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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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3 **1 Use of heated tobacco products may be associated with hypertensive disorders of**
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5 **2 pregnancy and low birth weight in Japan: An analysis of the JACSIS study**
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2
3 24 **ABSTRACT**
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5 25 **Background:** Little is known about heated tobacco product (HTP) use in pregnant women
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8 26 and associated maternal and neonatal risks for hypertensive disorders of pregnancy (HDP)
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10 27 and low birth weight (LBW). Thus, this study aimed to assess the status of HTP use among
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12 28 pregnant women in Japan and explore the risk of HDP and LBW associated with HTP use.

13
14 29 **Methods:** Using data from the Japan “COVID-19 and Society” Internet Survey (JACSIS)
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16
17 30 study, a web-based nationwide survey, we investigated 558 post-delivery and 365 currently
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19 31 pregnant women in October 2020. We assessed the prevalence of ever HTP smokers (defined
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21 32 as ever experiencing HTP use) in post-delivery and currently pregnant women. Among post-
22
23 33 delivery women, we collected the information regarding HDP and LBW based on their
24
25 34 Maternal and Child Health Handbooks (maternal and newborn records). In the multivariable
26
27 35 regression analysis, we estimated the adjusted odds ratios (ORs) and 95% confidence
28
29 36 intervals (CIs) of ever HTP smokers for HDP and LBW compared with those of never HTP
30
31 37 smokers using logistic regression. A stratified analysis with respect to combustible cigarette
32
33 38 smoking (never/ever) was also performed.

34
35 39 **Results:** The prevalence of ever HTP use were 11.7% and 12.6% in post-delivery and
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37 40 currently pregnant women, respectively. Among post-delivery women, ever HTP smokers
38
39 41 had higher HDP incidence (13.8% vs. 6.5%, $P=0.03$), with an OR of 2.78 (95% CI 0.84–
40
41 42 9.15) and higher LBW incidence (18.5% versus 8.9%, $P=0.02$), with an elevated OR of 2.08
42
43 43 (95% CI 0.80–5.39). A similar tendency was observed among never and ever combustible
44
45 44 cigarette smokers.

46
47 45 **Conclusion:** In Japan, the incidence of HTP use has exceeded 10% among pregnant women,
48
49 46 and HTP smoking may be associated with increased maternal and neonatal risks. School-
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51 47 based tobacco prevention and cessation programs should be conducted regardless of product
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53 48 types to prevent life-threatening perinatal complications and deaths.
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3 49 **Keywords:** heated tobacco products, hypertensive disorders of pregnancy, COVID-19,
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5 50 smoking, preconception
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10 52 **Strengths and limitations of this study:**
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- 12 53 ● Little is known about heated tobacco product (HTP) use and associated perinatal risks
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14 among pregnant women.
15
16 54 ● In Japan, the prevalence of ever HTP use exceeded 10% among pregnant women.
17
18 55 ● HTP use approximately doubled perinatal risk of hypertensive disorders of pregnancy
19
20 and low birth weight based on maternal and newborn records.
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22 56 ● When stratified by cigarette smoking status, a similar tendency was observed among
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24 never and ever cigarette smokers.
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26 57 ● The cross-sectional design does not allow firm conclusions.
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62 INTRODUCTION

63 The widespread use of heated tobacco products (HTPs) is an emerging public health
64 concern.[1] Since the initial marketing of HTPs in 2014, the prevalence of HTP use has
65 increased in Japan, exceeding 15% in the young population aged 20–39 years in 2019,[2] and
66 this incidence was maintained over 15% during the coronavirus disease (COVID-19)
67 pandemic in 2020.[3]

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

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

85 MATERIALS AND METHODS

86 Data setting

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3 87 This cross-sectional internet-based study is part of the Japan COVID-19 and Society Internet
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5 88 Survey (JACSIS) study. The JACSIS study comprises three surveys in the following three
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8 89 target populations: (a) young people and adults aged 15–79 years, (b) currently pregnant and
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10 90 post-delivery women, and (c) adults living in a single-parent household. The study samples
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12 91 for each survey were retrieved from the pooled panels of an internet research agency
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14 92 (Rakuten Insight, Inc., which had approximately 2.2 million panelists in 2019).[12] We used
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16 93 data from currently pregnant and post-delivery women, which were collected in October
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19 94 2020.

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21 95 The internet research agency identified 21,896 eligible women, randomly selected 4373
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23 96 women who gave birth after October 2019 or who were expected to give birth by March
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25 97 2021, and distributed the questionnaire comprising 61 questions to the selected women
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27 98 through a designated website. Next, we collected data from 1000 women (response rate,
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29 99 22.9%) stratified by delivery date as follows: (a) 600 post-delivery women who delivered
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31 100 during October 2019–March 2020 (n=200), April–May 2020 (n=200), and June–October
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33 101 2020 (n=200) and (b) 400 currently pregnant women who were expected to deliver during
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35 102 October 2020–March 2021. Among 1000 study participants, we excluded 77 who provided
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37 103 irrelevant or conflicting information (45 post-delivery and 32 currently pregnant women) as
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39 104 done in previous studies of the same research agency,[13] yielding a total of 923 study
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41 105 participants for the analysis (558 post-delivery and 365 currently pregnant women). Informed
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43 106 consent was obtained electronically, and the Institutional Review Board of the Osaka
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45 107 International Cancer Institute approved the study (Protocol Number 20084).
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109 **Definition of HDP and LBW**

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55 110 Data on HDP and LBW were extracted from the web-based self-reported questionnaires. We
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57 111 defined the incidence of HDP based on whether the study participants had been diagnosed as
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3 112 having HDP or preeclampsia during pregnancy. The criteria for HDP diagnosis in Japan were
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5 113 derived from the criteria of the American College of Obstetricians and Gynecologists (i.e.,
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7 114 systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg after the 20th
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9 115 week of gestation).[14] We defined the incidence of LBW on the basis of the diagnosis of
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11 116 LBW (birth weight < 2500 g).

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14 117 All participants were asked to provide information from their Maternal and Child
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16 118 Health Handbooks. In brief, as previously described,[15, 16] the Maternal and Child Health
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18 119 Handbooks are well-established integrated home-based records of maternal, newborn, and
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20 120 child health. As a part of a national maternal and child health policy, all municipalities issue a
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22 121 handbook to all women who report a pregnancy, and medical professionals record the health
23
24 122 information of the mother and child, including clinical outcomes (e.g., blood pressure and
25
26 123 birth weight) and incident diagnoses (e.g., HDP and LBW) during pregnancy. Mothers
27
28 124 seldom lose their Maternal and Child Health Handbooks (losing rate, $< 1\%$).[15]
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34 126 **HTP and cigarette smoking and other covariates**

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36 127 In the questionnaire, study participants were asked to indicate their smoking status (never,
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38 128 once or a few times but not habitually, former, sometimes, or every day) for each HTP
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40 129 available in the study period (Ploom Tech, Ploom Tech plus, Ploom S, IQOS, glo, glo sens,
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42 130 and PULZE). If they answered “never” for all HTPs, we defined them as never HTP smokers;
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44 131 the remaining participants were considered ever HTP smokers.
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49 132 We also classified the status of combustible cigarette smoking (never/ever). For other
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51 133 covariates, we included age, educational attainment (≤ 12 years [high school] or ≥ 13 years
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53 134 [college or university]), occupation (manager or others), household income (< 2 million JPY
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55 135 [approximately 20,000 USD], 2 to < 6 million JPY, and ≥ 6 million JPY), and comorbidity
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57 136 (having hypertension or diabetes).[17]
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6 138 **Statistical analysis**

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8 139 Descriptive statistics were computed, and t-test or chi-squared test was performed. We
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10 140 assessed the prevalence of ever HTP smokers among post-delivery and currently pregnant
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12 141 women. Additionally, we described detailed HTP smoking status cross-classified according
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14 142 to the combustible cigarette smoking status of currently pregnant and post-delivery women.

