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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

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ABSTRACT

Background: Little is known about heated tobacco product (HTP) use in pregnant women and associated maternal and neonatal risks for hypertensive disorders of pregnancy (HDP) and low birth weight (LBW). Thus, this study aimed to assess the status of HTP use among pregnant women in Japan and explore the risk of HDP and LBW associated with HTP use.

Methods: Using data from the Japan "COVID-19 and Society" Internet Survey (JACSIS) study, a web-based nationwide survey, we investigated 558 post-delivery and 365 currently pregnant women in October 2020. We assessed the prevalence of ever HTP smokers (defined as ever experiencing HTP use) in post-delivery and currently pregnant women. Among post-delivery women, we collected the information regarding HDP and LBW based on their Maternal and Child Health Handbooks (maternal and newborn records). 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.

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

Conclusion: 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.

Keywords: heated tobacco products, hypertensive disorders of pregnancy, COVID-19, smoking, preconception

Strengths and limitations of this study:

- 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.

INTRODUCTION

The widespread use of heated tobacco products (HTPs) is an emerging public health concern.[1] 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,[2] and this incidence was maintained over 15% during the coronavirus disease (COVID-19) pandemic in 2020.[3]

Although the impression of HTPs as a healthy alternative to combustible cigarettes is promoted by the advertising of HTPs (e.g., reduced harmfulness and a smoke-free image),[4] HTP-related unfavorable health outcomes, including acute respiratory and cardiovascular risks, are likely to occur.[5, 6] However, little is known about HTP use and associated maternal and neonatal risks in pregnant women, including hypertensive disorders of pregnancy (HDP) and low birth weight (LBW).[7, 8] Although some controversial associations have been reported for HDP with respect to combustible cigarettes,[9] this type of cigarettes increases various maternal and neonatal risks in Japan.[10, 11] Therefore, we hypothesized that HTP use is associated with HDP and LBW, regardless of combustible cigarette smoking.

This study aimed to assess the status of HTP use among pregnant women in Japan and explore the risk of HDP and LBW associated with the use of HTP by analyzing data from a nationwide web-based survey in Japan that contained pregnancy-related information and data related to behavioral factors (e.g., HTP use and combustible cigarette smoking), and social background.

MATERIALS AND METHODS

Data setting

This cross-sectional internet-based study is part of the Japan COVID-19 and Society Internet Survey (JACSIS) study. The JACSIS study comprises three surveys in the following three target populations: (a) young people and adults aged 15–79 years, (b) currently pregnant and post-delivery women, and (c) adults living in a single-parent household. The study samples for each survey were retrieved from the pooled panels of an internet research agency (Rakuten Insight, Inc., which had approximately 2.2 million panelists in 2019).[12] We used data from currently pregnant and post-delivery women, which were collected in October 2020.

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,[13] 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).

Definition of HDP and LBW

Data on HDP and LBW were extracted from the web-based self-reported questionnaires. We defined the incidence of HDP based on whether the study participants had been diagnosed as

having HDP or preeclampsia during pregnancy. The criteria for HDP diagnosis in Japan were derived from the criteria of the American College of Obstetricians and Gynecologists (i.e., systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg after the 20th week of gestation).[14] We defined the incidence of LBW on the basis of the diagnosis of LBW (birth weight <2500 g).

All participants were asked to provide information from their Maternal and Child Health Handbooks. In brief, as previously described,[15, 16] the Maternal and Child Health Handbooks are well-established integrated home-based records of maternal, newborn, and child health. As a part of a national maternal and child health policy, all municipalities issue a handbook to all women who report a pregnancy, and medical professionals record the health information of the mother and child, including clinical outcomes (e.g., blood pressure and birth weight) and incident diagnoses (e.g., HDP and LBW) during pregnancy. Mothers seldom lose their Maternal and Child Health Handbooks (losing rate, <1%).[15]

HTP and cigarette smoking and other covariates

In the questionnaire, study participants were asked to indicate their smoking status (never, once or a few times but not habitually, former, sometimes, or every day) for each HTP available in the study period (Ploom Tech, Ploom Tech plus, Ploom S, IQOS, glo, glo sens, and PULZE). If they answered "never" for all HTPs, we defined them as never HTP smokers; the remaining participants were considered ever HTP smokers.

We also classified the status of combustible cigarette smoking (never/ever). For other covariates, we included age, educational attainment (≤12 years [high school] or ≥13 years [college or university]), occupation (manager or others), household income (<2 million JPY [approximately 20,000 USD], 2 to <6 million JPY, and ≥6 million JPY), and comorbidity (having hypertension or diabetes).[17]

Statistical analysis

Descriptive statistics were computed, and t-test or chi-squared test was performed. We assessed the prevalence of ever HTP smokers among post-delivery and currently pregnant women. Additionally, we described detailed HTP smoking status cross-classified according to the combustible cigarette smoking status of currently pregnant and post-delivery women.

To assess the potential association between HTP smoking and perinatal risk of HDP and LBW, we restricted the sample to 558 post-delivery women who could complete all the assessments during their pregnancy (Table 1). In the multivariable logistic regression analyses, the odds ratio (OR) and 95% confidence interval (CI) of ever HTP smokers for HDP risk were estimated with adjustment for age (model 1, the main model in the present study). The reference group comprised never HTP smokers. In model 2, we fully adjusted for other explanatory variables (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) and excluded 64 participants with missing information on household income. The same analyses were performed for LBW. For sensitivity analysis, we conducted a stratified analysis with respect to combustible cigarette smoking (never/ever).

Alpha was set at 0.05, and all *P*-values were two sided. Data were analyzed using STATA/MP13.1 (StataCorp LLC, College Station, TX).

Patient and Public Involvement

No patients or the public involved.

RESULTS

Among 558 post-delivery women, the incidences of HDP and LBW were 7.3% (n=41) and 10.0% (n=56), respectively, and the prevalence of ever HTP smokers was 11.7% (n=65, Table 1). Furthermore, among 365 currently pregnant women, the prevalence of ever HTP smokers was 12.6% (n=46), which did not differ from that of HTP smokers among post-delivery women (*P*=0.66). 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.

Among post-delivery women, the HDP incidence was higher in ever HTP smokers than in never HTP smokers (13.8% vs. 6.5%; Table 1). Similarly, the incidence of LBW was higher among ever HTP smokers than among never HTP smokers (18.5% vs. 8.9%, Table 1). When stratified by combustible cigarette smoking, a similar tendency was observed among never and ever combustible cigarette smokers (Table 1).

In the regression analysis, the age-adjusted ORs for HDP and LBW were elevated in ever HTP smokers (model 1, Figure 1); the ORs for HDP and LBW were 2.48 (95% CI, 1.11–5.53) and 2.36 (95% CI, 1.16–4.78), respectively. 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. 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).

DISCUSSION

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.

To the best of our knowledge, this is the first report of a potential association between HTP use and perinatal risks. Although smoking plays a controversial role,[9] recent evidence suggests that combustible cigarette smoking is associated with increased HDP risk.[10, 11] Another study also reported the risk of snuff use for preeclampsia, a severe phenotype of HDP.[20] Although the biological and genetic pathways (e.g., CYP2A6 and nicotine)

underlying the associations observed in different phenotypes of HDP (e.g., preeclampsia and gestational hypertension) have not been elucidated,[21] HDP is recognized as a systemic disease attributable to placental circulatory dysfunction.[22] In experimental research, aerosol from HTPs was found to damage vascular endothelial function in rats.[5] Therefore, HDP risk associated with HTP use may involve acute and chronic vascular damage, irrespective of combustible cigarette smoking. Furthermore, as concluded in a recent systematic review, smoking is a strong risk factor for LBW.[18] Thus, given the fact that HTPs are smoking devices, our observed results are in line with established knowledge.

Finally, the impression of HTPs as a healthy alternative is promoted by the advertising of HTPs.[4] 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. However, our findings imply that HTP use is at least not a healthy alternative. Evidence for unfavorable health outcomes regarding HTPs is still lacking, particularly in the young population of reproductive age. Insufficient health knowledge may have led to the current increase of HTP use among pregnant women, as reflected in our results and the latest statistics in Japan.[2, 3] However, the question remains as to how multidimensional factors of the COVID-19 pandemic (e.g., the infection, mental health, and socioeconomic factors) and the smoking behaviors of others (e.g., partners and family) affect the association between HTP use and perinatal risks. Our sequential series of the JACSIS study planned in 2021 may provide updates regarding the present results.

