

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Heated tobacco product use and hypertensive disorders of pregnancy and low birth weight: Analysis of a cross-sectional, web-based survey in Japan
<b>AUTHORS</b>	Zaitzu, Masayoshi; Hosokawa, Yoshihiko; Okawa, Sumiyo; Hori, Ai; Kobashi, Gen; Tabuchi, Takahiro

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Barnoya, Joaquin Unidad de Cirugia Cardiovascular, Departamento de Investigacion
<b>REVIEW RETURNED</b>	27-May-2021

<b>GENERAL COMMENTS</b>	<p>I reviewed the paper “Use of heated tobacco products may be associated with hypertensive disorders of pregnancy and low birth weight in Japan: An analysis of the JACSIS study” by Zaitzu et. al. that provides evidence on the increase of HDP and LBW due to HTP consumption in Japan. In general, the manuscript raises an important issue, the consequences of HTP consumption during pregnancy. However, they present cross-sectional and self-reported data on a small number of HTP and cigarette consumers. The paper does present some novel findings, particularly the number of women who appear to quit due to pregnancy or switch to HTP. In my opinion, they have limited data and therefore hard to draw conclusions, mostly a hypothesis generating paper. The paper could also benefit from some English editing.</p> <p><b>Abstract</b> In general reads well. Would be good to include also the number of current HTP and cigarette smokers (not only ever). In the analysis, if possible, please include what were the adjusted OR controlled for. Line 43, page 3 is hard to follow, maybe edit. In the conclusion, I would include “ever HTP use” to be consistent with their findings and methods. I suggest they edit the policy implications (what they present is not particularly relevant for a “school-based tobacco prevention” program).</p> <p><b>Strengths and limitations</b> On the limitations, it should be noted the low prevalence of current HTP users, other confounders not taken into account as well as that this is web-based survey.</p> <p><b>Introduction</b> Line 63, not sure we can say HTP use is “widespread”. Authors might want to look for prevalence of HTP elsewhere to make the</p>
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introduction relevant to an international audience. In general, too focused on Japan.

#### Methods.

Would be good to read more on Rakuten and how the sample was randomly selected. The response rate appears to be low. Did they have any strategies to improve the response rate? Any data on those that did not respond? Any differences from the respondents? Paragraph from line 95 to 107 is hard to follow, particularly the numbers. I suggest they edit. The web-based, self-reported should be included as a major limitation and potential source of bias. Lines 112 to 116, please add how these were reported? Did they also ask about treatment or just diagnosis? Reporting is described on lines 120, I suggest they move up at the end of the first paragraph of page 7.

Line 128, "once or a few times" could also include "sometimes". On cigarette smoking, did they also include current and former? On the former, did they assess how long had they quit? Did they assess electronic cigarette use? Dual users (combustible cigarettes and HTPs)? Line 141, please add more on the "detailed HTP smoking status". To what details they refer? Intensity? Frequency? Flavors? On line 150, were the comorbidities, were they analyzed together or separately?

#### Results

The number of current (and even ever) users is low in their sample. Would be helpful that they include numbers also when they include % in the text, and add p-values. Line 172, not sure they can use the word "tendency" given the cross-sectional nature of the data. Line 179, "managerial workers predicted" is hard to follow, suggest editing. The wide confidence intervals might be a marker of small sample size, they should comment on this in the Discussion and Limitations.

#### Discussion.

They might want to tone down the first paragraph of the Discussion to make it more hypothesis generating. The limitations of the study are several and not sure they can reach too many conclusions. On line 194, can they provide the "general statistics" they are referring to? On line 197, would be good to read more on "they are known to use HTP more frequently than women of low SES." Lines 199 and 200 could be edited, hard to follow. Lines 202 and 203 could be deleted as this has already been mentioned before. Line 206 needs a reference at the end of that sentence. In line 210, the reference to "snuff" might not be relevant to this paper. It would be good to read more on what is included in line 220 to make their findings policy relevant. I suggest removing "current increase of HTP use" as they only have cross-sectional data and therefore not able to assess increase in use. In line 237 and 238, would be good to add something on conventional cigarettes and e-cigarettes. On line 244, I suggest deleting the "included detailed information on HTPs". More details on HTP use are needed and not included in this manuscript. Line 257, I suggest to remove any reference to school-based prevention and cessation programs as their data is not related to adolescents or schools.