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17 143 To assess the potential association between HTP smoking and perinatal risk of HDP
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19 144 and LBW, we restricted the sample to 558 post-delivery women who could complete all the
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21 145 assessments during their pregnancy (Table 1). In the multivariable logistic regression
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23 146 analyses, the odds ratio (OR) and 95% confidence interval (CI) of ever HTP smokers for
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25 147 HDP risk were estimated with adjustment for age (model 1, the main model in the present
26
27 148 study). The reference group comprised never HTP smokers. In model 2, we fully adjusted for
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29 149 other explanatory variables (combustible cigarette smoking, educational attainment,
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31 150 occupation, household income, and comorbidity) and excluded 64 participants with missing
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33 151 information on household income. The same analyses were performed for LBW. For
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35 152 sensitivity analysis, we conducted a stratified analysis with respect to combustible cigarette
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37 153 smoking (never/ever).

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42 154 Alpha was set at 0.05, and all *P*-values were two sided. Data were analyzed using
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44 155 STATA/MP13.1 (StataCorp LLC, College Station, TX).

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49 157 **Patient and Public Involvement**

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51 158 No patients or the public involved.

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58 161 **RESULTS**59
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3 162 Among 558 post-delivery women, the incidences of HDP and LBW were 7.3% (n=41) and
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5 163 10.0% (n=56), respectively, and the prevalence of ever HTP smokers was 11.7% (n=65,
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7
8 164 Table 1). Furthermore, among 365 currently pregnant women, the prevalence of ever HTP
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10 165 smokers was 12.6% (n=46), which did not differ from that of HTP smokers among post-
11
12 166 delivery women ($P=0.66$). Among currently pregnant women, 4.4% of former combustible
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14 167 cigarette smokers reported smoking HTPs during pregnancy (Table 2), corresponding to
15
16 168 1.1% (4 out of 365) of current HTP smokers.

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19 169 Among post-delivery women, the HDP incidence was higher in ever HTP smokers than
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21 170 in never HTP smokers (13.8% vs. 6.5%; Table 1). Similarly, the incidence of LBW was
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23 171 higher among ever HTP smokers than among never HTP smokers (18.5% vs. 8.9%, Table 1).
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25 172 When stratified by combustible cigarette smoking, a similar tendency was observed among
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27 173 never and ever combustible cigarette smokers (Table 1).
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31 174 In the regression analysis, the age-adjusted ORs for HDP and LBW were elevated in
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33 175 ever HTP smokers (model 1, Figure 1); the ORs for HDP and LBW were 2.48 (95% CI,
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35 176 1.11–5.53) and 2.36 (95% CI, 1.16–4.78), respectively. Although the elevated ORs were
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37 177 attenuated after fully controlling for other covariates, the tendency remained elevated (model
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39 178 2, Figure 1). In the same regression analyses (model 2), while ever combustible cigarette
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41 179 smokers did not predict perinatal outcomes, managerial workers predicted the incidence of
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43 180 HDP and LBW; the ORs for HDP and LBW were 3.92 (95% CI 1.16–13.2) and 3.74 (95% CI
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45 181 1.41–9.93), respectively. When stratified by combustible cigarette smoking, a similar
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47 182 tendency was observed independently in never and ever combustible cigarette smokers
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49 183 (Figure 1). For instance, among never combustible cigarette smokers, the age-adjusted OR of
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51 184 HTP use for LBW was 4.82 (95% CI, 1.19–19.6).
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187 **DISCUSSION**

188 During the COVID-19 pandemic in Japan, the incidence of HTP use among pregnant women
189 is likely to exceed 10%, and we found that HTP use may be associated with perinatal risk of
190 HDP and LBW. Although the impact was attenuated after controlling for other potential
191 explanatory factors and the significance disappeared due to weak statistical power, the
192 maternal risk might be high independent of combustible cigarette smoking. This result seems
193 to be reliable because the incidence estimate of approximately 7% HDP found in our study
194 (using Maternal and Child Health Handbooks) is consistent with the general statistics
195 reported for Japanese pregnant women.[14] In addition, pregnant women of high
196 socioeconomic status independently predicted the risk of HDP, which might also support our
197 findings because they are known to use HTP more frequently than women of lower
198 socioeconomic status.[17]

199 We also found that LBW, a well-known smoking-related neonatal risk,[18] was
200 associated with HTP use. In fact, the incidence of HTP use doubled the risk of LBW, and the
201 association was stronger among never combustible cigarette smokers. These results seem to
202 be reliable because the incidence estimate of approximately 10% LBW found in our study
203 (using Maternal and Child Health Handbooks) is consistent with the general statistics
204 reported for Japanese pregnant women.[19] This also implies that aerosols of HTPs
205 containing nicotine and other inhalable substances can cause acute adverse health events on
206 the development of infants.

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

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3 212 underlying the associations observed in different phenotypes of HDP (e.g., preeclampsia and
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5 213 gestational hypertension) have not been elucidated,[21] HDP is recognized as a systemic
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7 214 disease attributable to placental circulatory dysfunction.[22] In experimental research, aerosol
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10 215 from HTPs was found to damage vascular endothelial function in rats.[5] Therefore, HDP
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12 216 risk associated with HTP use may involve acute and chronic vascular damage, irrespective of
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14 217 combustible cigarette smoking. Furthermore, as concluded in a recent systematic review,
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16 218 smoking is a strong risk factor for LBW.[18] Thus, given the fact that HTPs are smoking
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18 219 devices, our observed results are in line with established knowledge.

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22 220 Finally, the impression of HTPs as a healthy alternative is promoted by the advertising
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24 221 of HTPs.[4] Indeed, among currently pregnant women, approximately 4% of former
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26 222 combustible cigarette smokers reported smoking HTPs in the present study. This result might
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28 223 reflect a change from combustible cigarettes to HTP smoking during pregnancy. However,
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30 224 our findings imply that HTP use is at least not a healthy alternative. Evidence for unfavorable
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32 225 health outcomes regarding HTPs is still lacking, particularly in the young population of
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34 226 reproductive age. Insufficient health knowledge may have led to the current increase of HTP
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36 227 use among pregnant women, as reflected in our results and the latest statistics in Japan.[2, 3]
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38 228 However, the question remains as to how multidimensional factors of the COVID-19
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40 229 pandemic (e.g., the infection, mental health, and socioeconomic factors) and the smoking
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42 230 behaviors of others (e.g., partners and family) affect the association between HTP use and
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44 231 perinatal risks. Our sequential series of the JACSIS study planned in 2021 may provide
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46 232 updates regarding the present results.