Our study had some limitations. First, our cross-sectional design does not allow to conclude causal mechanisms between HTP use and perinatal risks. However, the prevalence of HDP and HTP smokers were mostly parallel to the general population in Japan.[2, 3, 14] In addition, the incidence of HTP use did not differ between post-delivery and currently

pregnant women in our study. Second, recall and reporting bias cannot be discarded. Because self-report-based smoking status among pregnant women tends to misclassify ever smokers as never smokers,[23] our estimates might be biased toward the null. Third, the perinatal clinical information was self-reported and not based on medical charts, thereby limiting the precision of the results. However, all participants were asked to base their responses on their Maternal and Child Health Handbooks, a well-established home-base maternal and neonatal record during pregnancy.[16] Therefore, this limitation might not have affected our results or at least not largely. Despite these limitations, the strengths of the study included detailed information for HTPs, which covered all HTPs available during the study period. Additionally, this is the first report regarding the status of HTP use among pregnant women in Japan, and it highlights the potentially elevated maternal and neonatal risks associated with HTP use. Additionally, besides the present study, no other human studies to date have assessed the potential effect of the maternal use of new tobacco products (i.e., e-cigarette and HTP) on perinatal health.[24] Therefore, our findings shed light and motivate further investigations to estimate the life-threatening perinatal risks associated with new tobacco products.

In conclusion, the incidence of HTP use seems to exceed 10% among pregnant women, and HTP smoking may be associated with increased maternal and neonatal risks in Japan. With no doubt, smoking in reproductive age can cause unfavorable perinatal outcomes.[25] Hence, efforts should be made to investigate the risk of HTP use in reproductive age, and school-based tobacco prevention and cessation programs should be conducted regardless of product types to prevent life-threatening perinatal complications and deaths.

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Data availability statement: The data that support the findings of this study are available on reasonable request. However, restrictions apply to the availability of these data due to personal identification; research data are not shared. If any person wishes to verify our data, they are most welcome to contact the corresponding author.

Conflict of interest: The authors declare no potential conflicts of interest.

Author contributions: MZ and TT designed the study, and TT supervised the study. MZ, YH, and SO developed the methodology, and SO, AH, and TT created the dataset. MZ and YH analyzed the data and wrote the first draft of the manuscript. All authors revised the manuscript and approved the final version.

Ethics approval: The study was approved by the Institutional Review Board of the Osaka International Cancer Institute approved the study (Protocol Number 20084).

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FIGURE LEGEND

Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight compared with never heated tobacco product smokers. Age was adjusted in model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) were additionally adjusted in model 2. The samples for each analysis in model 2 were as follows: n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for low birth weight. Abbreviations: HTP, heated tobacco products; OR, odds ratio.

Table 1. Characteristics of 558 post-delivery women and 365 currently pregnant women

Characteristics	N (%) or mean (SD)			
	Post-delivery women		Currently pregnant women	
	Never HTP smokers	Ever HTP smokers	Never HTP smokers	Ever HTP smokers
Overall	*n=493*	*n=65*	*n=319*	*n=46*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	32 (6.5%)	9 (13.8%)*	NA	NA
Low birth weight <2500 g	44 (8.9%)	12 (18.5%)*	NA	NA
Preterm birth <37 weeks	19 (3.9%)	4 (6.2%)	NA	NA
Imminent preterm birth	82 (16.6%)	18 (27.7%)*	NA	NA
Age	32.4 (4.1)	30.9 (4.2)**	31.9 (4.3)	31.3 (4.7)
Ever combustible cigarette smoking	82 (16.6%)	55 (84.6%)***	54 (16.9%)	41 (89.1%)***
Educational attainment ≥13 years	410 (83.2%)	37 (56.9%)***	278 (87.1%)	31 (67.4%)**
Managerial workers	19 (3.9%)	5 (7.7%)	16 (5.0%)	2 (4.3%)
Comorbidity of hypertension or diabetes	35 (7.1%)	4 (6.2%)	4 (1.3%)	4 (8.7%)**
Household income	*n=436*	*n=58*	*n=263*	*n=41*
<200 million JPY	13 (3.0%)	3 (5.2%)	6 (2.3%)	1 (2.4%)
200 to <600 million JPY	200 (45.9%)	30 (51.7%)	115 (43.7%)	19 (46.3%)
≥600 million JPY	223 (51.1%)	25 (43.1%)	142 (54.0%)	21 (51.2%)
Never combustible cigarette smokers	*n=411*	*n=10*	*n=265*	*n=5*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	26 (6.3%)	1 (10.0%)	NA	NA
Low birth weight <2500 g	34 (8.3%)	3 (30.0%)*	NA	NA
Preterm birth <37 weeks	17 (4.1%)	0 (0%)	NA	NA
Imminent preterm birth	69 (16.8%)	3 (30.0%)	NA	NA
Age	32.2 (4.0)	33.3 (2.3)	31.7 (4.3)	30.2 (1.8)
Educational attainment ≥13 years	348 (84.7%)	7 (70%)	235 (88.7%)	4 (80.0%)
Managerial workers	16 (3.9%)	1 (10%)	14 (5.3%)	0 (0%)

Comorbidity of hypertension or diabetes	24 (5.8%)	0 (0%)	4 (1.5%)	0 (0%)
Household income	*n=361*	*n=9*	*n=219*	*n=5*
<200 million JPY	10 (2.8%)	0 (0%)	5 (2.3%)	0 (0%)
200 to <600 million JPY	160 (44.3%)	4 (44.4%)	97 (44.3%)	3 (60.0%)
≥600 million JPY	191 (52.9%)	5 (55.6%)	117 (53.45)	2 (40.0%)
Ever combustible cigarette smokers	*n=82*	*n=55*	*n=54*	*n=41*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	6 (7.3%)	8 (14.5%)	NA	NA
Low birth weight <2500 g	10 (12.2%)	9 (16.4%)	NA	NA
Preterm birth <37 weeks	2 (2.4%)	4 (7.3%)	NA	NA
Imminent preterm birth	13 (15.9%)	15 (27.3%)	NA	NA
Age	33.5 (4.3)	30.5 (4.3)***	32.9 (4.2)	31.4 (5.0)
Educational attainment ≥13 years	62 (75.6%)	30 (54.5%)**	43 (79.6%)	27 (65.9%)
Managerial workers	3 (3.7%)	4 (7.3%)	2 (3.7%)	2 (4.9%)
Comorbidity of hypertension or diabetes	11 (13.4%)	4 (7.3%)	0 (0%)	4 (9.8%)*
Household income	*n=75*	*n=49*	*n=44*	*n=36*
<200 million JPY	3 (4.0%)	3 (6.1%)	1 (2.3%)	1 (2.8%)
200 to <600 million JPY	40 (53.3%)	26 (53.1%)	18 (40.9%)	16 (44.4%)
≥600 million JPY	32 (42.7%)	20 (40.8%)	25 (56.8%)	19 (52.8%)

Abbreviation: HTP, heated tobacco product; NA, not applicable.

*P<0.05, **P<0.01, ***P<0.001 for chi-squared test or t-test.

Table 2. Detailed smoking status and use of heated tobacco products cross-classified according to combustible cigarette smoking status

Characteristics	HTP smoking status			
	Never	Former	Current	Total
Post-delivery women, *n=558*				
Never combustible cigarette smokers	411 (97.6%)	9 (2.1%)	1 (0.2%)	421 (100%)
Former combustible cigarette smokers	79 (64.2%)	32 (26.0%)	12 (9.8%)	123 (100%)
Current combustible cigarette smokers	3 (21.4%)	9 (64.3%)	2 (14.3%)	14 (100%)
Currently pregnant women, *n=365*				
Never combustible cigarette smokers	265 (98.1%)	5 (1.9%)	0 (0%)	270 (100%)
Former combustible cigarette smokers	54 (59.3%)	33 (36.3%)	4 (4.4%)	91 (100%)
Current combustible cigarette smokers	0 (0%)	4 (100%)	0 (0%)	4 (100%)

Abbreviation: HTP, heated tobacco product.

*P<0.05, **P<0.01, ***P<0.001 for chi-squared test or t-test.