	<p>Figure 1 most are non-significant, not sure how much it adds or just reference in the text those that were significant.</p> <p>Table 1. It reads that their sample is pretty homogenous in terms of income. Maybe they could collapse some categories to gain some power. The comorbidities are major confounders and more data on them would be needed, including medication and time since diagnosis. Unfortunately, few in the sample have them.</p> <p>Table 2. I think this is very relevant and maybe the most important contribution. Particularly, on the pregnant women, the former and current smokers are interesting and worth highlighting in the text and manuscript.</p>
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<b>REVIEWER</b>	Wojtyla, Cezary Calisia University, International Prevention Research Institute – Collaborating Centre
<b>REVIEW RETURNED</b>	19-Jun-2021

<b>GENERAL COMMENTS</b>	<p>The manuscript sent for review takes up an important, though still underestimated, problem of the impact of consuming heated tobacco products on pregnancy outcomes. The basis for the analysis was an online questionnaire addressed to women after childbirth and those who are currently pregnant. A total of 923 women were analyzed. Due to the methodology used (self-reported questionnaire), there is a risk of reporting bias. Nevertheless, the authors of the paper considered the above problem in the limitation section.</p> <p>I have a few minor comments on the submitted paper.</p> <ol style="list-style-type: none"> <li>1. The "Strengths and limitations of this study" section, below keywords, requires re-analysis. Some of the points used present a summary of the paper results rather than limitations. Please also note my next comment here.</li> <li>2. One of the main limitations is the inability to directly assess the impact of consuming HTP on pregnancy outcomes due to a lack of knowledge about consuming HTP during pregnancy. The HTP smokers group consisted of women who had ever consumed HTP products. Thus, they could consume them before pregnancy. This requires a detailed description in the article.</li> <li>3. In the logistic regression analysis, the reference group was never HTP smokers. Wouldn't it be better to refer to a group of women who have never smoked any form of tobacco? We would get more reliable data.</li> </ol> <p>Despite the minor comments, I believe that this type of paper is needed to better understand the impact of smoking various forms of tobacco on pregnancy outcomes.</p>
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### VERSION 1 – AUTHOR RESPONSE

Thank you for your remarks. We have specified that this is a web-based cross-sectional study and hypothesis-generating study. We have toned down our conclusions and deleted some information in the

Results/Discussions. Our point-by-point responses to each of your comments are as follows. Our manuscript has been edited by a professional language editing company again. We have acknowledged their service in the Acknowledgments section of the revised manuscript.

Abstract :

#1 In general reads well. Would be good to include also the number of current HTP and cigarette smokers (not only ever).

Response: Thank you for this suggestion. We have added the data of current HTP and cigarette smokers in the text and Table 2. The revised main text now reads as follows:

Revisions

Abstract, P2, Line 40:

(Original): The prevalence of ever HTP use were 11.7% and 12.6% in post-delivery and currently pregnant women, respectively.

(Revised): The prevalence of ever and current HTP use were 11.7% and 2.7% in post-delivery women and 12.6% and 1.1% in currently pregnant women, respectively.

#2. In the analysis, if possible, please include what were the adjusted OR controlled for. Line 43, page 3 is hard to follow, maybe edit.

Response: Thank you for these comments. As you pointed earlier, this is mainly a hypothesis-generating study due to the small sample size. Therefore, to clarify the limitations of our study and tone down our conclusions, we switched from reporting the fully adjusted ORs for all covariates (Model 2) to age-adjusted ORs (Model 1). In addition, due to the word count limit, we deleted the explanation for stratified analysis (Line 43). Accordingly, our revised text is as follows:

Revisions

Abstract, P2, Line 37:

(Original): In the multivariable regression analysis, we estimated the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of ever HTP smokers for HDP and LBW compared with those of never HTP smokers using logistic regression. A stratified analysis with respect to combustible cigarette smoking (never/ever) was also performed.

(Revised): We estimated the age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of ever HTP smokers for HDP and LBW and compared them with those of never HTP smokers in a logistic regression analysis.

Abstract, P2, Line 43:

(Original): Among post-delivery women, ever HTP smokers had higher HDP incidence (13.8% vs. 6.5%,  $P=0.03$ ), with an OR of 2.78 (95% CI 0.84–9.15) and higher LBW incidence (18.5% versus 8.9%,  $P=0.02$ ), with an elevated OR of 2.08 (95% CI 0.80–5.39). A similar tendency was observed among never and ever combustible cigarette smokers.

(Revised): Among post-delivery women, ever HTP smokers had a higher HDP incidence (13.8% vs. 6.5%,  $P=0.03$ ; age-adjusted OR=2.48, 95% CI 1.11–5.53) and higher LBW incidence (18.5% versus 8.9%,  $P=0.02$ ; age-adjusted OR=2.36, 95% CI 1.16–4.87).

#3. In the conclusion, I would include “ever HTP use” to be consistent with their findings and methods. I suggest they edit the policy implications (what they present is not particularly relevant for a “school-based tobacco prevention” program).

Response: Thank you for these comments. We have included “ever HTP use” in the manuscript. We also agree that our findings are not relevant to school-based tobacco prevention, and further large-scale studies are needed to conclude about the perinatal risks associated with HTP use. Therefore, we deleted this policy implication and toned down our conclusions as follows:

#### Revisions

Abstract, Conclusion, P2, Line 46:

(Original): In Japan, the incidence of HTP use has exceeded 10% among pregnant women, and HTP smoking may be associated with increased maternal and neonatal risks. School-based tobacco prevention and cessation programs should be conducted regardless of product types to prevent life-threatening perinatal complications and deaths.