51
52 233 Our study had some limitations. First, our cross-sectional design does not allow to
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54 234 conclude causal mechanisms between HTP use and perinatal risks. However, the prevalence
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56 235 of HDP and HTP smokers were mostly parallel to the general population in Japan.[2, 3, 14]
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58 236 In addition, the incidence of HTP use did not differ between post-delivery and currently
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3 237 pregnant women in our study. Second, recall and reporting bias cannot be discarded. Because
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5 238 self-report-based smoking status among pregnant women tends to misclassify ever smokers
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8 239 as never smokers,[23] our estimates might be biased toward the null. Third, the perinatal
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10 240 clinical information was self-reported and not based on medical charts, thereby limiting the
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12 241 precision of the results. However, all participants were asked to base their responses on their
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14 242 Maternal and Child Health Handbooks, a well-established home-base maternal and neonatal
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16 243 record during pregnancy.[16] Therefore, this limitation might not have affected our results or
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18 244 at least not largely. Despite these limitations, the strengths of the study included detailed
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20 245 information for HTPs, which covered all HTPs available during the study period.
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22 246 Additionally, this is the first report regarding the status of HTP use among pregnant women
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24 247 in Japan, and it highlights the potentially elevated maternal and neonatal risks associated with
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26 248 HTP use. Additionally, besides the present study, no other human studies to date have
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28 249 assessed the potential effect of the maternal use of new tobacco products (i.e., e-cigarette and
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30 250 HTP) on perinatal health.[24] Therefore, our findings shed light and motivate further
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32 251 investigations to estimate the life-threatening perinatal risks associated with new tobacco
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40 253 In conclusion, the incidence of HTP use seems to exceed 10% among pregnant women,
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42 254 and HTP smoking may be associated with increased maternal and neonatal risks in Japan.
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44 255 With no doubt, smoking in reproductive age can cause unfavorable perinatal outcomes.[25]
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46 256 Hence, efforts should be made to investigate the risk of HTP use in reproductive age, and
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48 257 school-based tobacco prevention and cessation programs should be conducted regardless of
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50 258 product types to prevent life-threatening perinatal complications and deaths.
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11 265 JP18K17351).

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14 266 **Data availability statement:** The data that support the findings of this study are available on
15
16 267 reasonable request. However, restrictions apply to the availability of these data due to
17
18 268 personal identification; research data are not shared. If any person wishes to verify our data,
19
20 269 they are most welcome to contact the corresponding author.

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22
23 270 **Conflict of interest:** The authors declare no potential conflicts of interest.

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25
26 271 **Author contributions:** MZ and TT designed the study, and TT supervised the study. MZ,
27
28 272 YH, and SO developed the methodology, and SO, AH, and TT created the dataset. MZ and
29
30 273 YH analyzed the data and wrote the first draft of the manuscript. All authors revised the
31
32 274 manuscript and approved the final version.

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34
35 275 **Ethics approval:** The study was approved by the Institutional Review Board of the Osaka
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37 276 International Cancer Institute approved the study (Protocol Number 20084).

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3 348 **FIGURE LEGEND**
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5 349 **Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive**
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7 **disorders of pregnancy and low birth weight compared with never heated tobacco**
8 350 **product smokers.** Age was adjusted in model 1, and other covariates (combustible cigarette
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10 351 smoking, educational attainment, occupation, household income, and comorbidity) were
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12 352 additionally adjusted in model 2. The samples for each analysis in model 2 were as follows:
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14 353 n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible
15
16 354 cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310
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18 355 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for
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20 356 low birth weight. Abbreviations: HTP, heated tobacco products; OR, odds ratio.
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360 **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	<i>n</i> =493	<i>n</i> =65	<i>n</i> =319	<i>n</i> =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				
<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	<i>n</i> =411	<i>n</i> =10	<i>n</i> =265	<i>n</i> =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	<i>n</i> =361	<i>n</i> =9	<i>n</i> =219	<i>n</i> =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	<i>n</i> =82	<i>n</i> =55	<i>n</i> =54	<i>n</i> =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	<i>n</i> =75	<i>n</i> =49	<i>n</i> =44	<i>n</i> =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%)

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

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

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364

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

Characteristics	HTP smoking status			Total
	Never	Former	Current	
Post-delivery women, <i>n</i> =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, <i>n</i> =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%)

367 Abbreviation: HTP, heated tobacco product.

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

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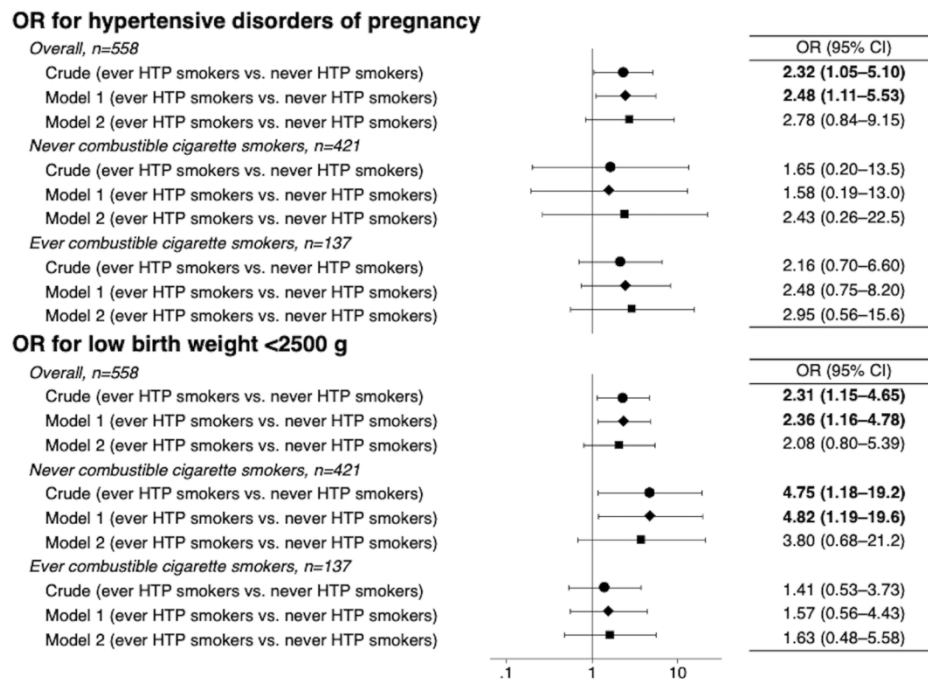


Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight, compared with never heated tobacco product smokers. Age was adjusted in Model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household 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
Title and abstract		
P1-4	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	2	Background/rationale Explain the scientific background and rationale for the investigation being reported
P5	3	Objectives State specific objectives, including any prespecified hypotheses
Methods		
P6	4	Study design Present key elements of study design early in the paper
P6	5	Setting Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
P6	6	Participants (a) Give the eligibility criteria, and the sources and methods of selection of participants
P6-8	7	Variables Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
P6-7	8*	Data sources/measurement 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	9	Bias Describe any efforts to address potential sources of bias
P6	10	Study size Explain how the study size was arrived at
P7-8	11	Quantitative variables Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
P8	12	Statistical methods (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	13*	Participants (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	14*	Descriptive data (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	15*	Outcome data Report numbers of outcome events or summary measures
P8-9	16	Main results (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	17	Other analyses Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

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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.

