PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors of non-responsive or lost-to-follow-up Japanese mothers during the first year postpartum following the Japan Environment and Children's Study: A longitudinal cohort study
AUTHORS	Kigawa, Mika; Tsuchida, Akiko; Matsumura, Kenta; Takamori, Ayako; Ito, Mika; Tanaka, Tomomi; Hamazaki, Kei; Adachi, Yuichi; Saito, Shigeru; Origasa, Hideki; Inadera, Hidekuni; group, The Japan Environment

VERSION 1 – REVIEW

REVIEWER	Alison Teyhan University of Bristol, UK
REVIEW RETURNED	28-May-2019

GENERAL COMMENTS	This Japan-based study investigates factors associated with attrition in a birth cohort. Attrition is a problem that affects all longitudinal studies to a greater or lesser extent, and this study could make an important contribution to the literature. Strengths include the large sample size and range of maternal and child factors considered. However, I found the methods hard to follow in places and the manuscript would benefit from greater clarity/more detail in general. I have the following suggestions/comments, which I hope the authors will find helpful. Introduction - Paragraph 2 of the introduction contains details which would be better placed in the methods section (details on JECS), and Paragraph 3 of the introduction contains results – these should be removed. - The sentence 'There are cross-sectional studies….' needs referenced. - I would have liked more detail in the introduction on existing literature in this field, and what the gaps are (i.e. why this study is important). Methods Overall, I found the methods section a bit unclear and disjointed. Some examples below: - What timepoint does 'baseline' refer to? How many mother and partner questionnaires were there, and when administered? A timeline diagram of questionnaire time points would be helpful. - Some more details on JECS are needed e.g. How were the women recruited? At what point in their pregnancy? What was the eligibility criteria? What was the response rate? - The early mother questionnaires (2 during pregnancy and one a month later) could be delivered via either the hospital or by mail. Similarly, the partner questionnaire by either hospital, mail, or the

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	mother. What determined the mode of delivery? Did the authors consider mode of delivery of these early questionnaires as a factor related to later attrition? - Did the 93,417 have to complete the early questionnaires in order to be eligible for your study sample? - In Figure 1, do these numbers refer to the number of women? What about the number of partners? I'm unclear who the 5647 removed for 'second and subsequent responses' are? - By the term 'abortion', do you mean miscarriage? - In the 'study design' section, the definitions of the 'lost to follow-up' and 'non-response' variables is unclear. - The definitions of the variables should be presented when they are first introduced, not in a separate section. - The variable presented in Figure 2 (non-response, resumed, discontinued, continued) should be described along with the other dependent variable – not at the end of the definitions section. Results - For me, the 'non-response, resumed, discontinued, continued' variable is the more interesting outcome, and I think the results would be more meaningful if analyses focused on it rather than the individual 6 and 12 month outcomes. Certainly, the numbers in these 4 categories should be reported up-front as it is hard to interpret the results in Tables 1 and 2 without knowing who is in non-responders group in each case (from Figure 2, the majority of non-responders are the same at both 6 and 12 months, meaning the results at the two time points are unsurprisingly very similar.) Discussion - I didn't understand the link the authors' make between GP effects on participation and partner effects on participation - these seem very separate things to me? - There needs to be more discussion on what the results mean for the study in general (e.g. in terms of representativeness of the cohort, but also on ways in which they could help inform ways to minimise attrition/maximise participation in the future) and on what they mean for researchers using the data (e.g. potential for bias). - How do attrition rates in this study compare to other cohort studies in Japan/elsewhere? - The 'limitations' section contains details that I think should be reported in the methods. The short follow-up period is a limitation. You should also mention your study's strengths.

REVIEWER	Jocelyn Anne Silvester Boston Children's Hospital, Harvard Medical School, Boston, MA, United States
REVIEW RETURNED	10-Jun-2019

GENERAL COMMENTS	This study addresses an important problem in longitudinal research: loss-to-follow-up. The authors have an impressive retention rate in their study; nevertheless, it is important to understand factors affecting response and study participation in post-partum mothers, particularly for prospective cohort studies. The authors conclude that partner participation and maternal depression are important factors contributing to loss to follow-up. Unfortunately, the methods are unclear at times, specifically with respect to consenting and communication with partners and the design which included pre- and post-partum surveys, but only