(Revised): In Japan, the incidence of ever HTP use exceeded 10% among pregnant women, and HTP smoking may be associated with maternal and neonatal risks.

#### Strengths and limitations:

#4. On the limitations, it should be noted the low prevalence of current HTP users, other confounders not taken into account as well as that this is web-based survey.

Thank you for this remark. We have revised the limitations as follows:

#### Revisions

Strengths and limitations of this study:

(Original):

- Little is known about heated tobacco product (HTP) use and associated perinatal risks among pregnant women.
- In Japan, the prevalence of ever HTP use exceeded 10% among pregnant women.
- HTP use approximately doubled perinatal risk of hypertensive disorders of pregnancy and low birth weight based on maternal and newborn records.
- When stratified by cigarette smoking status, a similar tendency was observed among never and ever cigarette smokers.
- The cross-sectional design does not allow firm conclusions.

(Revised):

- This study covered all heated tobacco products (HTPs) available during the study period.
- All participants were asked to base their responses on information in their Maternal and Child Health Handbooks, a well-established home-based maternal and neonatal record of pregnancy.
- The web-based, self-reported cross-sectional design with a small sample size was a source of bias, and causal mechanisms were not examined.
- The lack of information on HTP smoking during pregnancy limited the assessment of the direct impact of HTP use on pregnancy outcomes.
- The participants' relevant medical histories were not assessed.

#### Introduction:

#5. Line 63, not sure we can say HTP use is “widespread”. Authors might want to look for prevalence of HTP elsewhere to make the introduction relevant to an international audience. In general, too focused on Japan.

Response: Thank you for this suggestion. We agree that saying “widespread” for HTP use is not relevant in the international context; therefore, we deleted this phrase. In addition, we agree that data from other countries are useful for an international audience, although HTP prevalence is the highest in Japan. Recent studies suggested that HTP use has begun to increase worldwide, particularly in a younger population, and the prevalence of HTP use in Guatemala adolescents was 2.9% in 2020 (Gottschlich et al. 2020). We have added these points and have revised the main text as follows:

#### Revisions

Introduction, P4, Line 64:

(Original): The widespread use of heated tobacco products (HTPs) is an emerging public health concern.(Tabuchi et al. 2018) Since the initial marketing of HTPs in 2014, the prevalence of HTP use has increased in Japan, exceeding 15% in the young population aged 20–39 years in 2019,(Hori et al. 2020) and this incidence was maintained over 15% during the coronavirus disease (COVID-19) pandemic in 2020.(Odani et al. 2021)

(Revised): The use of heated tobacco products (HTPs) is an emerging public health concern (Tabuchi et al. 2018). Since the initial marketing of HTPs in 2014, the prevalence of HTP use has increased in Japan, with a registered prevalence above 15% in the young population aged 20–39 years in 2019 (Hori et al. 2020). This prevalence remained above 15% during the coronavirus disease (COVID-19) pandemic in 2020 (Odani et al. 2021). The use of HTPs is increasing worldwide, particularly in the younger population; the prevalence of HTP use among Guatemala adolescents was 2.9% in 2020 (Gottschlich et al. 2020).

#### References:

1. Tabuchi T, Gallus S, Shinozaki T, et al. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. *Tob Control* 2018;27:e25–e33.
2. Hori A, Tabuchi T, Kunugita N. Rapid increase in heated tobacco product (HTP) use from 2015 to 2019: from the Japan “Society and New Tobacco” Internet Survey (JASTIS). *Tob Control* [Epub ahead of print]. June 05, 2020 [cited 2021 July 08] [https://doi: 10.1136/tobaccocontrol-2020-055652](https://doi.org/10.1136/tobaccocontrol-2020-055652).
3. Odani S, Tabuchi T. Prevalence of heated tobacco product use in Japan: the 2020 JASTIS study. *Tob Control* [Epub ahead of print]. March 11, 2021 [cited 2021 July 08] [https://doi: 10.1136/tobaccocontrol-2020-056257](https://doi.org/10.1136/tobaccocontrol-2020-056257)
4. Gottschlich A, Mus S, Monzon JC, et al. Cross-sectional study on the awareness, susceptibility and use of heated tobacco products among adolescents in Guatemala City, Guatemala. *BMJ Open*. 2020;10:e039792.

#### Methods:

#6. Would be good to read more on Rakuten and how the sample was randomly selected. The response rate appears to be low. Did they have any strategies to improve the response rate? Any data on those that did not respond? Any differences from the respondents?

Response: Thank you for this question. The calculation of our response rate is slightly different from that of usual response rates. For instance, the internet research agency initially identified 21,896 eligible

women; however, our target sample size was 1000 women, due to the available study budget. Therefore, using a computer algorithm, the internet research agency randomly selected 4373 women, from whom 1000 women (target sample size) were selected in turn for this study. Informed consent was obtained electronically before the study participants answered the web-based questionnaire. In addition, data collection was started on October 15, 2020, and ended on October 25, 2020 (11 days), when the target sample size of 1000 was met by a natural course. Hypothetically, if we had a larger budget and extend the data collection period, the response rate would have been higher. Quality control methods for the sampling of panelists and other policies for panelists including rewards for responses by the internet research agency have been described elsewhere (Rakuten Insight Inc. Policies. 2019).