BMJ Open

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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Keywords:	COVID-19, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS, PUBLIC HEALTH, TOXICOLOGY, Epidemiology < THORACIC MEDICINE

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3 1 **Impact of heated tobacco product use and hypertensive disorders of pregnancy and low**
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5 2 **birth weight: Analysis of a web-based survey in Japan**
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10 4 Masayoshi Zaitu,^{1,*} Yoshihiko Hosokawa,^{1,2,*} Sumiyo Okawa,³ Ai Hori,⁴ Gen Kobashi,¹
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53 23 **Word count:** 2540 words
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3 24 **ABSTRACT**
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5 25 **Objectives:** Knowledge on the impact of heated tobacco product (HTP) use in pregnant
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8 26 women with associated maternal and neonatal risks for hypertensive disorders of pregnancy
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10 27 (HDP) and low birth weight (LBW) is limited. We aimed to assess the status of HTP use
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12 28 among pregnant women in Japan and explore the association of HTP use with HDP and
13
14 29 LBW.
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17 30 **Design:** cross-sectional study
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19 31 **Setting:** Data from the Japan “COVID-19 and Society” Internet Survey study, a web-based
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21 32 nationwide survey
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24 33 **Participants:** We investigated 558 post-delivery and 365 currently pregnant women in
25
26 34 October 2020.
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28 35 **Primary and secondary outcome measures:** Information on HDP and LBW was collected
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30 36 from the post-delivery women’s Maternal and Child Health Handbooks (maternal and
31
32 37 newborn records). We estimated the age-adjusted odds ratios (ORs) and 95% confidence
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34 38 intervals (CIs) of ever HTP smokers for HDP and LBW and compared them with those of
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36 39 never HTP smokers in a logistic regression analysis.
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39 40 **Results:** The prevalence of ever and current HTP use were 11.7% and 2.7% in post-delivery
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42 41 women and 12.6% and 1.1% in currently pregnant women, respectively. Among currently
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44 42 pregnant women who were former combustible cigarette smokers, 4.4% (4/91) were current
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46 43 HTP smokers. Among post-delivery women, ever HTP smokers had a higher HDP incidence
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48 44 (13.8% vs. 6.5%, $P=0.03$; age-adjusted OR=2.48, 95% CI 1.11–5.53) and higher LBW
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50 45 incidence (18.5% versus 8.9%, $P=0.02$; age-adjusted OR=2.36, 95% CI 1.16–4.87).
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53 46 **Conclusions:** In Japan, the incidence of ever HTP use exceeded 10% among pregnant
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55 47 women, and HTP smoking may be associated with maternal and neonatal risks.
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3 49 **Keywords:** heated tobacco products, hypertensive disorders of pregnancy, COVID-19,
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10 52 **Strengths and limitations of this study:**

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12 53 ● This study covered all heated tobacco products (HTPs) available during the study period.
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14 54 ● All participants were asked to base their responses on information in their Maternal and
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17 55 Child Health Handbooks, a well-established home-based maternal and neonatal record of
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19 56 pregnancy.
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21 57 ● The web-based, self-reported cross-sectional design with a small sample size was a
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24 58 source of bias, and causal mechanisms were not examined.
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26 59 ● The lack of information on HTP smoking during pregnancy limited the assessment of the
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29 60 direct impact of HTP use on pregnancy outcomes.
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31 61 ● The participants' relevant medical histories were not assessed.
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63 INTRODUCTION

64 The use of heated tobacco products (HTPs) is an emerging public health concern.[1] Since
65 the initial marketing of HTPs in 2014, the prevalence of HTP use has increased in Japan, with
66 a registered prevalence above 15% in the young population aged 20–39 years in 2019.[2]
67 This prevalence remained above 15% during the coronavirus disease (COVID-19) pandemic
68 in 2020.[3] The use of HTPs is increasing worldwide, particularly in the younger population;
69 the prevalence of HTP use among Guatemala adolescents was 2.9% in 2020.[4]

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

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

87 MATERIALS AND METHODS

88 **Study design, data setting, and participants**

89 This cross-sectional internet-based study is part of the Japan COVID-19 and Society Internet
90 Survey (JACSIS) study. The JACSIS study comprises three surveys in the following three
91 target populations: (a) young people and adults aged 15–79 years, (b) currently pregnant and
92 post-delivery women, and (c) adults living in a single-parent household. The study samples
93 for each survey were retrieved from the pooled panels of an internet research agency
94 (Rakuten Insight, Inc., which had approximately 2.2 million panelists in 2019).[13] We used
95 data from currently pregnant and post-delivery women, which were collected in October
96 2020.

97 The internet research agency initially identified 21,896 eligible women who gave birth
98 after October 2019 or who were expected to give birth by March 2021; however, our target
99 sample size was 1,000 women due to the available study budget. Using a computer algorithm,
100 the internet research agency randomly selected 4373 women to reach the target sample size of
101 1000. Quality control methods for the sampling of panelists and other policies for panelists
102 by the internet research agency have been described elsewhere.[14] An invitation e-mail was
103 sent to the selected 4373 women; they were to complete the questionnaire through a
104 designated website containing the survey questionnaire (made up of 61 questions, one
105 question per page). Data collection started on October 15, 2020, and ended on October 25,
106 2020, when the target sample size of 1000 by natural course (response rate, 22.9%) was met.
107 Next, we obtained de-identified data from 1000 women from the internet research agency,
108 and the study population was stratified by delivery date as follows: (a) 600 post-delivery
109 women who delivered in October 2019–October 2020 (the number for October 2019–March
110 2020, April–May 2020, and June–October 2020 was 200 each) and (b) 400 currently
111 pregnant women who were expected to deliver in October 2020–March 2021.

