culture and/or their socioeconomic situation. It is necessary to consider the results obtained from other participants from different cultures or nationalities." (p. 17, line 9)

Reviewer: 3

Reviewer Name: Dr Maria K Wolters

Institution and Country: School of Informatics, University of Edinburgh, United Kingdom

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This paper is a much needed and highly interesting complement to an extremely valuable epidemiological data set.

Below, I will detail my concerns regarding the discussion of study limitations, and the overall interpretation of the findings. I hope that the authors will find these of value.

1. Limitations of the study

First of all, you state on p. 5 that „in recent years, the response rates have decreased in several epidemiological studies, which may lead to selection bias." Selection bias has always been present in epidemiological studies, which is why papers such as yours are important, and should be published for each major epidemiological survey. Therefore, I would rephrase this sentence.

In this context, you should also highlight that you studied people who had already consented to taking part in a study, and were then lost to follow up. This is very different from a population that does not respond to initial questionnaires, initial contact, or declines to be recruited into a trial. Therefore, it would be good to get more information about the representativeness of the sample that was recruited into the main study with respect to the general population of Japanese mothers

Thank you for your comment. The participants of JECS was plan more than 50% of pregnant women at recruit. Please check reference No.1. Now, the proportion of agreement to participate to JECS is 79%. These participants were recruited from 15 areas in Japan. The proportions of their age were similar to general Japanese population. Hence, I believe pregnant women participating in the JECS women were representative of the Japanese population. Please check reference No.2.

2. Discussion and Conclusions

The indicators of non-response may have been affected by common latent variables related to personality or socioeconomic status. In the UK, I would expect people from higher socioeconomic strata to be more healthy (in less pain, less likely to have a family member who smokes), and more

likely to be in a relationship. I would like to see you discuss these possible explanations in a Japanese context, just as you discuss the reasons for the „mother-in-law" effect, which I find very illuminating.

In several previous studies, it was clear that the non-response rate was related to socioeconomic status. In the JECS study, however, the socioeconomic and education status data were collected with the MT2 questionnaire, which was used to examine the non-response factor. Thus, I could not examine these factors. I wrote about this in the "Limitations of this study" section.

On the subject of the „mother-in-law" effect, I wonder whether this might also reflect a latent variable of „conscientiousness", part of the OCEAN model of personality. If a woman is conscientious enough to have her mother in law live with her and her partner, even though it is potentially stressful, she might also be conscientious enough to return a questionnaire.

Thank you for your comment. I also thought it was interesting.

I conclude with some minor editorial suggestions:

* Specify the number of mothers in the abstract

I added this to the paper.

* On p. 8, you need a formal reference for the SF-8 questionnaire

I added this to the paper.

* What exactly is a positive health status in pregnancy? Does it mean that the woman is healthy?

On the transcription sheet, the participants' height, weight, blood pressure, and value of 50 g GCT were measured when participants visited the obstetric hospital during pregnancy. Some participants had symptoms or signs of being unhealthy based on this information; however, I did not have access to the specifics.

* You state on page 16 that you were unable to "confirm participant's medical or obstetric history" - does that mean that you have no medical records linkage?

In this study, I collected data about medical or obstetric history directly from the participants, and could not link this information to medical records.

VERSION 2 – REVIEW

REVIEWER	Anna Rosofsky Health Effects Institute United States
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	The investigators investigate differences in demographic and lifestyle factors between respondents and non-respondents to understanding the potential for selection bias in the Japan Environment Children's Study pregnancy cohort. They use a simple study design and analytical methods to address their research questions, and find, interestingly, that non-response is associated with presence of a mother-in-law in the participant's household, and that higher odds of participation was associated with allergic rhinitis, body pain, and alcohol use. My major comment is that lack of economic and socioeconomic factors in the analysis is a huge limitation, and presents some remaining knowledge gaps and incomplete answering of the investigators' research question. On pg. 18, line 9, the investigators state that inclusion of these factors is beyond the scope of the study, but it is unclear why. The investigation would benefit from inclusion of these factors. Additionally, it is unclear whether the results are generalizable outside of the cohort of focus. Minor comments: -Pg. 10, lines 12-13: It is unclear what a health status of "positive" represents. Is this a binary variable? Is positive a synonym for "good" in this case? -Pg. 12, lines 5-11: Please provide more details on each variable, sufficient for replications (e.g., whether the variable was modeled as continuous or categorical) -Pg. 17, line 12: Start a new paragraph before "further" -Pg. 18, line 9: Why are socioeconomic status and educational data beyond the scope of the study objectives?

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Reviewer Name: Anna Rosofsky

Institution and Country: Health Effects Institute

United States

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The investigators investigate differences in demographic and lifestyle factors between respondents and non-respondents to understanding the potential for selection bias in the Japan Environment Children's Study pregnancy cohort. They use a simple study design and analytical methods to address their research questions, and find, interestingly, that non-response is associated with presence of a mother-in-law in the participant's household, and that higher odds of participation was associated with allergic rhinitis, body pain, and alcohol use.

My major comment is that lack of economic and socioeconomic factors in the analysis is a huge limitation, and presents some remaining knowledge gaps and incomplete answering of the investigators' research question. On pg. 18, line 9, the investigators state that inclusion of these factors is beyond the scope of the study, but it is unclear why. The investigation would benefit from inclusion of these factors. Additionally, it is unclear whether the results are generalizable outside of the cohort of focus.

Thank you for your comment.

In several previous studies, it was clear that the non-response rate was related to socioeconomic status. In the JECS study, however, the socioeconomic and education status data were collected with the MT2 questionnaire, which was used to examine the non-response factor. Thus, I could not examine these factors. I wrote about this in the "Limitations of this study" section.

I changed the sentences as follows;

"In the JECS study, however, the socioeconomic and education status data were collected with the MT2 questionnaire, which was used to examine the non-response factor. Thus, I could not examine these factors." (p. 17, L 9-12)

Minor comments:

-Pg. 10, lines 12-13: It is unclear what a health status of "positive" represents. Is this a binary variable? Is positive a synonym for "good" in this case?

Thank you for your comment.

I made a mistake in the writing. I changed the sentence as follows:

"Participants' obstetric visiting status was a binary variable and was defined as present for a participant when the transcription sheet was returned if they had reported 'multiple obstetric visits to collaborating hospitals during pregnancy.'" (p. 9, L 12-14)

-Pg. 12, lines 5-11: Please provide more details on each variable, sufficient for replications (e.g., whether the variable was modeled as continuous or categorical)

Thank you for your comment.

I changed the sentence, as follows:

"Of these variables, a Student's t-test or Welch's t-test for independent groups was used for physical and mental health variables (SF-8, K6), or number of cohabiting family members (continuous variables), and a Pearson's chi-square test or Fisher's exact test was used for other variables (categorical variables)."

-Pg. 17, line 12: Start a new paragraph before "further"

Thank you for your comment.

Based on your suggestion, I added a new paragraph.

-Pg. 18, line 9: Why are socioeconomic status and educational data beyond the scope of the study objectives?

Thank you for your comment.

Please read the response above.