In the comparison between non-responders and responders, the original information for the identified 21,896 eligible women is not available due to the real-time updating system of the Rakuten Insight internet panelists. Thus, we cannot directly compare the backgrounds between responders and non-responders. However, among currently active panelists (as of July 2, 2021), we identified 20,176 eligible women based on our study inclusion criteria. In this population, the mean age was 32.7 (SD 4.6) years, which did not largely differ to that of our analyzed samples (mean 32.1 [SD 4.2] years, n=923). Therefore, the random sampling method to reduce non-response bias and the survey period are acceptable, and the characteristics of the target population and the source population might not differ substantially.

Accordingly, we have included details of the survey methods and quality in the Methods and added the small sample size as one of the limitations in the Discussion in the revised manuscript.

## Revisions

Method, P5, line 97:

(Original): The internet research agency identified 21,896 eligible women, randomly selected 4373 women who gave birth after October 2019 or who were expected to give birth by March 2021, and distributed the questionnaire comprising 61 questions to the selected women through a designated website. Next, we collected data from 1000 women (response rate, 22.9%) stratified by delivery date as follows: (a) 600 post-delivery women who delivered during October 2019–March 2020 (n=200), April–May 2020 (n=200), and June–October 2020 (n=200) and (b) 400 currently pregnant women who were expected to deliver during October 2020–March 2021. Among 1000 study participants, we excluded 77 who provided irrelevant or conflicting information (45 post-delivery and 32 currently pregnant women) as done in previous studies of the same research agency, (Tabuchi T et al. 2019) yielding a total of 923 study participants for the analysis (558 post-delivery and 365 currently pregnant women). Informed consent was obtained electronically, and the Institutional Review Board of the Osaka International Cancer Institute approved the study (Protocol Number 20084).

(Revised): The internet research agency initially identified 21,896 eligible women, who gave birth after October 2019 or who were expected to give birth by March 2021; however, our target sample size was 1,000 women due to the available study budget. Using a computer algorithm, the internet research agency randomly selected 4373 women to reach the target sample size of 1000. Quality control methods for the sampling of panelists and other policies for panelists by the internet research agency have been described elsewhere. (Rakuten Insight Inc. Policies. 2019) An invitation e-mail was sent to the selected 4373 women; they were to complete the questionnaire through a designated website containing the survey questionnaire (made up of 61 questions, one question per page). Data collection started on October 15, 2020, and ended on October 25, 2020, when the target sample size of 1000 by natural course (response rate, 22.9%) was met. Next, we obtained de-identified data from 1000 women from the internet research agency, and the study population was stratified by delivery date as follows: (a) 600 post-delivery women who delivered in October 2019–October 2020 (the number for October 2019–March 2020, April–May 2020, and June–October 2020 was 200 each) and (b) 400 currently pregnant women who were expected to deliver in October 2020–March 2021.

Seventy-seven (42 post-delivery and 35 currently pregnant women) participants who provided irrelevant or conflicting information were excluded, like it was done in previous studies of the same research agency.(Tabuchi T et al. 2019) A total of 923 (558 post-delivery and 365 currently pregnant women) participants were included in the analysis. Informed consent was obtained electronically before the study participants answered the web-based questionnaire, and the Institutional Review Board of the Osaka International Cancer Institute approved the study (Protocol Number 20084).

Discussion, P11, line 251:

(Original): Our study had some limitations. First, our cross-sectional design does not allow to conclude causal mechanisms between HTP use and perinatal risks.

(Revised): Our study has limitations. First, this was a web-based, self-reported cross-sectional study with a small sample size, which may be a source of bias and a limitation to explaining the causal mechanisms between HTP use and perinatal risks.

References:

1. Rakuten Insight Inc. Policies. 2019 (Last updated: Oct 6, 2019)  
<https://member.insight.rakuten.co.in/policies> (accessed 26 Jun 2021)
2. Tabuchi T, Shinozaki T, Kunugita N, et al. Study profile: The Japan “Society and New Tobacco” Internet Survey (JASTIS): A longitudinal internet cohort study of heat-not-burn tobacco products, electronic cigarettes, and conventional tobacco products in Japan. *J Epidemiol* 2019;29:444–50.

#7. Paragraph from line 95 to 107 is hard to follow, particularly the numbers. I suggest they edit. The web-based, self-reported should be included as a major limitation and potential source of bias.

Response: Thank you for this remark. We have thoroughly revised this paragraph, which is in line with comment #6. We also revised one of the limitations as follows:

Revisions

Discussion, P11, line 251:

(Original): Our study had some limitations. First, our cross-sectional design does not allow to conclude causal mechanisms between HTP use and perinatal risks.