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3 112 Seventy-seven (42 post-delivery and 35 currently pregnant women) participants who
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5 113 provided irrelevant or conflicting information were excluded, like it was done in previous
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7 114 studies of the same research agency.[15] A total of 923 (558 post-delivery and 365 currently
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9 115 pregnant women) participants were included in the analysis. Informed consent was obtained
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11 116 electronically before the study participants answered the web-based questionnaire, and the
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13 117 Institutional Review Board of the Osaka International Cancer Institute approved the study
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15 118 (Protocol Number 20084).
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22 120 **Definition of HDP and LBW**

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24 121 Data on HDP and LBW were extracted from the web-based self-reported
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26 122 questionnaires. The incidence of HDP was based on whether the study participants had been
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28 123 diagnosed with HDP or preeclampsia during pregnancy. The criteria for HDP diagnosis in
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30 124 Japan were derived from the criteria of the American College of Obstetricians and
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32 125 Gynecologists (i.e., systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90
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34 126 mmHg after the 20th week of gestation).[16] The incidence of LBW was defined on the basis
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36 127 of the diagnosis of LBW (birth weight < 2500 g). All municipalities issue a handbook to all
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38 128 pregnant women in which medical professionals record the health information of the mother
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40 129 and child, including clinical outcomes (e.g., blood pressure and birth weight) and incident
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42 130 diagnoses (e.g., HDP and LBW) during pregnancy; this is part of a national maternal and
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44 131 child health policy. Mothers seldom lose their Maternal and Child Health Handbooks (losing
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46 132 rate, $< 1\%$).[17]
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51 133 All participants were asked to provide information from their Maternal and Child
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53 134 Health Handbooks. Although the definitions of HDP and LBW were based on diagnosis only
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55 135 (treatment information was not obtained), the information was reliable, since Maternal and
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3 136 Child Health Handbooks are well-established integrated home-based records of maternal,
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5 137 newborn, and child health.[17, 18]
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10 139 **HTP and cigarette smoking and other covariates**

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12 140 In the questionnaire, study participants were asked to indicate their smoking status (never,
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14 141 once or a few times [trial smoking and not habitual], former, sometimes [habitual], or every
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16 142 day) for each HTP that was available in the study period (Ploom Tech, Ploom Tech plus,
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18 143 Ploom S, IQOS, glo, glo sens, and PULZE). Participants who answered “never” for all HTPs
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20 144 were considered as never HTP smokers; the remaining participants were considered as ever
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22 145 HTP smokers. Therefore, the ever HTP smoking group included those who used HTPs before
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24 146 pregnancy and during pregnancy altogether. We could not specifically distinguish the impacts
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26 147 of HTP smoking during pregnancy from that of HTP smoking before pregnancy.
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31 148 The status of combustible cigarette smoking was classified as never smoker and ever
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33 149 smoker. It was impossible to further classify the smokers into former or dual smokers due to
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35 150 the nature of the study. The other covariates included age, educational attainment (≤ 12 years
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37 151 [high school] or ≥ 13 years [college or university]), occupation (manager or others),
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39 152 household income (< 2 million JPY [approximately 20,000 USD], 2 to < 6 million JPY, and ≥ 6
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41 153 million JPY), and comorbidity (having hypertension or diabetes).[19]
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47 155 **Statistical analysis**

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49 156 Descriptive statistics were computed and compared using the t-test or chi-squared test. The
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51 157 prevalence of ever HTP smokers was assessed among the post-delivery and currently
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53 158 pregnant women. Additionally, the HTP smoking status was cross-classified according to the
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55 159 combustible cigarette smoking status of the currently pregnant and post-delivery women.
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3 160 To assess the potential association between HTP smoking and perinatal risk of HDP
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5 161 and LBW, the sample was reduced to 558 post-delivery women who could complete all the
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8 162 assessments during their pregnancy (Table 1). In the multivariable logistic regression
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10 163 analyses, the odds ratio (OR) and 95% confidence interval (CI) of ever HTP smokers for
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12 164 HDP risk were estimated after adjustment for age (Model 1, the main model in this study).
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14 165 The never HTP smokers comprised the reference group. In Model 2, full adjustments for
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16 166 other explanatory variables (combustible cigarette smoking, educational attainment,
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18 167 occupation, household income, and comorbidity) were performed, and 64 participants with
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20 168 missing information on household income were excluded. The same analyses were performed
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22 169 for LBW.

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26 170 For the sensitivity analysis, a stratified analysis with respect to combustible cigarette
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28 171 smoking (never/ever) was performed. In addition, using a different reference group that
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30 172 included those who never smoked any form of tobacco (HTPs and combustible cigarettes),
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32 173 the ORs of ever HTP smokers for HDP and LBW risks were estimated.

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35 174 Alpha was set at 0.05, and all *P* values were two sided. Data were analyzed using
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37 175 STATA/MP13.1 (StataCorp LLC, College Station, TX).

38 176 39 40 41 42 177 **Patient and Public Involvement**

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44 178 Neither patients nor the public was involved.
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50 51 181 **RESULTS**

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53 182 Among 558 post-delivery women, the incidences of HDP and LBW were 7.3% (n=41) and
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55 183 10.0% (n=56), respectively, and the prevalence of ever HTP smokers was 11.7% (n=65,
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57
58 184 Table 1). Furthermore, among the 365 currently pregnant women, the prevalence of ever HTP
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3 185 smokers was 12.6% (n=46), which did not differ from that of HTP smokers among post-
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5 186 delivery women ($P=0.66$).
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8 187 Among the currently pregnant women, 4.4% (4/91 participants) of the former
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10 188 combustible cigarette smokers reported smoking HTPs during pregnancy (Table 2),
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12 189 corresponding to 1.1% (4/365 participants) of currently pregnant women. In addition, 36.3%
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14 190 (33/91 participants) of former combustible cigarette smokers quit HTP smoking during
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16 191 pregnancy, corresponding to 11.5% (42/365 participants) of currently pregnant women.
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19 192 Among the post-delivery women, the HDP incidence was higher in ever HTP smokers
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21 193 than in never HTP smokers (13.8% [n=9] vs. 6.5% [n=35], $P=0.03$; Table 1). Similarly, the
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23 194 incidence of LBW was higher among ever HTP smokers than among never HTP smokers
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25 195 (18.5% [n=12] vs. 8.9% [n=44], $P=0.02$; Table 1). When stratified by combustible cigarette
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27 196 smoking, a similar pattern was observed among never and ever combustible cigarette
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29 197 smokers (Table 1).
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33 198 In the regression analysis, the age-adjusted ORs for HDP and LBW were elevated in
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35 199 ever HTP smokers (Model 1); the ORs for HDP and LBW were 2.48 (95% CI, 1.11–5.53)
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37 200 and 2.36 (95% CI, 1.16–4.78), respectively. However, the elevated ORs were not significant
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39 201 after adjusting for other covariates (Model 2, Figure 1). In the same regression analyses
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41 202 (Model 2), while ever combustible cigarette smokers were not associated with perinatal
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43 203 outcomes, the ORs of managerial workers for HDP and LBW were 3.92 (95% CI 1.16–13.2)
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45 204 and 3.74 (95% CI 1.41–9.93), respectively.
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49 205 In the sensitivity analyses, when stratified by combustible cigarette smoking, a similar
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51 206 pattern was observed independently in never and ever combustible cigarette smokers (Figure
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53 207 1). For instance, among never combustible cigarette smokers, the age-adjusted OR of HTP
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55 208 use for LBW was 4.82 (95% CI, 1.19–19.6). A further analysis comparing 65 ever HTP
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57 209 smokers in the post-delivery group and 411 never tobacco smokers showed similar results:
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3 210 compared with those who never smoked any form of tobacco, the age-adjusted ORs of ever
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5 211 HTP smokers for HDP and LBW were 2.56 (95% CI 1.13–5.80) and 2.52 (95% CI 1.22–
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7 212 5.20), respectively (Model 1). However, after adjusting for other covariates (Model 2), the
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9 213 ORs were not significant due to the small sample size: the ORs for HDP and LBW were 2.40
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11 214 (95% CI 0.27–21.2) and 3.59 (95% CI 0.66–19.5), respectively.
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19 217 **DISCUSSION**