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	considered loss-to-follow-up at 6 and 12 months (and is not clearly loss to follow-up post-partum as there is also a 1 month survey). As well, the measure of "depression" - the Kessler Psychological distress scale, is non-diagnostic and measures both anxiety and depression. - The “baseline” includes up to 2 surveys before delivery and 1 survey within 1 month of delivery. How were participants who did not complete all of these surveys handled? Were participants who only completed the initial pre-partum survey(s) considered lost at 6 months? Should they have been excluded as they were already lost prior to delivery? Can the authors explain why they chose to look at 6 and 12 months survey follow-up rather than comparing pre-partum and post-partum surveys (e.g., include the within 1 month of delivery survey as a follow-up point?) - Can the authors provide more information on how partners were consented and participated in the study in the methods? Was the partner consented in person? If partner did not attend visit, were they consented separately? Also, were any measures taken to confirm that partners received surveys delivered through the mother? [text on lines 297-301 of discussion does address these issues, but should be in methods] - Methods – last paragraph – sentence not clear – did you examine data from questionnaires distributed at 6 and 12 months of age? Are you actually looking at loss to follow-up after delivery in a cohort of women (and their partners) who were recruited during pregnancy? - Kessler psychological distress scale is appropriate for population surveys, but this is designed to measure both anxiety and depression and is non-diagnostic. This should be made clear in the methods and in the text and should not be implied to be diagnostic of depression.

REVIEWER	Per Magnus Norwegian Institute of Public Health, Oslo, Norway I am collaborating with other scientists in JECS in two consortia: one on childhood cancer and another regarding environmental toxicants. I have not published papers together with the authors of this manuscript
REVIEW RETURNED	12-Jun-2019

GENERAL COMMENTS	This paper gives important information about loss-to-follow up in a large, Japanese cohort. It will be of value for interpretation of later analytic studies. I have only two small concerns.: - the dependent variable described in lines 117-120 on page 5. The distinction between "lost-to-follow-up" and "non-response" is unclear to me. Also, the definition of the variable should be "yes" or "no" on an individual level, not a number of participants. - p-values are unnecessary. There is no prior hypothesis. The confidence limits give the precision.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Alison Teyhan

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Institution and Country: University of Bristol, UK
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
This Japan-based study investigates factors associated with attrition in a birth cohort. Attrition is a problem that affects all longitudinal studies to a greater or lesser extent, and this study could make an important contribution to the literature. Strengths include the large sample size and range of maternal and child factors considered.
However, I found the methods hard to follow in places and the manuscript would benefit from greater clarity/more detail in general. I have the following suggestions/comments, which I hope the authors will find helpful.

Introduction
- Paragraph 2 of the introduction contains details which would be better placed in the methods section (details on JECS), and Paragraph 3 of the introduction contains results – these should be removed.

Thank you for your comment. Based on your suggestion, I moved and/or added the sentences in Paragraph 2 to the methods section, as follows:
(In the introduction section) "JECS covered approximately 45% of the total number of live births within the study area in 2013; moreover, the characteristics of the participating mothers and their children were similar to those obtained from Japan's 2013 Vital Statistics Survey. [11] The follow-up period is currently in progress, and the data on the children's first year have been finalised. We now have data on the children's first year.
The authors of this study analysed lost-to-follow-up to the questionnaires and identified participants' medical history, multiple visits to hospitals collaborating with JECS, and partner participation as significant factors. We examined the factors related to the response rate to the two questionnaires administered to the participants by mail during the first year after delivery. In this study, we examined the factors related to the non-response and/or lost-to-follow-up to the two questionnaires administered to participants by mail during the first year after delivery using data from JECS."

(In the method section) "JECS collects data on health status, socioeconomic status, etc. using self-administered questionnaires. The baseline questionnaires were distributed and collected by JECS coordinators at collaborating obstetric hospitals or by mail, twice during pregnancy as well as one month after delivery. JECS also requested participants' partners to participate in the study via self-administered questionnaires. The partner questionnaires were distributed and collected by JECS investigators at collaborating hospitals, through the female participants, or by mail. Maternal medical information during pregnancy and at delivery, as well as medical information on the newborn children of the participants, were transcribed with patient consent by physicians, midwives/nurses, and/or research coordinators based on the medical records of collaborating hospitals.
Information on JECS participants' children's health and growth metrics was collected from questionnaires. We examined this study using for six-month-olds and one-year-olds. Both questionnaires were distributed and collected by mail.
Participants were recruited by JECS Research Co-ordinators at JECS collaborating obstetric hospitals when they came for a health check-up during their first trimester. There were two baseline questionnaires that were administered during pregnancy (first trimester and second or third trimester) and one month after delivery. These questionnaires were distributed by JECS Research Co-ordinators at the collaborating obstetric hospitals and were collected by them at the hospitals or by mail. JECS also requested participants' partners (i.e., fathers of the children) to participate in the study. For the participating partners, self-administered questionnaires were distributed to them once during the mothers' pregnancy. The partner questionnaires were distributed by JECS Research Co-ordinators at the collaborating hospitals, or through the participating mothers, and were collected by JECS Research Co-ordinators through the mothers or by mail. Maternal medical information during pregnancy and at delivery, as well as medical information on the new-born children of the participants,

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were transcribed by physicians, midwives/nurses, and/or JECS Research Co-ordinators from the medical records of the collaborating hospitals.
One month after delivery, the participating mothers and their children mostly did not use the obstetric hospital for health check-ups; thus, information on JECS participants' children's health and growth metrics was collected through questionnaires. In this study, we examined data on six-month-old and one-year-old children. Both questionnaires were distributed and collected by mail."