(Revised): Our study has limitations. First, this was a web-based, self-reported cross-sectional study with a small sample size, which may be a source of bias and a limitation to explaining the causal mechanisms between HTP use and perinatal risks.

#8. Lines 112 to 116, please add how these were reported? Did they also ask about treatment or just diagnosis? Reporting is described on lines 120, I suggest they move up at the end of the first paragraph of page 7.

Response: Thank you for this suggestion. We collected information on diagnosis only (treatment information was not obtained). This was clarified in the text. In addition, we have moved the information related to the Maternal and Child Health Handbooks as suggested.

Revisions

Method, P6, line 133:



(Original): All participants were asked to provide information from their Maternal and Child Health Handbooks. In brief, as previously described, the Maternal and Child Health Handbooks are well-established integrated home-based records of maternal, newborn, and child health.

(Revised): All participants were asked to provide information from their Maternal and Child Health Handbooks. Although the definitions of HDP and LBW were based on diagnosis only (treatment information was not obtained), the information was reliable, since Maternal and Child Health Handbooks are well-established integrated home-based records of maternal, newborn, and child health.

#9. Line 128, “once or a few times” could also include “sometimes”. On cigarette smoking, did they also include current and former? On the former, did they assess how long had they quit? Did they assess electronic cigarette use? Dual users (combustible cigarettes and HTPs)?

Response: Thank you for this suggestion. We distinguished smoking just “once or a few times” (was considered as trial smoking and not habitual smoking) from “sometimes,” which is habitual smoking. On combustible cigarette smoking, we included current and former smokers. However, due to the small sample size, we could only use a binary variable (never/ever) for combustible cigarette smoking in the main analysis, and the categories for former smokers and dual users were not possible. As well, in Japan, the sale of e-cigarette is not official. Therefore, the assessment of e-cigarette smoking was not possible due to the small sample size. Details of the women’s smoking habits such as smoking intensity and duration of smoking abstinence were not available. Accordingly, we have clarified these points and limitations. The revised main text now reads as follows:

Revisions

Method, P7, line 140:

(Original): smoking status (never, once or a few times but not habitually, former, sometimes, or every day)

(Revised): smoking status (never, once or a few times [trial smoking and not habitual], former, sometimes [habitual], or every day)

Method, P7, line 148:

(Original): We also classified the status of combustible cigarette smoking (never/ever).

(Revised): The status of combustible cigarette smoking was classified as never smoker and ever smoker. It was impossible to further classify the smokers into former or dual smokers due to the nature of the study.

Discussion, P11, line 253:

(Revised): Due to the lack of information on HTP smoking during pregnancy, the direct impact of HTP smoking on pregnancy outcomes could not be assessed. Furthermore, details on the participants’ medical histories including relevant comorbidities, and detailed smoking information such as smoking intensity and duration of smoking abstinence were not available. In addition, electronic cigarette use was not assessed.

#10. Line 141, please add more on the “detailed HTP smoking status”. To what details they refer? Intensity? Frequency? Flavors?

Response: Thank you for this comment. Because smoking intensity and frequency were not available, we have deleted “detailed” from the main text and title of Table 2.

#11. On line 150, were the comorbidities, were they analyzed together or separately?

Response: Thank you for this question. The comorbidities were analyzed together.

Results:

#12. The number of current (and even ever) users is low in their sample. Would be helpful that they include numbers also when they include % in the text, and add p-values.

Response: Thank you for this suggestion. We have added numbers and p values where appropriate.

#13. Line 172, not sure they can use the word “tendency” given the cross-sectional nature of the data.

Response: Thank you for this comment. We have changed “tendency” to “pattern” (P9, line 195, line 205).

#14. Line 179, “managerial workers predicted” is hard to follow, suggest editing. The wide confidence intervals might be a marker of small sample size, they should comment on this in the Discussion and Limitations.

Response: Thank you for this comment. We have toned down the Discussion and included the small sample size as one of the study limitations.

Revisions

Result, P9, line 200:

(Original): Although the elevated ORs were attenuated after fully controlling for other covariates, the tendency remained elevated (model 2, Figure 1). In the same regression analyses (model 2), while ever combustible cigarette smokers did not predict perinatal outcomes, managerial workers predicted the incidence of HDP and LBW; the ORs for HDP and LBW were 3.92 (95% CI 1.16–13.2) and 3.74 (95% CI 1.41–9.93), respectively.

(Revised): However, the elevated ORs were not significant after adjusting for other covariates (Model 2, Figure 1). In the same regression analyses (Model 2), while ever combustible cigarette smokers were not associated with perinatal outcomes, the ORs of managerial workers for HDP and LBW were 3.92 (95% CI 1.16–13.2) and 3.74 (95% CI 1.41–9.93), respectively.

Discussion, P10, line 220:

(Original): Although the impact was attenuated after controlling for other potential explanatory factors and the significance disappeared due to weak statistical power, the maternal risk might be high independent of combustible cigarette smoking.

(Revised): However, after adjusting for potential explanatory factors, there was no significant association, which may be due to the weak statistical power because of the small sample size.