21 218 During the first wave of the COVID-19 pandemic in Japan, the incidence of HTP use among
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23 219 pregnant women exceeded 10%, and there was a suspected association of HTP use and
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25 220 perinatal risk of HDP and LBW. However, after adjusting for potential explanatory factors,
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27 221 there was no significant association, which may be due to the weak statistical power because
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29 222 of the small sample size.
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33 223 To the best of our knowledge, this is the first report of a potential association between
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35 224 HTP use and perinatal risks. Although smoking plays a controversial role,[10] recent
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37 225 evidence suggests that combustible cigarette smoking is associated with increased HDP
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39 226 risk.[11, 12] Although the biological and genetic pathways (e.g., CYP2A6 and nicotine)
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41 227 underlying the associations observed in different phenotypes of HDP (e.g., preeclampsia and
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43 228 gestational hypertension) have not been elucidated,[20] HDP is recognized as a systemic
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45 229 disease attributable to placental circulatory dysfunction.[21] In experimental research, aerosol
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47 230 from HTPs was found to damage vascular endothelial function in rats.[6] Therefore, the
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49 231 association between HDP risk and HTP use may involve acute and chronic vascular damage,
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51 232 irrespective of combustible cigarette smoking. Furthermore, as concluded in a recent
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53 233 systematic review, smoking is a strong risk factor for LBW.[22] Thus, given the fact that
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55 234 HTPs are smoking devices, our observed results are in line with established reports.
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3 235 Although HTP-related unfavorable health outcomes (e.g., acute respiratory and
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6 236 cardiovascular risks) are likely to occur,[6, 7] the impression of HTPs as a healthy alternative
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8 237 is promoted by HTP use advertisements.[5] The Japanese HTP market share accounted for
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10 238 21% of total tobacco sales in 2018, and the weak restrictions on tobacco advertisements and
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12 239 promotion in this country contribute to increased HTP use.[23] Among currently pregnant
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14 240 women, approximately 4% of former combustible cigarette smokers reported smoking HTPs
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16 241 in the present study. This result might explain the change from combustible cigarettes to HTP
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18 242 smoking during pregnancy. In a setting of weak tobacco restrictions such as Guatemala, even
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20 243 though the prevalence of HTP use is low (2.9%) among adolescents, a high prevalence is
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22 244 anticipated.[4] However, our findings imply that HTP use is not a healthy alternative.
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24 245 Evidence for unfavorable HTP-related health outcomes is still insufficient, particularly
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26 246 among reproductive age women. In addition, the impact of multidimensional factors of the
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28 247 COVID-19 pandemic (e.g., the infection, mental health, and socioeconomic factors) and the
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30 248 smoking behaviors of others (e.g., partners and family) on the association between HTP use
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32 249 and perinatal risks remains unknown. The ongoing JACSIS study may provide updates in this
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34 250 regard.

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39 251 Our study has limitations. First, this was a web-based, self-reported cross-sectional
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41 252 study with a small sample size, which may be a source of bias and a limitation to explaining
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43 253 the causal mechanisms between HTP use and perinatal risks. Due to the lack of information
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45 254 on HTP smoking during pregnancy, the direct impact of HTP smoking on pregnancy
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47 255 outcomes could not be assessed. Furthermore, details on the participants' medical histories
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49 256 including relevant comorbidities, and detailed smoking information such as smoking intensity
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51 257 and duration of smoking abstinence were not available. In addition, electronic cigarette use
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53 258 was not assessed. However, the prevalences of HDP and HTP smokers were mostly parallel
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55 259 to the general population in Japan.[2, 3, 16] The incidence of HTP use did not differ between
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3 260 post-delivery and currently pregnant women in our study. Second, recall and reporting bias of
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5 261 HTP use could not be discarded, as suggested in a study on combustible cigarette and
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8 262 electronic cigarette smoking.[4] Because self-report-based smoking status among pregnant
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10 263 women tends to misclassify ever smokers as never smokers,[24] our estimates might be
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12 264 biased toward the null. Third, the perinatal clinical information was self-reported and not
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14 265 based on medical charts, thereby limiting the precision of the results. However, all
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16 266 participants were asked to base their responses on information in their Maternal and Child
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18 267 Health Handbooks, a well-established home-based maternal and neonatal record during
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20 268 pregnancy.[18] Therefore, this limitation might not have affected our results, or at least not
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22 269 largely. Despite these limitations, all HTPs that were available during the study period were
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24 270 assessed. This is the first report on the status of HTP use among pregnant women in Japan,
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26 271 and it highlights the potentially elevated maternal and neonatal risks associated with HTP
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28 272 use. Additionally, to date, besides the present study, no other human studies have assessed the
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30 273 potential effect of the maternal use of new tobacco products (i.e., e-cigarettes and HTPs) on
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32 274 perinatal health.[25] Therefore, our findings shed light and motivate further investigations to
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34 275 assess the life-threatening perinatal risks associated with new tobacco products.
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40 276 In conclusion, the incidence of HTP use seems to exceed 10% among pregnant women,
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42 277 and HTP smoking may be associated with increased maternal and neonatal risks in Japan.
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44 278 Undoubtedly, smoking in reproductive age women can cause unfavorable perinatal
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46 279 outcomes.[26] Hence, efforts should be made to investigate the risk of HTP use in
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48 280 reproductive age women, to prevent life-threatening perinatal complications and deaths.
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57
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4
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7 287 JP18K17351).
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10 288 **Data availability statement:** The data that support the findings of this study are available on
11
12 289 reasonable request. However, restrictions apply to the availability of these data due to
13
14 290 personal identification; research data are not shared. If any person wishes to verify our data,
15
16 291 they are most welcome to contact the corresponding author.
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19 292 **Conflict of interest:** The authors declare no potential conflicts of interest.
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21 293 **Author contributions:** MZ and TT designed the study. TT supervised the study. MZ, YH,
22
23 294 and SO developed the methodology. SO, AH, and TT created the dataset. MZ and YH
24
25 295 analyzed the data. MZ and YH wrote the first draft of the manuscript. SO, AH, GK, and TT
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27 296 commented on the manuscript. All authors read and approved the final version.
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30 297 **Ethics approval:** The study was approved by the Institutional Review Board of the Osaka
31
32 298 International Cancer Institute approved the study (Protocol Number 20084).
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3 375 **FIGURE LEGEND**
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5 376 **Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive**
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8 377 **disorders of pregnancy and low birth weight, compared with never heated tobacco**
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10 378 **product smokers.** Age was adjusted in Model 1, and other covariates (combustible cigarette
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12 379 smoking, educational attainment, occupation, household income, and comorbidity) were
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14 380 additionally adjusted in Model 2. The samples for each analysis in Model 2 were as follows:
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16 381 n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible
17
18 382 cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310
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20 383 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for
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22 384 low birth weight. Abbreviations: HTP, heated tobacco products; OR, Odds ratio.
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387 **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	<i>n</i> =493	<i>n</i> =65	<i>n</i> =319	<i>n</i> =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				
<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	<i>n</i> =411	<i>n</i> =10	<i>n</i> =265	<i>n</i> =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	<i>n</i> =361	<i>n</i> =9	<i>n</i> =219	<i>n</i> =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	<i>n</i> =82	<i>n</i> =55	<i>n</i> =54	<i>n</i> =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	<i>n</i> =75	<i>n</i> =49	<i>n</i> =44	<i>n</i> =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%)