- The sentence 'There are cross-sectional studies….' needs referenced.

Thank you for your comments. I have added this information to the text.

- I would have liked more detail in the introduction on existing literature in this field, and what the gaps are (i.e. why this study is important).

Thank you for your comment. I added the following sentences:

On the other hand, a study using participants of longitudinal birth cohort study found an association between socioeconomic status and mother's age. [7-9] However, few studies have examined the factors related to partial follow-up participants. Therefore, it is necessary to examine the characteristics of participants who do not return questionnaires."

Methods
Overall, I found the methods section a bit unclear and disjointed. Some examples below:
- What timepoint does 'baseline' refer to? How many mother and partner questionnaires were there, and when administered? A timeline diagram of questionnaire time points would be helpful.

Thank you for your suggestion. I added sentences regarding the research design of the questionnaire in the JECS study design section, as follows:

"Participants were recruited by JECS Research Co-ordinators at JECS collaborating obstetric hospitals when they came for a health check-up during their first trimester. There were two baseline questionnaires that were administered during pregnancy (first trimester and second or third trimester) and one month after delivery. These questionnaires were distributed by JECS Research Co-ordinators at the collaborating obstetric hospitals and were collected by them at the hospitals or by mail. JECS also requested participants' partners (i.e., fathers of the children) to participate in the study. For the participating partners, self-administered questionnaires were distributed to them once during the mothers' pregnancy. The partner questionnaires were distributed by JECS Research Co-ordinators at the collaborating hospitals, or through the participating mothers, and were collected by JECS Research Co-ordinators through the mothers or by mail. Maternal medical information during pregnancy and at delivery, as well as medical information on the new-born children of the participants, were transcribed by physicians, midwives/nurses, and/or JECS Research Co-ordinators from the medical records of the collaborating hospitals.
One month after delivery, the participating mothers and their children mostly did not visit the obstetric hospital for health check-ups; thus, information on JECS participants' children's health and growth metrics was collected through questionnaires. In this study, we examined data on six-month-old and one-year-old children. Both questionnaires were distributed and collected by mail."

- Some more details on JECS are needed e.g. How were the women recruited? At what point in their pregnancy? What was the eligibility criteria? What was the response rate?

Thank you for asking these questions. I have added information to respond to these questions in the introduction and method sections. Please check the contents of the response to the previous comment.

- The early mother questionnaires (2 during pregnancy and one a month later) could be delivered via either the hospital or by mail. Similarly, the partner questionnaire by either hospital, mail, or the mother. What determined the mode of delivery? Did the authors consider mode of delivery of these early questionnaires as a factor related to later attrition?

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Thank you for asking these questions. I have added information to respond to these questions in the introduction and method sections. Please check the contents of my previous response.

- Did the 93,417 have to complete the early questionnaires in order to be eligible for your study sample?

Thank you for your question. Some people from the study sample did not respond to the baseline questionnaires. I added the numbers to Table 1 where there were incomplete or corrected data.

- In Figure 1, do these numbers refer to the number of women? What about the number of partners? I'm unclear who the 5647 removed for 'second and subsequent responses' are?

Thank you for asking these questions. Based on a suggestion from another reviewer, I changed the figure. Please check.
In the dataset, the numbers refer to total numbers. If a mother agreed to participate more than once within the recruitment period, she would be counted for each time she consented. For example, if one mother agreed to participate based on two pregnancies, the number of data points is two. We thus excluded these duplicates. This is what we mean by "second and subsequent responses."

- By the term 'abortion', do you mean miscarriage?

Thank you for your comment. I have changed this text.

- In the 'study design' section, the definitions of the 'lost to follow-up' and 'non-response' variables is unclear.

Thank you for this question. I rewrote the definitions of "lost-to-follow-up" and "non-response," as follows:

"Participants were divided into the following four groups based on the response status to the two questionnaires administered within one year: the 'lost-to-follow-up group' (non-response to both questionnaires), the 'resumed group' (non-response to the questionnaire for six-month-olds only), the 'discontinuation group' (non-response to the questionnaire for one-year-olds only), and the 'continuation group' (responses to both questionnaires)."