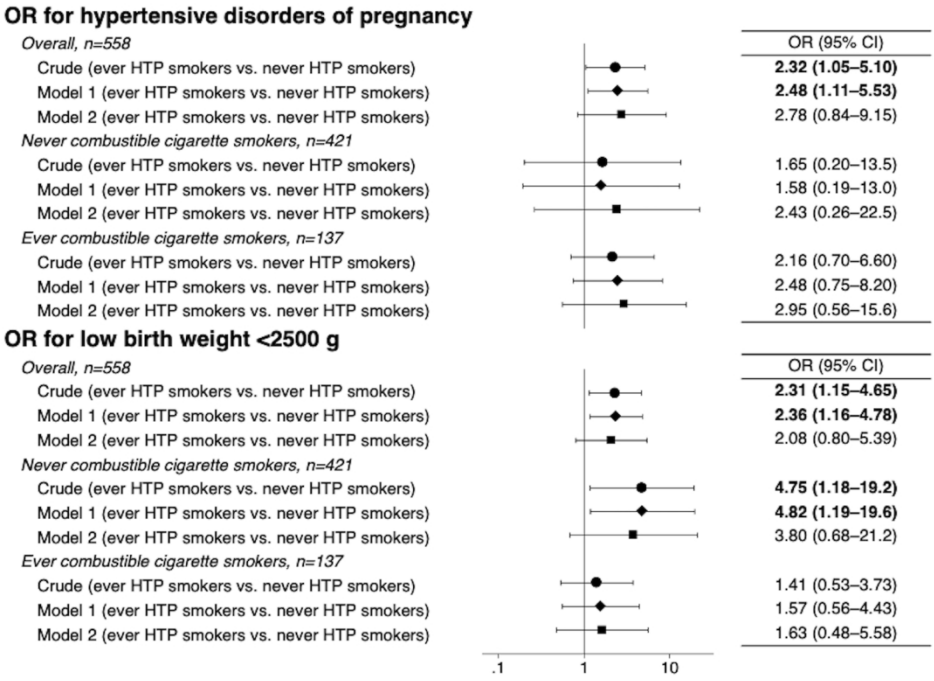

Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight, compared with never heated tobacco product smokers. Age was adjusted in Model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) were additionally adjusted in Model 2. The samples for each analysis in Model 2 were as follows: n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for low birth weight. Abbreviations: HTP, heated tobacco products; OR, Odds ratio.

139x99mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

		Item No	Recommendation
P1-4	**Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
			(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
	Introduction		
P5	Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
P5	Objectives	3	State specific objectives, including any prespecified hypotheses
	Methods		
P6	Study design	4	Present key elements of study design early in the paper
P6	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
P6	Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
P6-8	Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
P6-7	Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
P12	Bias	9	Describe any efforts to address potential sources of bias
P6	Study size	10	Explain how the study size was arrived at
P7-8	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
P8	Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
			(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			(*d*) If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses
	Results		
P8	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
P8-9	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
			(b) Indicate number of participants with missing data for each variable of interest
P8-9	Outcome data	15*	Report numbers of outcome events or summary measures
P8-9	Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
P8-9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

	Discussion		
P9-10	Key results	18	Summarise key results with reference to study objectives
P11-12	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
P9-10	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
P12	Generalisability	21	Discuss the generalisability (external validity) of the study results
	Other information		
P12	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of heated tobacco product use and hypertensive disorders of pregnancy and low birth weight: Analysis of a web-based survey in Japan

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ABSTRACT

Objectives: Knowledge on the impact of heated tobacco product (HTP) use in pregnant women with associated maternal and neonatal risks for hypertensive disorders of pregnancy (HDP) and low birth weight (LBW) is limited. We aimed to assess the status of HTP use among pregnant women in Japan and explore the association of HTP use with HDP and LBW.

Design: cross-sectional study

Setting: Data from the Japan "COVID-19 and Society" Internet Survey study, a web-based nationwide survey

Participants: We investigated 558 post-delivery and 365 currently pregnant women in October 2020.

Primary and secondary outcome measures: Information on HDP and LBW was collected from the post-delivery women's Maternal and Child Health Handbooks (maternal and newborn records). 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.

Results: 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. Among currently pregnant women who were former combustible cigarette smokers, 4.4% (4/91) were current HTP smokers. 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).

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

Keywords: heated tobacco products, hypertensive disorders of pregnancy, COVID-19, smoking, preconception

Strengths and limitations of this study:

- 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

The use of heated tobacco products (HTPs) is an emerging public health concern.[1] 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.[2] This prevalence remained above 15% during the coronavirus disease (COVID-19) pandemic in 2020.[3] 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.[4]

Although the advertisement of HTPs (e.g., reduced harmfulness and a smoke-free image) promotes the impression that HTPs are healthy alternatives to combustible cigarettes,[5] HTP-related unfavorable health outcomes, including acute respiratory and cardiovascular risks, are likely to occur.[6, 7] However, existing knowledge on HTP use and its association with maternal and neonatal risks in pregnant women is limited. The two commonest life-threatening maternal and neonatal risks are hypertensive disorders of pregnancy (HDP) and low birth weight (LBW).[8, 9] Although there are controversial reports on the association between HDP and combustible cigarette use,[10] combustible cigarettes are known to increase various maternal and neonatal risks in Japan.[11, 12] Therefore, in this study, we focused on the association of HTP use with HDP and LBW, which are partly linked to other perinatal risks such as preterm birth.

This study aimed to assess the status of HTP use among pregnant women in Japan and explore HTP-associated perinatal risks, in particular the risk of HDP and LBW, by analyzing data from a nationwide web-based survey in Japan that contained information on pregnancy, behavioral factors (e.g., HTP use and combustible cigarette smoking), and social background.

MATERIALS AND METHODS

Study design, data setting, and participants

This cross-sectional internet-based study is part of the Japan COVID-19 and Society Internet Survey (JACSIS) study. The JACSIS study comprises three surveys in the following three target populations: (a) young people and adults aged 15–79 years, (b) currently pregnant and post-delivery women, and (c) adults living in a single-parent household. The study samples for each survey were retrieved from the pooled panels of an internet research agency (Rakuten Insight, Inc., which had approximately 2.2 million panelists in 2019).[13] We used data from currently pregnant and post-delivery women, which were collected in October 2020.

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.[14] 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.[15] 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).

Definition of HDP and LBW

Data on HDP and LBW were extracted from the web-based self-reported questionnaires. The incidence of HDP was based on whether the study participants had been diagnosed with HDP or preeclampsia during pregnancy. The criteria for HDP diagnosis in Japan were derived from the criteria of the American College of Obstetricians and Gynecologists (i.e., systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg after the 20th week of gestation).[16] The incidence of LBW was defined on the basis of the diagnosis of LBW (birth weight <2500 g). All municipalities issue a handbook to all pregnant women in which medical professionals record the health information of the mother and child, including clinical outcomes (e.g., blood pressure and birth weight) and incident diagnoses (e.g., HDP and LBW) during pregnancy; this is part of a national maternal and child health policy. Mothers seldom lose their Maternal and Child Health Handbooks (losing rate, <1%).[17]

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.[17, 18]

HTP and cigarette smoking and other covariates

In the questionnaire, study participants were asked to indicate their smoking status (never, once or a few times [trial smoking and not habitual], former, sometimes [habitual], or every day) for each HTP that was available in the study period (Ploom Tech, Ploom Tech plus, Ploom S, IQOS, glo, glo sens, and PULZE). 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.

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. The other covariates included age, educational attainment (≤12 years [high school] or ≥13 years [college or university]), occupation (manager or others), household income (<2 million JPY [approximately 20,000 USD], 2 to <6 million JPY, and ≥6 million JPY), and comorbidity (having hypertension or diabetes).[19]

Statistical analysis

Descriptive statistics were computed and compared using the t-test or chi-squared test. The prevalence of ever HTP smokers was assessed among the post-delivery and currently pregnant women. Additionally, the HTP smoking status was cross-classified according to the combustible cigarette smoking status of the currently pregnant and post-delivery women.

To assess the potential association between HTP smoking and perinatal risk of HDP and LBW, the sample was reduced to 558 post-delivery women who could complete all the assessments during their pregnancy (Table 1). In the multivariable logistic regression analyses, the odds ratio (OR) and 95% confidence interval (CI) of ever HTP smokers for HDP risk were estimated after adjustment for age (Model 1, the main model in this study). The never HTP smokers comprised the reference group. In Model 2, full adjustments for other explanatory variables (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) were performed, and 64 participants with missing information on household income were excluded. The same analyses were performed for LBW.

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.

Alpha was set at 0.05, and all *P* values were two sided. Data were analyzed using STATA/MP13.1 (StataCorp LLC, College Station, TX).

Patient and Public Involvement

Neither patients nor the public was involved.

RESULTS

Among 558 post-delivery women, the incidences of HDP and LBW were 7.3% (n=41) and 10.0% (n=56), respectively, and the prevalence of ever HTP smokers was 11.7% (n=65, Table 1). Furthermore, among the 365 currently pregnant women, the prevalence of ever HTP

smokers was 12.6% (n=46), which did not differ from that of HTP smokers among post-delivery women (*P*=0.66).

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 quitted HTP smoking during pregnancy, corresponding to 11.5% (42/365 participants) of currently pregnant women.

Among the post-delivery women, the HDP incidence was higher in ever HTP smokers than in never HTP smokers (13.8% [n=9] vs. 6.5% [n=35], *P*=0.03; Table 1). Similarly, the incidence of LBW was higher among ever HTP smokers than among never HTP smokers (18.5% [n=12] vs. 8.9% [n=44], *P*=0.02; Table 1). When stratified by combustible cigarette smoking, a similar pattern was observed among never and ever combustible cigarette smokers (Table 1).