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

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

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391

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

Characteristics	HTP smoking status			
	Never	Former	Current	Total
Post-delivery women, <i>total</i>	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, <i>total</i>	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%)

394 Abbreviation: HTP, heated tobacco product.

395

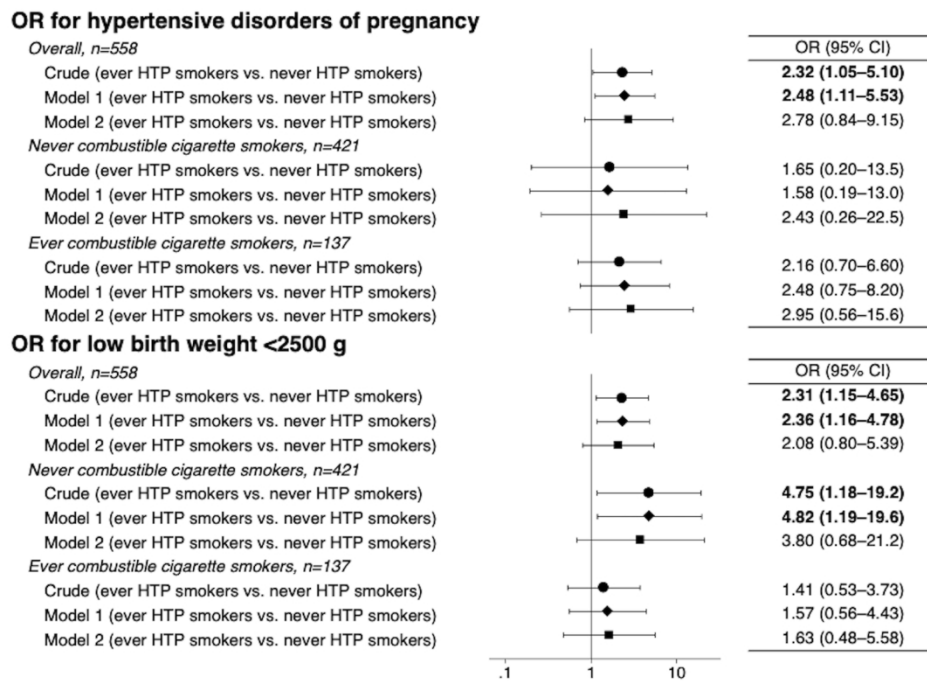


Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight, compared with never heated tobacco product smokers. Age was adjusted in Model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household 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)

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 an 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

1	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".)	
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6	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
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11	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
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18	Log file analysis	Indicate whether other techniques to analyze the log file for identification of multiple entries were used. If so, please describe.	P5
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21	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
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25	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
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28	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
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32	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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36 This checklist has been modified from Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res. 2004 Sep 29;6(3):e34 [erratum in J Med Internet Res. 2012; 14(1): e8.]. Article available at
37 <https://www.jmir.org/2004/3/e34/>; erratum available <https://www.jmir.org/2012/1/e8/>. Copyright ©Gunther Eysenbach. Originally published in the
38 [Journal of Medical Internet](https://www.jmir.org/2004/3/e34/) Research, 29.9.2004 and 04.01.2012.
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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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3 **1 Heated tobacco product use and hypertensive disorders of pregnancy and low birth**
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5 **2 weight: Analysis of a cross-sectional, web-based survey in Japan**
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54 23 **Word count:** 2544 words
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2
3 24 **ABSTRACT**
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5 25 **Objectives:** Knowledge on the impact of heated tobacco product (HTP) use in pregnant
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7
8 26 women with associated maternal and neonatal risks for hypertensive disorders of pregnancy
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10 27 (HDP) and low birth weight (LBW) is limited. We aimed to assess the status of HTP use
11
12 28 among pregnant women in Japan and explore the association of HTP use with HDP and
13
14 29 LBW.
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16
17 30 **Design:** cross-sectional study
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19 31 **Setting:** Data from the Japan “COVID-19 and Society” Internet Survey study, a web-based
20
21 32 nationwide survey
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24 33 **Participants:** We investigated 558 post-delivery and 365 currently pregnant women in
25
26 34 October 2020.
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28 35 **Primary and secondary outcome measures:** Information on HDP and LBW was collected
29
30 36 from the post-delivery women’s Maternal and Child Health Handbooks (maternal and
31
32 37 newborn records). We estimated the age-adjusted odds ratios (ORs) and 95% confidence
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34 38 intervals (CIs) of ever HTP smokers for HDP and LBW and compared them with those of
35
36 39 never HTP smokers in a logistic regression analysis.
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39 40 **Results:** The prevalence of ever and current HTP use were 11.7% and 2.7% in post-delivery
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42 41 women and 12.6% and 1.1% in currently pregnant women, respectively. Among currently
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44 42 pregnant women who were former combustible cigarette smokers, 4.4% (4/91) were current
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46 43 HTP smokers. Among post-delivery women, ever HTP smokers had a higher HDP incidence
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48 44 (13.8% vs. 6.5%, $P=0.03$; age-adjusted OR=2.48, 95% CI 1.11–5.53) and higher LBW
49
50 45 incidence (18.5% versus 8.9%, $P=0.02$; age-adjusted OR=2.36, 95% CI 1.16–4.87).
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53 46 **Conclusions:** In Japan, the incidence of ever HTP use exceeded 10% among pregnant
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55 47 women, and HTP smoking may be associated with maternal and neonatal risks.
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3 49 **Keywords:** heated tobacco products, hypertensive disorders of pregnancy, COVID-19,
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5 50 smoking, preconception
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10 52 **Strengths and limitations of this study:**

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12 53 ● This study covered all heated tobacco products (HTPs) available during the study period.
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14 54 ● All participants were asked to base their responses on information in their Maternal and
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16 55 Child Health Handbooks, a well-established home-based maternal and neonatal record of
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18 56 pregnancy.
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20 57 ● The web-based, self-reported, cross-sectional study had a small sample size and thus
21
22 58 involved a selection bias and reduced statistical precision, and causal mechanisms could
23
24 59 not be examined.
25
26 60 ● The lack of information on HTP smoking during pregnancy limited the assessment of the
27
28 61 direct impact of HTP use on pregnancy outcomes.
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30 62 ● The participants' relevant medical histories were not assessed.
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64 INTRODUCTION

65 The use of heated tobacco products (HTPs) is an emerging public health concern.[1] Since
66 the initial marketing of HTPs in 2014, the prevalence of HTP use has increased in Japan, with
67 a registered prevalence above 15% in the young population aged 20–39 years in 2019.[2]
68 This prevalence remained above 15% during the coronavirus disease (COVID-19) pandemic
69 in 2020.[3] The use of HTPs is increasing worldwide, particularly in the younger population;
70 the prevalence of HTP use among Guatemala adolescents was 2.9% in 2020.[4]

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

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

88 MATERIALS AND METHODS

89 **Study design, data setting, and participants**

90 This cross-sectional internet-based study is part of the Japan COVID-19 and Society Internet
91 Survey (JACSIS) study. The JACSIS study comprises three surveys in the following three
92 target populations: (a) young people and adults aged 15–79 years, (b) currently pregnant and
93 post-delivery women, and (c) adults living in a single-parent household. The study samples
94 for each survey were retrieved from the pooled panels of an internet research agency
95 (Rakuten Insight, Inc., which had approximately 2.2 million panelists in 2019).[13] We used
96 data from currently pregnant and post-delivery women, which were collected in October
97 2020.