- The definitions of the variables should be presented when they are first introduced, not in a separate section.

Thank you for your comment. I have moved the sentences showing the definitions.

- The variable presented in Figure 2 (non-response, resumed, discontinued, continued) should be described along with the other dependent variable – not at the end of the definitions section.

Thank you for this question. Based on a suggestion from another reviewer, I changed Figure 1 and removed Figure 2. Please check.

Results

- For me, the 'non-response, resumed, discontinued, continued' variable is the more interesting outcome, and I think the results would be more meaningful if analyses focused on it rather than the individual 6 and 12 month outcomes. Certainly, the numbers in these 4 categories should be reported up-front as it is hard to interpret the results in Tables 1 and 2 without knowing who is in non-responders group in each case (from Figure 2, the majority of non-responders are the same at both 6 and 12 months, meaning the results at the two time points are unsurprisingly very similar.)

Thank you for your comment. Based on the suggestions from you and other reviewer, I have focused only on the "lost-to-follow-up" group and changed Tables 1 and 2. Additionally, I rewrote the result section regarding the lost-to-follow-up group during the first year after delivery using four categories according to the response status of the two questionnaires. Please check.

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Discussion

- I didn't understand the link the authors' make between GP effects on participation and partner effects on participation - these seem very separate things to me?

Thank you for your comment. As you note, the relationship between doctors and patients was different from the relationship between participants and their partners. However, the relationship between research participants and their neighbors who understand the research seems to be similar. I wrote about this point as follows:

"Active participating partners agreed to participate in JECS and returned the questionnaires, so they were considered to be familiar with JECS. They might have played a role similar to that of the GP in Alessi et al.'s study; therefore, the lost-to-follow-up rate of participants decreased as a result of having such a partner."

- There needs to be more discussion on what the results mean for the study in general (e.g. in terms of representativeness of the cohort, but also on ways in which they could help inform ways to minimize attrition/maximise participation in the future) and on what they mean for researchers using the data (e.g. potential for bias).

Thank you for your suggestion. I have added some sentences regarding the limitation of this study section as follows:

"This study has the following limitations: a) the follow-up period was only one year, and b) not all partners of the JECS participants were contacted for participation in this study. As the dropout rate only during the first year of follow-up was examined, factors affecting the lost-to-follow-up rate for longer periods is not clear. The partners of the participants were contacted in person by the investigator during the pregnancy of the participants to obtain informed consent. However, in cases in which the investigators were not able to contact the partner to request participation, it was classified as participation refusal in the data set because of the lack of informed consent."

- How do attrition rates in this study compare to other cohort studies in Japan/elsewhere?

Thank you for your question. The attrition rate of this study is similar or slightly higher than other cohort studies in Japan. For example, it in another birth cohort study in Japan, the attrition rate for one year after delivery was around 88%, similar to that of JECS.

- The 'limitations' section contains details that I think should be reported in the methods. The short follow-up period is a limitation. You should also mention your study's strengths.

Thank you for your comments. I added some information about the short follow-up period, and removed the sentences regarding the methods.

In addition, I added sentences about the strengths of this study, as follows:

"This study's strengths lie in its sample size and the participants' characteristics. There were 93,417 participants, which is sufficient for examining the risk factors of the lost-to-follow-up group. JECS covered about 45% of live births within the study area, and the characteristics of mothers who participated in JECS were similar to those of mothers in the Japanese Vital Statistics. Therefore, the results of this study have sufficient power for our analysis."

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Reviewer: 2
Reviewer Name: Jocelyn Anne Silvester
Institution and Country: Boston Children's Hospital, Harvard Medical School, Boston, MA, United States
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This study addresses an important problem in longitudinal research: loss-to-follow-up. The authors have an impressive retention rate in their study; nevertheless, it is important to understand factors affecting response and study participation in post-partum mothers, particularly for prospective cohort studies.

The authors conclude that partner participation and maternal depression are important factors contributing to loss to follow-up. Unfortunately, the methods are unclear at times, specifically with respect to consenting and communication with partners and the design which included pre- and post-partum surveys, but only considered loss-to-follow-up at 6 and 12 months (and is not clearly loss to follow-up post-partum as there is also a 1 month survey).