In the regression analysis, the age-adjusted ORs for HDP and LBW were elevated in ever HTP smokers (Model 1); the ORs for HDP and LBW were 2.48 (95% CI, 1.11–5.53) and 2.36 (95% CI, 1.16–4.78), respectively. 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.

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.

DISCUSSION

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.

To the best of our knowledge, this is the first report of a potential association between HTP use and perinatal risks. Although smoking plays a controversial role,[10] recent evidence suggests that combustible cigarette smoking is associated with increased HDP risk.[11, 12] Although the biological and genetic pathways (e.g., CYP2A6 and nicotine) underlying the associations observed in different phenotypes of HDP (e.g., preeclampsia and gestational hypertension) have not been elucidated,[20] HDP is recognized as a systemic disease attributable to placental circulatory dysfunction.[21] In experimental research, aerosol from HTPs was found to damage vascular endothelial function in rats.[6] Therefore, the association between HDP risk and HTP use may involve acute and chronic vascular damage, irrespective of combustible cigarette smoking. Furthermore, as concluded in a recent systematic review, smoking is a strong risk factor for LBW.[22] Thus, given the fact that HTPs are smoking devices, our observed results are in line with established reports.

Although HTP-related unfavorable health outcomes (e.g., acute respiratory and cardiovascular risks) are likely to occur,[6, 7] the impression of HTPs as a healthy alternative is promoted by HTP use advertisements.[5] 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.[23] 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.[4] However, our findings imply that HTP use is not a healthy alternative. Evidence for unfavorable HTP-related health outcomes is still insufficient, particularly among reproductive age women. In addition, the impact of multidimensional factors of the COVID-19 pandemic (e.g., the infection, mental health, and socioeconomic factors) and the smoking behaviors of others (e.g., partners and family) on the association between HTP use and perinatal risks remains unknown. The ongoing JACSIS study may provide updates in this regard.

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. 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. However, the prevalences of HDP and HTP smokers were mostly parallel to the general population in Japan.[2, 3, 16] The incidence of HTP use did not differ between

post-delivery and currently pregnant women in our study. Second, recall and reporting bias of HTP use could not be discarded, as suggested in a study on combustible cigarette and electronic cigarette smoking.[4] Because self-report-based smoking status among pregnant women tends to misclassify ever smokers as never smokers,[24] our estimates might be biased toward the null. Third, the perinatal clinical information was self-reported and not based on medical charts, thereby limiting the precision of the results. However, 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 during pregnancy.[18] Therefore, this limitation might not have affected our results, or at least not largely. Despite these limitations, all HTPs that were available during the study period were assessed. This is the first report on the status of HTP use among pregnant women in Japan, and it highlights the potentially elevated maternal and neonatal risks associated with HTP use. Additionally, to date, besides the present study, no other human studies have assessed the potential effect of the maternal use of new tobacco products (i.e., e-cigarettes and HTPs) on perinatal health.[25] Therefore, our findings shed light and motivate further investigations to assess the life-threatening perinatal risks associated with new tobacco products.

In conclusion, the incidence of HTP use seems to exceed 10% among pregnant women, and HTP smoking may be associated with increased maternal and neonatal risks in Japan. Undoubtedly, smoking in reproductive age women can cause unfavorable perinatal outcomes.[26] Hence, efforts should be made to investigate the risk of HTP use in reproductive age women, to prevent life-threatening perinatal complications and deaths.

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Data availability statement: The data that support the findings of this study are available on reasonable request. However, restrictions apply to the availability of these data due to personal identification; research data are not shared. If any person wishes to verify our data, they are most welcome to contact the corresponding author.

Conflict of interest: The authors declare no potential conflicts of interest.

Author contributions: MZ and TT designed the study. TT supervised the study. MZ, YH, and SO developed the methodology. SO, AH, and TT created the dataset. MZ and YH analyzed the data. MZ and YH wrote the first draft of the manuscript. SO, AH, GK, and TT commented on the manuscript. All authors read and approved the final version.

Ethics approval: The study was approved by the Institutional Review Board of the Osaka International Cancer Institute approved the study (Protocol Number 20084).

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FIGURE LEGEND

Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight, compared with never heated tobacco product smokers. Age was adjusted in Model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) were additionally adjusted in Model 2. The samples for each analysis in Model 2 were as follows: n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for low birth weight. Abbreviations: HTP, heated tobacco products; OR, Odds ratio.

Table 1. Characteristics of 558 post-delivery women and 365 currently pregnant women

Characteristics	N (%) or mean (SD)			
	Post-delivery women		Currently pregnant women	
	Never HTP smokers	Ever HTP smokers	Never HTP smokers	Ever HTP smokers
Overall	*n=493*	*n=65*	*n=319*	*n=46*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	32 (6.5%)	9 (13.8%)*	NA	NA
Low birth weight <2500 g	44 (8.9%)	12 (18.5%)*	NA	NA
Preterm birth <37 weeks	19 (3.9%)	4 (6.2%)	NA	NA
Imminent preterm birth	82 (16.6%)	18 (27.7%)*	NA	NA
Age	32.4 (4.1)	30.9 (4.2)**	31.9 (4.3)	31.3 (4.7)
Ever combustible cigarette smoking	82 (16.6%)	55 (84.6%)***	54 (16.9%)	41 (89.1%)***
Educational attainment ≥13 years	410 (83.2%)	37 (56.9%)***	278 (87.1%)	31 (67.4%)**
Managerial workers	19 (3.9%)	5 (7.7%)	16 (5.0%)	2 (4.3%)
Comorbidity of hypertension or diabetes	35 (7.1%)	4 (6.2%)	4 (1.3%)	4 (8.7%)**
Household income	*n=436*	*n=58*	*n=263*	*n=41*
<200 million JPY	13 (3.0%)	3 (5.2%)	6 (2.3%)	1 (2.4%)
200 to <600 million JPY	200 (45.9%)	30 (51.7%)	115 (43.7%)	19 (46.3%)
≥600 million JPY	223 (51.1%)	25 (43.1%)	142 (54.0%)	21 (51.2%)
Never combustible cigarette smokers	*n=411*	*n=10*	*n=265*	*n=5*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	26 (6.3%)	1 (10.0%)	NA	NA
Low birth weight <2500 g	34 (8.3%)	3 (30.0%)*	NA	NA
Preterm birth <37 weeks	17 (4.1%)	0 (0%)	NA	NA
Imminent preterm birth	69 (16.8%)	3 (30.0%)	NA	NA
Age	32.2 (4.0)	33.3 (2.3)	31.7 (4.3)	30.2 (1.8)
Educational attainment ≥13 years	348 (84.7%)	7 (70%)	235 (88.7%)	4 (80.0%)
Managerial workers	16 (3.9%)	1 (10%)	14 (5.3%)	0 (0%)

Comorbidity of hypertension or diabetes	24 (5.8%)	0 (0%)	4 (1.5%)	0 (0%)
Household income	*n=361*	*n=9*	*n=219*	*n=5*
<200 million JPY	10 (2.8%)	0 (0%)	5 (2.3%)	0 (0%)
200 to <600 million JPY	160 (44.3%)	4 (44.4%)	97 (44.3%)	3 (60.0%)
≥600 million JPY	191 (52.9%)	5 (55.6%)	117 (53.45)	2 (40.0%)
Ever combustible cigarette smokers	*n=82*	*n=55*	*n=54*	*n=41*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	6 (7.3%)	8 (14.5%)	NA	NA
Low birth weight <2500 g	10 (12.2%)	9 (16.4%)	NA	NA
Preterm birth <37 weeks	2 (2.4%)	4 (7.3%)	NA	NA
Imminent preterm birth	13 (15.9%)	15 (27.3%)	NA	NA
Age	33.5 (4.3)	30.5 (4.3)***	32.9 (4.2)	31.4 (5.0)
Educational attainment ≥13 years	62 (75.6%)	30 (54.5%)**	43 (79.6%)	27 (65.9%)
Managerial workers	3 (3.7%)	4 (7.3%)	2 (3.7%)	2 (4.9%)
Comorbidity of hypertension or diabetes	11 (13.4%)	4 (7.3%)	0 (0%)	4 (9.8%)*
Household income	*n=75*	*n=49*	*n=44*	*n=36*
<200 million JPY	3 (4.0%)	3 (6.1%)	1 (2.3%)	1 (2.8%)
200 to <600 million JPY	40 (53.3%)	26 (53.1%)	18 (40.9%)	16 (44.4%)
≥600 million JPY	32 (42.7%)	20 (40.8%)	25 (56.8%)	19 (52.8%)

Abbreviation: HTP, heated tobacco product; NA, not applicable.