Discussion:

#15. They might want to tone down the first paragraph of the Discussion to make it more hypothesis generating. The limitations of the study are several and not sure they can reach too many conclusions.

Response: Thank you for this comment. We agree that we need to tone down our discussion because this should be a hypothesis-generating study. Therefore, we combined the second and first paragraph in the Discussion. We also deleted definitive statements or irrelevant explanations. The revised Discussion is as follows:

#### Revisions

Discussion, P10, line 218:

(Original): During the COVID-19 pandemic in Japan, the incidence of HTP use among pregnant women is likely to exceed 10%, and we found that HTP use may be associated with perinatal risk of HDP and LBW. Although the impact was attenuated after controlling for other potential explanatory factors and the significance disappeared due to weak statistical power, the maternal risk might be high independent of combustible cigarette smoking. This result seems to be reliable because the incidence estimate of approximately 7% HDP found in our study (using Maternal and Child Health Handbooks) is consistent with the general statistics reported for Japanese pregnant women.[14] In addition, pregnant women of high socioeconomic status independently predicted the risk of HDP, which might also support our findings because they are known to use HTP more frequently than women of lower socioeconomic status.[17] We also found that LBW, a well-known smoking-related neonatal risk,[18] was associated with HTP use. In fact, the incidence of HTP use doubled the risk of LBW, and the association was stronger among never combustible cigarette smokers. These results seem to be reliable because the incidence estimate of approximately 10% LBW found in our study (using Maternal and Child Health Handbooks) is consistent with the general statistics reported for Japanese pregnant women.[19] This also implies that aerosols of HTPs containing nicotine and other inhalable substances can cause acute adverse health events on the development of infants.

(Revised): During the first wave of the COVID-19 pandemic in Japan, the incidence of HTP use among pregnant women exceeded 10%, and there was a suspected association of HTP use and perinatal risk of HDP and LBW. However, after adjusting for potential explanatory factors, there was no significant association, which may be due to the weak statistical power because of the small sample size.

#16. On line 194, can they provide the “general statistics” they are referring to?

Response: Thank you for this comment. Following comment #15, we have deleted this part.

#17. On line 197, would be good to read more on “they are known to use HTP more frequently than women of low SES.”

Response: Thank you for this comment. To tone down our findings, following comment #15, we have deleted this part.

#18. Lines 199 and 200 could be edited, hard to follow.

Response: Thank you for this comment. We have deleted these lines following comment #15.

#19. Lines 202 and 203 could be deleted as this has already been mentioned before.

Response: Thank you for this comment. We have deleted these lines following comment #15.

#20. Line 206 needs a reference at the end of that sentence.

Response: Thank you for this comment. We have deleted these lines following comment #15.

#21. In line 210, the reference to “snuff” might not be relevant to this paper.

Response: Thank you for this comment. We have deleted the snuff-related information.

#22. It would be good to read more on what is included in line 220 to make their findings policy relevant. I suggest removing “current increase of HTP use” as they only have cross-sectional data and therefore not able to assess increase in use.

Response: Thank you for this comment. Although HTP-related unfavorable health outcomes (e.g., acute respiratory and cardiovascular risks) are likely to occur, advertisements of HTPs promote the impression of HTPs as healthy alternatives to combustible cigarettes. In a previous study, the Japanese HTP market share was 21% in total tobacco sales in 2018, and the weak restrictions on tobacco advertisement and promotion in this country contribute to increased HTP use (Lorraine et al. 2020). In a setting of weak tobacco restrictions such as Guatemala, even though the prevalence of HTP use is low (2.9%) among adolescents, a high prevalence is anticipated (Gottschlich et al. 2020). Accordingly, we have revised this part as follows:

#### Revisions

Discussion, P11, line 235:

(Original): Finally, the impression of HTPs as a healthy alternative is promoted by the advertising of HTPs.(Hair et al. 2018) Indeed, among currently pregnant women, approximately 4% of former combustible cigarette smokers reported smoking HTPs in the present study. This result might reflect a change from combustible cigarettes to HTP smoking during pregnancy.

(Revised): Although HTP-related unfavorable health outcomes (e.g., acute respiratory and cardiovascular risks) are likely to occur (Nabavizadeh et al. 2018; Simonavicius et al. 2019), the impression of HTPs as a healthy alternative is promoted by HTP use advertisements (Hair et al. 2018). The Japanese HTP market share accounted for 21% of total tobacco sales in 2018, and the weak restrictions on tobacco advertisements and promotion in this country contribute to increased HTP use (Lorraine et al. 2020). Among currently pregnant women, approximately 4% of former combustible cigarette smokers reported smoking HTPs in the present study. This result might explain the change from combustible cigarettes to HTP smoking during pregnancy. In a setting of weak tobacco restrictions such as Guatemala, even though the prevalence of HTP use is low (2.9%) among adolescents, a high prevalence is anticipated (Gottschlich et al. 2020).