Thank you for your comment. I have added the information about the JECS research design in the JECS research design section, as follows:
“Participants were recruited by JECS Research Co-ordinators at JECS collaborating obstetric hospitals when they came for a health check-up during their first trimester. There were two baseline questionnaires that were administered during pregnancy (first trimester and second or third trimester) and one month after delivery. These questionnaires were distributed by JECS Research Co-ordinators at the collaborating obstetric hospitals and were collected by them at the hospitals or by mail. JECS also requested participants’ partners (i.e., fathers of the children) to participate in the study. For the participating partners, self-administered questionnaires were distributed to them once during the mothers’ pregnancy. The partner questionnaires were distributed by JECS Research Co-ordinators at the collaborating hospitals, or through the participating mothers, and were collected by JECS Research Co-ordinators through the mothers or by mail. Maternal medical information during pregnancy and at delivery, as well as medical information on the new-born children of the participants, were transcribed by physicians, midwives/nurses, and/or JECS Research Co-ordinators from the medical records of the collaborating hospitals.
One month after delivery, the participating mothers and their children mostly did not use the obstetric hospital for health check-ups; thus, information on JECS participants’ children’s health and growth metrics was collected through questionnaires. In this study, we examined data on six-month-old and one-year-old children. Both questionnaires were distributed and collected by mail.”

As well, the measure of "depression" - the Kessler Psychological distress scale, is non-diagnostic and measures both anxiety and depression.

Thank you for your suggestion. I changed the variable name to “psychological distress.”

- The “baseline” includes up to 2 surveys before delivery and 1 survey within 1 month of delivery. How were participants who did not complete all of these surveys handled? Were participants who only completed the initial pre-partum survey(s) considered lost at 6 months? Should they have been excluded as they were already lost prior to delivery? Can the authors explain why they chose to look at 6 and 12 months survey follow-up rather than comparing pre-partum and post-partum surveys (e.g., include the within 1 month of delivery survey as a follow-up point?)

Thank you for your comment. Certainly, the questionnaire administered one month after childbirth was the follow-up point for the state of pregnancy. However, in this study, we considered the contents of this questionnaire to be baseline information for future tracking.

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- Can the authors provide more information on how partners were consented and participated in the study in the methods? Was the partner consented in person? If partner did not attend visit, were they consented separately? Also, were any measures taken to confirm that partners received surveys delivered through the mother? [text on lines 297-301 of discussion does address these issues, but should be in methods]

Thank you for your suggestion. I have added the information about recruitment for JECS in the JECS study design section. Please check the sentences as mentioned above.

- Methods – last paragraph – sentence not clear – did you examine data from questionnaires distributed at 6 and 12 months of age? Are you actually looking at loss to follow-up after delivery in a cohort of women (and their partners) who were recruited during pregnancy?

Thank you for your comment. Based on your suggestion that it is better to focus more on the lost-to-follow-up, I changed the relevant sentences. Thus, I removed the sentences of the last paragraph in the method section.

- Kessler psychological distress scale is appropriate for population surveys, but this is designed to measure both anxiety and depression and is non-diagnostic. This should be made clear in the methods and in the text and should not be implied to be diagnostic of depression.

Thank you for your suggestion. I changed the variable name to “psychological distress.”

Reviewer: 3
Reviewer Name: Per Magnus
Institution and Country: Norwegian Institute of Public Health, Oslo, Norway
Please state any competing interests or state ‘None declared’: I am collaborating with other scientists in JECS in two consortia: one on childhood cancer and another regarding environmental toxicants. I have not published papers together with the authors of this manuscript

Please leave your comments for the authors below
This paper gives important information about loss-to-follow up in a large, Japanese cohort. It will be of value for interpretation of later analytic studies. I have only two small concerns.:

- the dependent variable described in lines 117-120 on page 5. The distinction between "lost-to-follow-up" and "non-response" is unclear to me. Also, the definition of the variable should be "yes" or "no" on an individual level, not a number of participants.

Thank you for your comment. Based on the reviewer’s comment, I focused more on lost-to-follow-up one year after delivery, and changed the sentences about the definition as follows:

“Participants were divided into the following four groups based on the response status to the two questionnaires administered within one year: the ‘lost-to-follow-up group’ (non-response to both questionnaires), the ‘resumed group’ (non-response to the questionnaire for six-month-olds only), the ‘discontinuation group’ (non-response to the questionnaire for one-year-olds only), and the ‘continuation group’ (responses to both questionnaires).”

- p-values are unnecessary. There is no prior hypothesis. The confidence limits give the precision.

Thank you for your suggestion. I think that the p-values are necessary when it comes to examining lost-to-follow-up and variables. Thus, I changed the sentences, as follows:

“…and the presence or absence of partner responses to the questionnaires were examined by Pearson’s chi-square test or Fisher’s exact test. A significance level of 0.01 (two-tailed) was used for all statistical analyses.”

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