*P<0.05, **P<0.01, ***P<0.001 for chi-squared test or t-test.

Table 2. Smoking status and use of heated tobacco products cross-classified according to combustible cigarette smoking status

Characteristics	HTP smoking status			
	Never	Former	Current	Total
Post-delivery women, *total*	493 (88.4%)	50 (9.0%)	15 (2.7%)	558 (100%)
Never combustible cigarette smokers	411 (97.6%)	9 (2.1%)	1 (0.2%)	421 (100%)
Former combustible cigarette smokers	79 (64.2%)	32 (26.0%)	12 (9.8%)	123 (100%)
Current combustible cigarette smokers	3 (21.4%)	9 (64.3%)	2 (14.3%)	14 (100%)
Currently pregnant women, *total*	319 (87.4%)	42 (11.5%)	4 (1.1%)	365 (100%)
Never combustible cigarette smokers	265 (98.1%)	5 (1.9%)	0 (0%)	270 (100%)
Former combustible cigarette smokers	54 (59.3%)	33 (36.3%)	4 (4.4%)	91 (100%)
Current combustible cigarette smokers	0 (0%)	4 (100%)	0 (0%)	4 (100%)

Abbreviation: HTP, heated tobacco product.

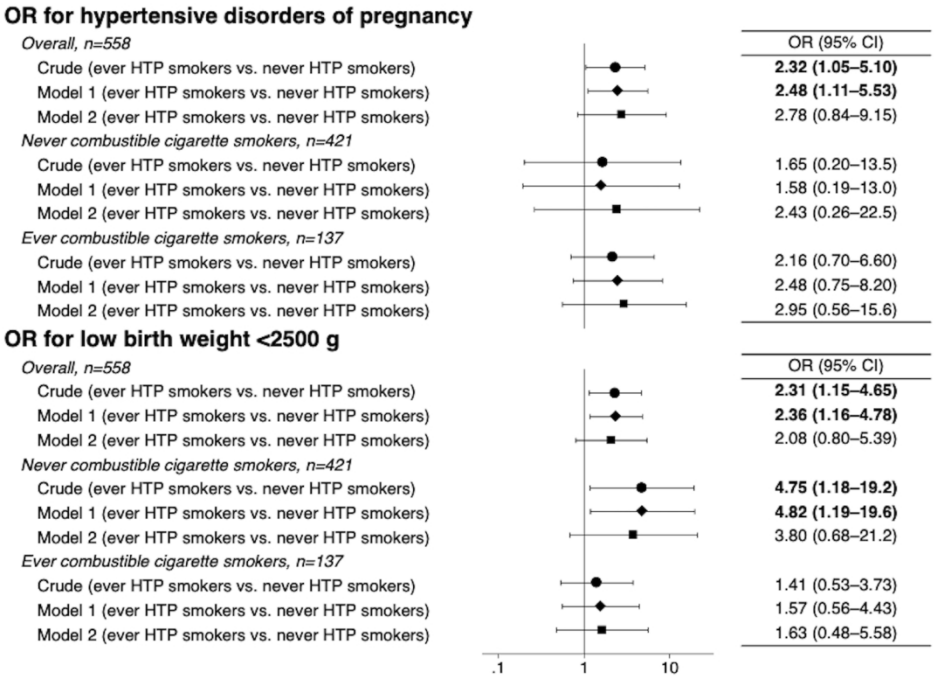

Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight, compared with never heated tobacco product smokers. Age was adjusted in Model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) were additionally adjusted in Model 2. The samples for each analysis in Model 2 were as follows: n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for low birth weight. Abbreviations: HTP, heated tobacco products; OR, Odds ratio.

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Checklist for Reporting Results of Internet E-Surveys (CHERRIES)

Checklist Item	***Explanation***	***Page Number***
Describe survey design	Describe target population, sample frame. Is the sample a convenience sample? (In "open" surveys this is most likely.)	P5
IRB approval	Mention whether the study has been approved by an IRB.	P6
Informed consent	Describe the informed consent process. Where were the participants told the length of time of the survey, which data were stored and where and for how long, who the investigator was, and the purpose of the study?	P6
Data protection	If any personal information was collected or stored, describe what mechanisms were used to protect unauthorized access.	P5
Development and testing	State how the survey was developed, including whether the usability and technical functionality of the electronic questionnaire had been tested before fielding the questionnaire.	P5
Open survey versus closed survey	An "open survey" is a survey open for each visitor of a site, while a closed survey is only open to a sample which the investigator knows (password-protected survey).	P5
Contact mode	Indicate whether or not the initial contact with the potential participants was made on the Internet. (Investigators may also send out questionnaires by mail and allow for Web-based data entry.)	P5
Advertising the survey	How/where was the survey announced or advertised? Some examples are offline media (newspapers), or online (mailing lists – If yes, which ones?) or banner ads (Where were these banner ads posted and what did they look like?). It is important to know the wording of the announcement as it will heavily influence who chooses to participate. Ideally the survey announcement should be published as an appendix.	P5
Web/E-mail	State the type of e-survey (eg, one posted on a Web site, or one sent out through e-mail). If it is an e-mail survey, were the responses entered manually into a database, or was there an automatic method for capturing responses?	P5
Context	Describe the Web site (for mailing list/newsgroup) in which the survey was posted. What is the Web site about, who is visiting it, what are visitors normally looking for? Discuss to what degree the content of the Web site could pre-select the sample or influence the results. For example, a survey about vaccination on a anti-immunization Web site will have different results from a Web survey conducted on a government Web site	P5
Mandatory/voluntary	Was it a mandatory survey to be filled in by every visitor who wanted to enter the Web site, or was it a voluntary survey?	P5
Incentives	Were any incentives offered (eg, monetary, prizes, or non-monetary incentives such as an offer to provide the survey results)?	Yes (P5)

Time/Date	In what timeframe were the data collected?	P5
Randomization of items or questionnaires	To prevent biases items can be randomized or alternated.	Not used
Adaptive questioning	Use adaptive questioning (certain items, or only conditionally displayed based on responses to other items) to reduce number and complexity of the questions.	Yes
Number of Items	What was the number of questionnaire items per page? The number of items is an important factor for the completion rate.	P5
Number of screens (pages)	Over how many pages was the questionnaire distributed? The number of items is an important factor for the completion rate.	P5
Completeness check	It is technically possible to do consistency or completeness checks before the questionnaire is submitted. Was this done, and if “yes”, how (usually JAVAScript)? An alternative is to check for completeness after the questionnaire has been submitted (and highlight mandatory items). If this has been done, it should be reported. All items should provide a non-response option such as “not applicable” or “rather not say”, and selection of one response option should be enforced.	No
Review step	State whether respondents were able to review and change their answers (eg, through a Back button or a Review step which displays a summary of the responses and asks the respondents if they are correct).	No
Unique site visitor	If you provide view rates or participation rates, you need to define how you determined a unique visitor. There are different techniques available, based on IP addresses or cookies or both.	P5
View rate (Ratio of unique survey visitors/unique site visitors)	Requires counting unique visitors to the first page of the survey, divided by the number of unique site visitors (not page views!). It is not unusual to have view rates of less than 0.1 % if the survey is voluntary.	N/A
Participation rate (Ratio of unique visitors who agreed to participate/unique first survey page visitors)	Count the unique number of people who filled in the first survey page (or agreed to participate, for example by checking a checkbox), divided by visitors who visit the first page of the survey (or the informed consents page, if present). This can also be called “recruitment” rate.	P5
Completion rate (Ratio of users who finished the survey/users who	The number of people submitting the last questionnaire page, divided by the number of people who agreed to participate (or submitted the first survey page). This is only relevant if there is a separate “informed consent” page or if the survey goes over several pages. This is a measure for attrition. Note that	N/A

agreed to participate)	"completion" can involve leaving questionnaire items blank. This is not a measure for how completely questionnaires were filled in. (If you need a measure for this, use the word "completeness rate".)	
Cookies used	Indicate whether cookies were used to assign a unique user identifier to each client computer. If so, mention the page on which the cookie was set and read, and how long the cookie was valid. Were duplicate entries avoided by preventing users access to the survey twice; or were duplicate database entries having the same user ID eliminated before analysis? In the latter case, which entries were kept for analysis (eg, the first entry or the most recent)?	P5
IP check	Indicate whether the IP address of the client computer was used to identify potential duplicate entries from the same user. If so, mention the period of time for which no two entries from the same IP address were allowed (eg, 24 hours). Were duplicate entries avoided by preventing users with the same IP address access to the survey twice; or were duplicate database entries having the same IP address within a given period of time eliminated before analysis? If the latter, which entries were kept for analysis (eg, the first entry or the most recent)?	P5
Log file analysis	Indicate whether other techniques to analyze the log file for identification of multiple entries were used. If so, please describe.	P5
Registration	In "closed" (non-open) surveys, users need to login first and it is easier to prevent duplicate entries from the same user. Describe how this was done. For example, was the survey never displayed a second time once the user had filled it in, or was the username stored together with the survey results and later eliminated? If the latter, which entries were kept for analysis (eg, the first entry or the most recent)?	P5
Handling of incomplete questionnaires	Were only completed questionnaires analyzed? Were questionnaires which terminated early (where, for example, users did not go through all questionnaire pages) also analyzed?	P5
Questionnaires submitted with an atypical timestamp	Some investigators may measure the time people needed to fill in a questionnaire and exclude questionnaires that were submitted too soon. Specify the timeframe that was used as a cut-off point, and describe how this point was determined.	Not used
Statistical correction	Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for the non-representative sample; if so, please describe the methods.	Not used