1. References:Nabavizadeh P, Liu J, Havel CM, et al. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. *Tob Control* 2018;27(Suppl 1):s13–9.
2. Simonavicius E, McNeill A, Shahab L, et al. Heat-not-burn tobacco products: a systematic literature review. *Tob Control* 2019;28:582–94.
3. Hair EC, Bennett M, Sheen E, et al. Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland. *Tob Control* 2018;27(Suppl 1):s70–3.
4. Lorraine V. C, Itsuro Y, Geoffrey T.F, et al. Awareness of Marketing of Heated Tobacco Products and Cigarettes and Support for Tobacco Marketing Restrictions in Japan: Findings from the 2018 International Tobacco Control (ITC) Japan Survey. *Int J Environ Res Public Health* 2020;17:8418.

5. Gottschlich A, Mus S, Monzon JC, et al. Cross-sectional study on the awareness, susceptibility and use of heated tobacco products among adolescents in Guatemala City, Guatemala. *BMJ Open*. 2020;10:e039792.

#22. In line 237 and 238, would be good to add something on conventional cigarettes and e-cigarettes.

Response: Thank you for this comment. We have modified this part as follows:

Revisions

Discussion, P11, line 260:

(Original): Second, recall and reporting bias cannot be discarded.

(Revised): Second, recall and reporting bias of HTP use could not be discarded, as suggested in a study on combustible cigarette and electronic cigarette smoking (Gottschlich et al. 2020).

References:

1. Gottschlich A, Mus S, Monzon JC, et al. Cross-sectional study on the awareness, susceptibility and use of heated tobacco products among adolescents in Guatemala City, Guatemala. *BMJ Open*. 2020;10:e039792.

#23. On line 244, I suggest deleting the “included detailed information on HTPs”. More details on HTP use are needed and not included in this manuscript.

Response: Thank you for this comment. We have deleted the phrase of “detailed information on HTPs” and revised this part as follows:

Revisions

Discussion, P12, Line 269:

(Original): Despite these limitations, the strengths of the study included detailed information for HTPs, which covered all HTPs available during the study period.

(Revised): Despite these limitations, all HTPs that were available during the study period were assessed.

#24. Line 257, I suggest to remove any reference to school-based prevention and cessation programs as their data is not related to adolescents or schools.

Response: Thank you for this comment. We have deleted all the school-based data.

Figure 1:

#25. Most are non-significant, not sure how much it adds or just reference in the text those that were significant.

Response: Thank you for this comment. Since we made extensive deletion in the main text to tone down our discussions, we would like to keep Figure 1.

Table 1:

#26. It reads that their sample is pretty homogenous in terms of income. Maybe they could collapse some categories to gain some power. The comorbidities are major confounders and more data on them would be needed, including medication and time since diagnosis. Unfortunately, few in the sample have them.

Response: We thank the reviewer for this comment. We used a binary category grouping for household income (<6 million JPY and ≥6 million JPY) and re-did all analyses. However, the results did not differ. For example, in the regression Model 2, which was adjusted for all covariates, the ORs of ever HTP smokers for HDP were 2.78 (95% CI, 0.84–9.15) in the original model and 2.79 (95% CI, 0.85–9.18) in the re-analysis model, when compared with never HTP smokers. Therefore, we would like to keep our original classification for household income.

We also acknowledge that detailed comorbidities were not assessed, which is a major limitation in this study. We have added this as one of the limitations.

Table 2:

#26. I think this is very relevant and maybe the most important contribution. Particularly, on the pregnant women, the former and current smokers are interesting and worth highlighting in the text and manuscript.

Response: Thank you for appreciating our table. We have included the relevant data in the text.

Revisions

Result, P8, Line 187:

(Original): Among currently pregnant women, 4.4% of former combustible cigarette smokers reported smoking HTPs during pregnancy (Table 2), corresponding to 1.1% (4 out of 365) of current HTP smokers.

(Revised): Among the currently pregnant women, 4.4% (4/91 participants) of the former combustible cigarette smokers reported smoking HTPs during pregnancy (Table 2), corresponding to 1.1% (4/365 participants) of currently pregnant women. In addition, 36.3% (33/91 participants) of former combustible cigarette smokers quit HTP smoking during pregnancy, corresponding to 11.5% (42/365 participants) of currently pregnant women.

Response to Review #2

Thank you for appreciating our study and your valuable comments. Our point-by-point responses to each of your comments are found below.

#1. The "Strengths and limitations of this study" section, below keywords, requires re-analysis. Some of the points used present a summary of the paper results rather than limitations. Please also note my next comment here.

Response: Thank you for this remark. We have thoroughly revised the limitations section as follows:

Revisions

Strengths and limitations of this study:

(Original):

- Little is known about heated tobacco product (HTP) use and associated perinatal risks among pregnant women.
- In Japan, the prevalence of ever HTP use exceeded 10% among pregnant women.

- HTP use approximately doubled perinatal risk of hypertensive disorders of pregnancy and low birth weight based on maternal and newborn records.
- When stratified by cigarette smoking status, a similar tendency was observed among never and ever cigarette smokers.
- The cross-sectional design does not allow firm conclusions.