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Heated tobacco product use and hypertensive disorders of pregnancy and low birth weight: Analysis of a cross-sectional, web-based survey in Japan

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ABSTRACT

Objectives: Knowledge on the impact of heated tobacco product (HTP) use in pregnant women with associated maternal and neonatal risks for hypertensive disorders of pregnancy (HDP) and low birth weight (LBW) is limited. We aimed to assess the status of HTP use among pregnant women in Japan and explore the association of HTP use with HDP and LBW.

Design: cross-sectional study

Setting: Data from the Japan "COVID-19 and Society" Internet Survey study, a web-based nationwide survey

Participants: We investigated 558 post-delivery and 365 currently pregnant women in October 2020.

Primary and secondary outcome measures: Information on HDP and LBW was collected from the post-delivery women's Maternal and Child Health Handbooks (maternal and newborn records). 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.

Results: 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. Among currently pregnant women who were former combustible cigarette smokers, 4.4% (4/91) were current HTP smokers. 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).

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

Keywords: heated tobacco products, hypertensive disorders of pregnancy, COVID-19, smoking, preconception

Strengths and limitations of this study:

- 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 study had a small sample size and thus involved a selection bias and reduced statistical precision, and causal mechanisms could not be 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

The use of heated tobacco products (HTPs) is an emerging public health concern.[1] 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.[2] This prevalence remained above 15% during the coronavirus disease (COVID-19) pandemic in 2020.[3] 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.[4]

Although the advertisement of HTPs (e.g., reduced harmfulness and a smoke-free image) promotes the impression that HTPs are healthy alternatives to combustible cigarettes,[5] HTP-related unfavorable health outcomes, including acute respiratory and cardiovascular risks, are likely to occur.[6, 7] However, existing knowledge on HTP use and its association with maternal and neonatal risks in pregnant women is limited. The two commonest life-threatening maternal and neonatal risks are hypertensive disorders of pregnancy (HDP) and low birth weight (LBW).[8, 9] Although there are controversial reports on the association between HDP and combustible cigarette use,[10] combustible cigarettes are known to increase various maternal and neonatal risks in Japan.[11, 12] Therefore, in this study, we focused on the association of HTP use with HDP and LBW, which are partly linked to other perinatal risks such as preterm birth.

This study aimed to assess the status of HTP use among pregnant women in Japan and explore HTP-associated perinatal risks, in particular the risk of HDP and LBW, by analyzing data from a nationwide web-based survey in Japan that contained information on pregnancy, behavioral factors (e.g., HTP use and combustible cigarette smoking), and social background.

MATERIALS AND METHODS

Study design, data setting, and participants

This cross-sectional internet-based study is part of the Japan COVID-19 and Society Internet Survey (JACSIS) study. The JACSIS study comprises three surveys in the following three target populations: (a) young people and adults aged 15–79 years, (b) currently pregnant and post-delivery women, and (c) adults living in a single-parent household. The study samples for each survey were retrieved from the pooled panels of an internet research agency (Rakuten Insight, Inc., which had approximately 2.2 million panelists in 2019).[13] We used data from currently pregnant and post-delivery women, which were collected in October 2020.

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.[14] 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.[15] 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).

Definition of HDP and LBW

Data on HDP and LBW were extracted from the web-based self-reported questionnaires. The incidence of HDP was based on whether the study participants had been diagnosed with HDP or preeclampsia during pregnancy. The criteria for HDP diagnosis in Japan were derived from the criteria of the American College of Obstetricians and Gynecologists (i.e., systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg after the 20th week of gestation).[16] The incidence of LBW was defined on the basis of the diagnosis of LBW (birth weight <2500 g). All municipalities issue a handbook to all pregnant women in which medical professionals record the health information of the mother and child, including clinical outcomes (e.g., blood pressure and birth weight) and incident diagnoses (e.g., HDP and LBW) during pregnancy; this is part of a national maternal and child health policy. Mothers seldom lose their Maternal and Child Health Handbooks (losing rate, <1%).[17]

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.[17, 18]

HTP and cigarette smoking and other covariates

In the questionnaire, study participants were asked to indicate their smoking status (never, once or a few times [trial smoking and not habitual], former, sometimes [habitual], or every day) for each HTP that was available in the study period (Ploom Tech, Ploom Tech plus, Ploom S, IQOS, glo, glo sens, and PULZE). 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.

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. The other covariates included age, educational attainment (≤12 years [high school] or ≥13 years [college or university]), occupation (manager or others), household income (<2 million JPY [approximately 20,000 USD], 2 to <6 million JPY, and ≥6 million JPY), and comorbidity (having hypertension or diabetes).[19]

Statistical analysis

Descriptive statistics were computed and compared using the t-test or chi-squared test. The prevalence of ever HTP smokers was assessed among the post-delivery and currently pregnant women. Additionally, the HTP smoking status was cross-classified according to the combustible cigarette smoking status of the currently pregnant and post-delivery women.

To assess the potential association between HTP smoking and perinatal risk of HDP and LBW, the sample was reduced to 558 post-delivery women who could complete all the assessments during their pregnancy (Table 1). In the multivariable logistic regression analyses, the odds ratio (OR) and 95% confidence interval (CI) of ever HTP smokers for HDP risk were estimated after adjustment for age (Model 1, the main model in this study). The never HTP smokers comprised the reference group. In Model 2, full adjustments for other explanatory variables (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) were performed, and 64 participants with missing information on household income were excluded. The same analyses were performed for LBW.

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.

Alpha was set at 0.05, and all *P* values were two sided. Data were analyzed using STATA/MP13.1 (StataCorp LLC, College Station, TX).

Patient and Public Involvement

Neither patients nor the public was involved.

RESULTS

Among 558 post-delivery women, the incidences of HDP and LBW were 7.3% (n=41) and 10.0% (n=56), respectively, and the prevalence of ever HTP smokers was 11.7% (n=65, Table 1). Furthermore, among the 365 currently pregnant women, the prevalence of ever HTP

smokers was 12.6% (n=46), which did not differ from that of HTP smokers among post-delivery women (*P*=0.66).

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 quitted HTP smoking during pregnancy, corresponding to 11.5% (42/365 participants) of currently pregnant women.

Among the post-delivery women, the HDP incidence was higher in ever HTP smokers than in never HTP smokers (13.8% [n=9] vs. 6.5% [n=35], *P*=0.03; Table 1). Similarly, the incidence of LBW was higher among ever HTP smokers than among never HTP smokers (18.5% [n=12] vs. 8.9% [n=44], *P*=0.02; Table 1). When stratified by combustible cigarette smoking, a similar pattern was observed among never and ever combustible cigarette smokers (Table 1).

In the regression analysis, the age-adjusted ORs for HDP and LBW were elevated in ever HTP smokers (Model 1); the ORs for HDP and LBW were 2.48 (95% CI, 1.11–5.53) and 2.36 (95% CI, 1.16–4.78), respectively. 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.

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.

DISCUSSION

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.

To the best of our knowledge, this is the first report of a potential association between HTP use and perinatal risks. Although smoking plays a controversial role,[10] recent evidence suggests that combustible cigarette smoking is associated with increased HDP risk.[11, 12] Although the biological and genetic pathways (e.g., CYP2A6 and nicotine) underlying the associations observed in different phenotypes of HDP (e.g., preeclampsia and gestational hypertension) have not been elucidated,[20] HDP is recognized as a systemic disease attributable to placental circulatory dysfunction.[21] In experimental research, aerosol from HTPs was found to damage vascular endothelial function in rats.[6] Therefore, the association between HDP risk and HTP use may involve acute and chronic vascular damage, irrespective of combustible cigarette smoking. Furthermore, as concluded in a recent systematic review, smoking is a strong risk factor for LBW.[22] Thus, given the fact that HTPs are smoking devices, our observed results are in line with established reports.

Although HTP-related unfavorable health outcomes (e.g., acute respiratory and cardiovascular risks) are likely to occur,[6, 7] the impression of HTPs as a healthy alternative is promoted by HTP use advertisements.[5] 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.[23] 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.[4] However, our findings imply that HTP use is not a healthy alternative. Evidence for unfavorable HTP-related health outcomes is still insufficient, particularly among reproductive age women. In addition, the impact of multidimensional factors of the COVID-19 pandemic (e.g., the infection, mental health, and socioeconomic factors) and the smoking behaviors of others (e.g., partners and family) on the association between HTP use and perinatal risks remains unknown. The ongoing JACSIS study may provide updates in this regard.

Our study has limitations. First, this web-based, self-reported, cross-sectional study had a small sample size, which may thus involve a selection bias and weak statistical precision, and it cannot provide an explanation of the causal mechanisms between HTP use and perinatal risks. 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. However, the prevalences of HDP and HTP smokers were mostly parallel to the general population in Japan.[2, 3, 16] The

incidence of HTP use did not differ between post-delivery and currently pregnant women in our study. Second, recall and reporting bias of HTP use could not be discarded, as suggested in a study on combustible cigarette and electronic cigarette smoking.[4] Because self-report-based smoking status among pregnant women tends to misclassify ever smokers as never smokers,[24] our estimates might be biased toward the null. Third, the perinatal clinical information was self-reported and not based on medical charts, thereby limiting the precision of the results. However, 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 during pregnancy.[18] Therefore, this limitation might not have affected our results, or at least not largely. Despite these limitations, all HTPs that were available during the study period were assessed. This is the first report on the status of HTP use among pregnant women in Japan, and it highlights the potentially elevated maternal and neonatal risks associated with HTP use. Additionally, to date, besides the present study, no other human studies have assessed the potential effect of the maternal use of new tobacco products (i.e., e-cigarettes and HTPs) on perinatal health.[25] Therefore, our findings shed light and motivate further investigations to assess the life-threatening perinatal risks associated with new tobacco products.

In conclusion, the incidence of HTP use seems to exceed 10% among pregnant women, and HTP smoking may be associated with increased maternal and neonatal risks in Japan. Undoubtedly, smoking in reproductive age women can cause unfavorable perinatal outcomes.[26] Hence, efforts should be made to investigate the risk of HTP use in reproductive age women, to prevent life-threatening perinatal complications and deaths.

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Data availability statement: The data that support the findings of this study are available on reasonable request. However, restrictions apply to the availability of these data due to personal identification; research data are not shared. If any person wishes to verify our data, they are most welcome to contact the corresponding author.

Conflict of interest: The authors declare no potential conflicts of interest.

Author contributions: MZ and TT designed the study. TT supervised the study. MZ, YH, and SO developed the methodology. SO, AH, and TT created the dataset. MZ and YH analyzed the data. MZ and YH wrote the first draft of the manuscript. SO, AH, GK, and TT commented on the manuscript. All authors read and approved the final version.

Ethics approval: The study was approved by the Institutional Review Board of the Osaka International Cancer Institute approved the study (Protocol Number 20084).

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FIGURE LEGEND

Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight, compared with never heated tobacco product smokers. Age was adjusted in Model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) were additionally adjusted in Model 2. The samples for each analysis in Model 2 were as follows: n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for low birth weight. Abbreviations: HTP, heated tobacco products; OR, Odds ratio.

389 **Table 1. Characteristics of 558 post-delivery women and 365 currently pregnant women**

Characteristics	N (%) or mean (SD)			
	Post-delivery women		Currently pregnant women	
	Never HTP smokers	Ever HTP smokers	Never HTP smokers	Ever HTP smokers
Overall	*n=493*	*n=65*	*n=319*	*n=46*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	32 (6.5%)	9 (13.8%)*	NA	NA
Low birth weight <2500 g	44 (8.9%)	12 (18.5%)*	NA	NA
Preterm birth <37 weeks	19 (3.9%)	4 (6.2%)	NA	NA
Imminent preterm birth	82 (16.6%)	18 (27.7%)*	NA	NA
Age	32.4 (4.1)	30.9 (4.2)**	31.9 (4.3)	31.3 (4.7)
Ever combustible cigarette smoking	82 (16.6%)	55 (84.6%)***	54 (16.9%)	41 (89.1%)***
Educational attainment ≥13 years	410 (83.2%)	37 (56.9%)***	278 (87.1%)	31 (67.4%)**
Managerial workers	19 (3.9%)	5 (7.7%)	16 (5.0%)	2 (4.3%)
Comorbidity of hypertension or diabetes	35 (7.1%)	4 (6.2%)	4 (1.3%)	4 (8.7%)**
Household income	*n=436*	*n=58*	*n=263*	*n=41*
<200 million JPY	13 (3.0%)	3 (5.2%)	6 (2.3%)	1 (2.4%)
200 to <600 million JPY	200 (45.9%)	30 (51.7%)	115 (43.7%)	19 (46.3%)
≥600 million JPY	223 (51.1%)	25 (43.1%)	142 (54.0%)	21 (51.2%)
Never combustible cigarette smokers	*n=411*	*n=10*	*n=265*	*n=5*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	26 (6.3%)	1 (10.0%)	NA	NA
Low birth weight <2500 g	34 (8.3%)	3 (30.0%)*	NA	NA
Preterm birth <37 weeks	17 (4.1%)	0 (0%)	NA	NA
Imminent preterm birth	69 (16.8%)	3 (30.0%)	NA	NA
Age	32.2 (4.0)	33.3 (2.3)	31.7 (4.3)	30.2 (1.8)
Educational attainment ≥13 years	348 (84.7%)	7 (70%)	235 (88.7%)	4 (80.0%)
Managerial workers	16 (3.9%)	1 (10%)	14 (5.3%)	0 (0%)

Comorbidity of hypertension or diabetes	24 (5.8%)	0 (0%)	4 (1.5%)	0 (0%)
Household income	*n=361*	*n=9*	*n=219*	*n=5*
<200 million JPY	10 (2.8%)	0 (0%)	5 (2.3%)	0 (0%)
200 to <600 million JPY	160 (44.3%)	4 (44.4%)	97 (44.3%)	3 (60.0%)
≥600 million JPY	191 (52.9%)	5 (55.6%)	117 (53.45)	2 (40.0%)
Ever combustible cigarette smokers	*n=82*	*n=55*	*n=54*	*n=41*
Maternal and neonatal risk				
Hypertensive disorders of pregnancy	6 (7.3%)	8 (14.5%)	NA	NA
Low birth weight <2500 g	10 (12.2%)	9 (16.4%)	NA	NA
Preterm birth <37 weeks	2 (2.4%)	4 (7.3%)	NA	NA
Imminent preterm birth	13 (15.9%)	15 (27.3%)	NA	NA
Age	33.5 (4.3)	30.5 (4.3)***	32.9 (4.2)	31.4 (5.0)
Educational attainment ≥13 years	62 (75.6%)	30 (54.5%)**	43 (79.6%)	27 (65.9%)
Managerial workers	3 (3.7%)	4 (7.3%)	2 (3.7%)	2 (4.9%)
Comorbidity of hypertension or diabetes	11 (13.4%)	4 (7.3%)	0 (0%)	4 (9.8%)*
Household income	*n=75*	*n=49*	*n=44*	*n=36*
<200 million JPY	3 (4.0%)	3 (6.1%)	1 (2.3%)	1 (2.8%)
200 to <600 million JPY	40 (53.3%)	26 (53.1%)	18 (40.9%)	16 (44.4%)
≥600 million JPY	32 (42.7%)	20 (40.8%)	25 (56.8%)	19 (52.8%)

390 Abbreviation: HTP, heated tobacco product; NA, not applicable.

391 *P<0.05, **P<0.01, ***P<0.001 for chi-squared test or t-test.

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Table 2. Smoking status and use of heated tobacco products cross-classified according to combustible cigarette smoking status

Characteristics	HTP smoking status			
	Never	Former	Current	Total
Post-delivery women, *total*	493 (88.4%)	50 (9.0%)	15 (2.7%)	558 (100%)
Never combustible cigarette smokers	411 (97.6%)	9 (2.1%)	1 (0.2%)	421 (100%)
Former combustible cigarette smokers	79 (64.2%)	32 (26.0%)	12 (9.8%)	123 (100%)
Current combustible cigarette smokers	3 (21.4%)	9 (64.3%)	2 (14.3%)	14 (100%)
Currently pregnant women, *total*	319 (87.4%)	42 (11.5%)	4 (1.1%)	365 (100%)
Never combustible cigarette smokers	265 (98.1%)	5 (1.9%)	0 (0%)	270 (100%)
Former combustible cigarette smokers	54 (59.3%)	33 (36.3%)	4 (4.4%)	91 (100%)
Current combustible cigarette smokers	0 (0%)	4 (100%)	0 (0%)	4 (100%)

Abbreviation: HTP, heated tobacco product.