(Revised):

- This study covered all heated tobacco products (HTPs) available during the study period.
- All participants were asked to base their responses on information in their Maternal and Child Health Handbooks, a well-established home-based maternal and neonatal record of pregnancy.
- The web-based, self-reported cross-sectional design with a small sample size was a source of bias, and causal mechanisms were not examined.
- The lack of information on HTP smoking during pregnancy limited the assessment of the direct impact of HTP use on pregnancy outcomes.
- The participants' relevant medical histories were not assessed.

#2. One of the main limitations is the inability to directly assess the impact of consuming HTP on pregnancy outcomes due to a lack of knowledge about consuming HTP during pregnancy. The HTP smokers group consisted of women who had ever consumed HTP products. Thus, they could consume them before pregnancy. This requires a detailed description in the article.

Response: Thank you for this valuable suggestion. Although the status of HTP use did not differ between currently pregnant women and post-delivery women (line 182), the impact of HTP use before pregnancy and during pregnancy could not be assessed. We did not ask the participants (in particular, post-delivery women from whom perinatal outcomes could be measured) about the specific use of HTP before and during pregnancy, separately: this is one of the major limitations of this study. We clarified this point in the main text as follows:

Revisions

Method, P7, line 143:

(Original): If they answered "never" for all HTPs, we defined them as never HTP smokers; the remaining participants were considered ever HTP smokers.

(Revised): Participants who answered "never" for all HTPs were considered as never HTP smokers; the remaining participants were considered as ever HTP smokers. Therefore, the ever HTP smoking group included those who used HTPs before pregnancy and during pregnancy altogether. We could not specifically distinguish the impacts of HTP smoking during pregnancy from that of HTP smoking before pregnancy.

Discussion, P11, line 253:

(Revised): Due to the lack of information on HTP smoking during pregnancy, the direct impact of HTP smoking on pregnancy outcomes could not be assessed.

#3. In the logistic regression analysis, the reference group was never HTP smokers. Wouldn't it be better to refer to a group of women who have never smoked any form of tobacco? We would get more reliable data.

Response: Thank you for this insightful suggestion. We performed additional analyses to compare 65 post-delivery women who ever smoked HTPs and 411 who never smoked any form of tobacco (HTPs and

combustible cigarettes). The odds ratios (ORs) were similar: the age-adjusted ORs of ever HTP smokers for HDP and LBW were 2.56 (95% CI 1.13–5.80) and 2.52 (95% CI 1.22–5.20), respectively (Model 1). However, after adjusting for other covariates (model 2), the ORs were not significant, due to the small sample size: the ORs for HDP and LBW were 2.40 (95% CI 0.27–21.2) and 3.59 (95% CI 0.66–19.5), respectively. Therefore, we revised the Methods and Results as follows:

#### Revisions

Methods, P8, Line 170:

(Original): For sensitivity analysis, we conducted a stratified analysis with respect to combustible cigarette smoking (never/ever).

(Revised): For the sensitivity analysis, a stratified analysis with respect to combustible cigarette smoking (never/ever) was performed. In addition, using a different reference group that included those who never smoked any form of tobacco (HTPs and combustible cigarettes), the ORs of ever HTP smokers for HDP and LBW risks were estimated.

Results, P9, Line 205:

(Original): When stratified by combustible cigarette smoking, a similar tendency was observed independently in never and ever combustible cigarette smokers (Figure 1). For instance, among never combustible cigarette smokers, the age-adjusted OR of HTP use for LBW was 4.82 (95% CI, 1.19–19.6).

(Revised): In the sensitivity analyses, when stratified by combustible cigarette smoking, a similar pattern was observed independently in never and ever combustible cigarette smokers (Figure 1). For instance, among never combustible cigarette smokers, the age-adjusted OR of HTP use for LBW was 4.82 (95% CI, 1.19–19.6). A further analysis comparing 65 ever HTP smokers in the post-delivery group and 411 never tobacco smokers showed similar results: compared with those who never smoked any form of tobacco, the age-adjusted ORs of ever HTP smokers for HDP and LBW were 2.56 (95% CI 1.13–5.80) and 2.52 (95% CI 1.22–5.20), respectively (Model 1). However, after adjusting for other covariates (Model 2), the ORs were not significant due to the small sample size: the ORs for HDP and LBW were 2.40 (95% CI 0.27–21.2) and 3.59 (95% CI 0.66–19.5), respectively.

#4. Despite the minor comments, I believe that this type of paper is needed to better understand the impact of smoking various forms of tobacco on pregnancy outcomes.

Response: Thank you for appreciating our study. We hope that the revised manuscript would be suitable for publication in the journal.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Wojtyla, Cezary Calisia University, International Prevention Research Institute – Collaborating Centre
<b>REVIEW RETURNED</b>	01-Aug-2021
<b>GENERAL COMMENTS</b>	I have no objections to the current form of the paper. Congratulations.