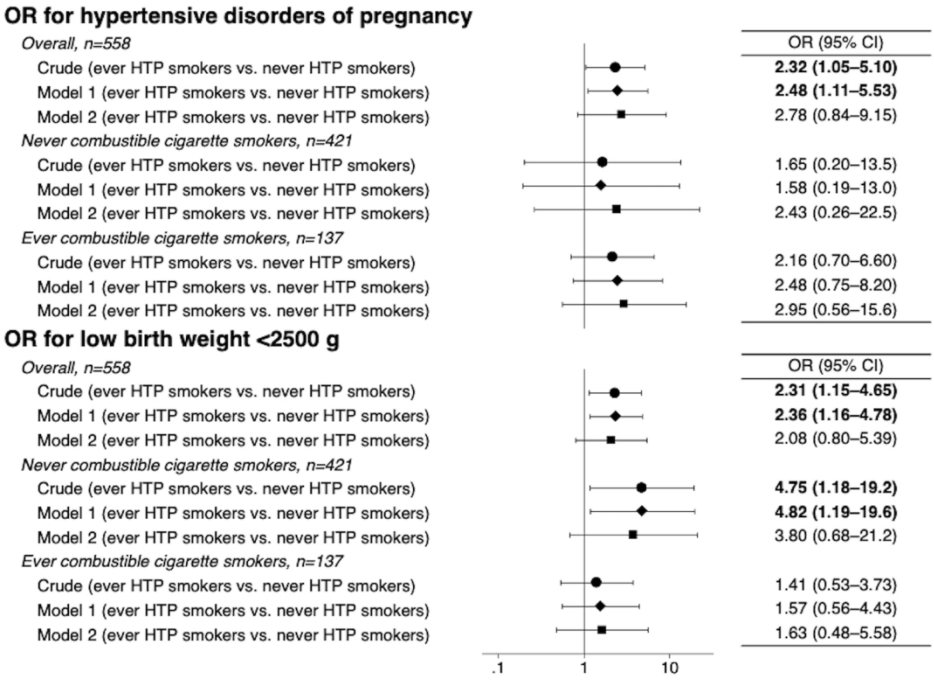

Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight, compared with never heated tobacco product smokers. Age was adjusted in Model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household income, and comorbidity) were additionally adjusted in Model 2. The samples for each analysis in Model 2 were as follows: n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for low birth weight. Abbreviations: HTP, heated tobacco products; OR, Odds ratio.

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Checklist for Reporting Results of Internet E-Surveys (CHERRIES)

Checklist Item	***Explanation***	***Page Number***
Describe survey design	Describe target population, sample frame. Is the sample a convenience sample? (In "open" surveys this is most likely.)	P5
IRB approval	Mention whether the study has been approved by an IRB.	P6
Informed consent	Describe the informed consent process. Where were the participants told the length of time of the survey, which data were stored and where and for how long, who the investigator was, and the purpose of the study?	P6
Data protection	If any personal information was collected or stored, describe what mechanisms were used to protect unauthorized access.	P5
Development and testing	State how the survey was developed, including whether the usability and technical functionality of the electronic questionnaire had been tested before fielding the questionnaire.	P5
Open survey versus closed survey	An "open survey" is a survey open for each visitor of a site, while a closed survey is only open to a sample which the investigator knows (password-protected survey).	P5
Contact mode	Indicate whether or not the initial contact with the potential participants was made on the Internet. (Investigators may also send out questionnaires by mail and allow for Web-based data entry.)	P5
Advertising the survey	How/where was the survey announced or advertised? Some examples are offline media (newspapers), or online (mailing lists – If yes, which ones?) or banner ads (Where were these banner ads posted and what did they look like?). It is important to know the wording of the announcement as it will heavily influence who chooses to participate. Ideally the survey announcement should be published as an appendix.	P5
Web/E-mail	State the type of e-survey (eg, one posted on a Web site, or one sent out through e-mail). If it is an e-mail survey, were the responses entered manually into a database, or was there an automatic method for capturing responses?	P5
Context	Describe the Web site (for mailing list/newsgroup) in which the survey was posted. What is the Web site about, who is visiting it, what are visitors normally looking for? Discuss to what degree the content of the Web site could pre-select the sample or influence the results. For example, a survey about vaccination on a anti-immunization Web site will have different results from a Web survey conducted on a government Web site	P5
Mandatory/voluntary	Was it a mandatory survey to be filled in by every visitor who wanted to enter the Web site, or was it a voluntary survey?	P5
Incentives	Were any incentives offered (eg, monetary, prizes, or non-monetary incentives such as an offer to provide the survey results)?	Yes (P5)

Time/Date	In what timeframe were the data collected?	P5
Randomization of items or questionnaires	To prevent biases items can be randomized or alternated.	Not used
Adaptive questioning	Use adaptive questioning (certain items, or only conditionally displayed based on responses to other items) to reduce number and complexity of the questions.	Yes
Number of Items	What was the number of questionnaire items per page? The number of items is an important factor for the completion rate.	P5
Number of screens (pages)	Over how many pages was the questionnaire distributed? The number of items is an important factor for the completion rate.	P5
Completeness check	It is technically possible to do consistency or completeness checks before the questionnaire is submitted. Was this done, and if “yes”, how (usually JAVAScript)? An alternative is to check for completeness after the questionnaire has been submitted (and highlight mandatory items). If this has been done, it should be reported. All items should provide a non-response option such as “not applicable” or “rather not say”, and selection of one response option should be enforced.	No
Review step	State whether respondents were able to review and change their answers (eg, through a Back button or a Review step which displays a summary of the responses and asks the respondents if they are correct).	No
Unique site visitor	If you provide view rates or participation rates, you need to define how you determined a unique visitor. There are different techniques available, based on IP addresses or cookies or both.	P5
View rate (Ratio of unique survey visitors/unique site visitors)	Requires counting unique visitors to the first page of the survey, divided by the number of unique site visitors (not page views!). It is not unusual to have view rates of less than 0.1 % if the survey is voluntary.	N/A
Participation rate (Ratio of unique visitors who agreed to participate/unique first survey page visitors)	Count the unique number of people who filled in the first survey page (or agreed to participate, for example by checking a checkbox), divided by visitors who visit the first page of the survey (or the informed consents page, if present). This can also be called “recruitment” rate.	P5
Completion rate (Ratio of users who finished the survey/users who	The number of people submitting the last questionnaire page, divided by the number of people who agreed to participate (or submitted the first survey page). This is only relevant if there is a separate “informed consent” page or if the survey goes over several pages. This is a measure for attrition. Note that	N/A

agreed to participate)	"completion" can involve leaving questionnaire items blank. This is not a measure for how completely questionnaires were filled in. (If you need a measure for this, use the word "completeness rate".)	
Cookies used	Indicate whether cookies were used to assign a unique user identifier to each client computer. If so, mention the page on which the cookie was set and read, and how long the cookie was valid. Were duplicate entries avoided by preventing users access to the survey twice; or were duplicate database entries having the same user ID eliminated before analysis? In the latter case, which entries were kept for analysis (eg, the first entry or the most recent)?	P5
IP check	Indicate whether the IP address of the client computer was used to identify potential duplicate entries from the same user. If so, mention the period of time for which no two entries from the same IP address were allowed (eg, 24 hours). Were duplicate entries avoided by preventing users with the same IP address access to the survey twice; or were duplicate database entries having the same IP address within a given period of time eliminated before analysis? If the latter, which entries were kept for analysis (eg, the first entry or the most recent)?	P5
Log file analysis	Indicate whether other techniques to analyze the log file for identification of multiple entries were used. If so, please describe.	P5
Registration	In "closed" (non-open) surveys, users need to login first and it is easier to prevent duplicate entries from the same user. Describe how this was done. For example, was the survey never displayed a second time once the user had filled it in, or was the username stored together with the survey results and later eliminated? If the latter, which entries were kept for analysis (eg, the first entry or the most recent)?	P5
Handling of incomplete questionnaires	Were only completed questionnaires analyzed? Were questionnaires which terminated early (where, for example, users did not go through all questionnaire pages) also analyzed?	P5
Questionnaires submitted with an atypical timestamp	Some investigators may measure the time people needed to fill in a questionnaire and exclude questionnaires that were submitted too soon. Specify the timeframe that was used as a cut-off point, and describe how this point was determined.	Not used
Statistical correction	Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for the non-representative sample; if so, please describe the methods.	Not used