98 The internet research agency initially identified 21,896 eligible women who gave birth
99 after October 2019 or who were expected to give birth by March 2021; however, our target
100 sample size was 1,000 women due to the available study budget. Using a computer algorithm,
101 the internet research agency randomly selected 4373 women to reach the target sample size of
102 1000. Quality control methods for the sampling of panelists and other policies for panelists
103 by the internet research agency have been described elsewhere.[14] An invitation e-mail was
104 sent to the selected 4373 women; they were to complete the questionnaire through a
105 designated website containing the survey questionnaire (made up of 61 questions, one
106 question per page). Data collection started on October 15, 2020, and ended on October 25,
107 2020, when the target sample size of 1000 by natural course (response rate, 22.9%) was met.
108 Next, we obtained de-identified data from 1000 women from the internet research agency,
109 and the study population was stratified by delivery date as follows: (a) 600 post-delivery
110 women who delivered in October 2019–October 2020 (the number for October 2019–March
111 2020, April–May 2020, and June–October 2020 was 200 each) and (b) 400 currently
112 pregnant women who were expected to deliver in October 2020–March 2021.

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3 113 Seventy-seven (42 post-delivery and 35 currently pregnant women) participants who
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5 114 provided irrelevant or conflicting information were excluded, like it was done in previous
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8 115 studies of the same research agency.[15] A total of 923 (558 post-delivery and 365 currently
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10 116 pregnant women) participants were included in the analysis. Informed consent was obtained
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12 117 electronically before the study participants answered the web-based questionnaire, and the
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14 118 Institutional Review Board of the Osaka International Cancer Institute approved the study
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17 119 (Protocol Number 20084).
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22 121 **Definition of HDP and LBW**

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24 122 Data on HDP and LBW were extracted from the web-based self-reported
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26 123 questionnaires. The incidence of HDP was based on whether the study participants had been
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28 124 diagnosed with HDP or preeclampsia during pregnancy. The criteria for HDP diagnosis in
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30 125 Japan were derived from the criteria of the American College of Obstetricians and
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32 126 Gynecologists (i.e., systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90
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34 127 mmHg after the 20th week of gestation).[16] The incidence of LBW was defined on the basis
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36 128 of the diagnosis of LBW (birth weight < 2500 g). All municipalities issue a handbook to all
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38 129 pregnant women in which medical professionals record the health information of the mother
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40 130 and child, including clinical outcomes (e.g., blood pressure and birth weight) and incident
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42 131 diagnoses (e.g., HDP and LBW) during pregnancy; this is part of a national maternal and
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44 132 child health policy. Mothers seldom lose their Maternal and Child Health Handbooks (losing
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46 133 rate, $< 1\%$).[17]
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51 134 All participants were asked to provide information from their Maternal and Child
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53 135 Health Handbooks. Although the definitions of HDP and LBW were based on diagnosis only
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55 136 (treatment information was not obtained), the information was reliable, since Maternal and
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3 137 Child Health Handbooks are well-established integrated home-based records of maternal,
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5 138 newborn, and child health.[17, 18]
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10 140 **HTP and cigarette smoking and other covariates**

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12 141 In the questionnaire, study participants were asked to indicate their smoking status (never,
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14 142 once or a few times [trial smoking and not habitual], former, sometimes [habitual], or every
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16 143 day) for each HTP that was available in the study period (Ploom Tech, Ploom Tech plus,
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18 144 Ploom S, IQOS, glo, glo sens, and PULZE). Participants who answered “never” for all HTPs
19
20 145 were considered as never HTP smokers; the remaining participants were considered as ever
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22 146 HTP smokers. Therefore, the ever HTP smoking group included those who used HTPs before
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24 147 pregnancy and during pregnancy altogether. We could not specifically distinguish the impacts
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26 148 of HTP smoking during pregnancy from that of HTP smoking before pregnancy.
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31 149 The status of combustible cigarette smoking was classified as never smoker and ever
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33 150 smoker. It was impossible to further classify the smokers into former or dual smokers due to
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35 151 the nature of the study. The other covariates included age, educational attainment (≤ 12 years
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37 152 [high school] or ≥ 13 years [college or university]), occupation (manager or others),
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39 153 household income (< 2 million JPY [approximately 20,000 USD], 2 to < 6 million JPY, and ≥ 6
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41 154 million JPY), and comorbidity (having hypertension or diabetes).[19]
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47 156 **Statistical analysis**

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49 157 Descriptive statistics were computed and compared using the t-test or chi-squared test. The
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51 158 prevalence of ever HTP smokers was assessed among the post-delivery and currently
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53 159 pregnant women. Additionally, the HTP smoking status was cross-classified according to the
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55 160 combustible cigarette smoking status of the currently pregnant and post-delivery women.
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3 161 To assess the potential association between HTP smoking and perinatal risk of HDP
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5 162 and LBW, the sample was reduced to 558 post-delivery women who could complete all the
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7 163 assessments during their pregnancy (Table 1). In the multivariable logistic regression
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9 164 analyses, the odds ratio (OR) and 95% confidence interval (CI) of ever HTP smokers for
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11 165 HDP risk were estimated after adjustment for age (Model 1, the main model in this study).
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13 166 The never HTP smokers comprised the reference group. In Model 2, full adjustments for
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15 167 other explanatory variables (combustible cigarette smoking, educational attainment,
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17 168 occupation, household income, and comorbidity) were performed, and 64 participants with
18
19 169 missing information on household income were excluded. The same analyses were performed
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21 170 for LBW.

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26 171 For the sensitivity analysis, a stratified analysis with respect to combustible cigarette
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28 172 smoking (never/ever) was performed. In addition, using a different reference group that
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30 173 included those who never smoked any form of tobacco (HTPs and combustible cigarettes),
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32 174 the ORs of ever HTP smokers for HDP and LBW risks were estimated.

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35 175 Alpha was set at 0.05, and all *P* values were two sided. Data were analyzed using
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37 176 STATA/MP13.1 (StataCorp LLC, College Station, TX).

38 177 39 40 41 42 178 **Patient and Public Involvement**

43
44 179 Neither patients nor the public was involved.
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52 182 **RESULTS**

53
54 183 Among 558 post-delivery women, the incidences of HDP and LBW were 7.3% (n=41) and
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56 184 10.0% (n=56), respectively, and the prevalence of ever HTP smokers was 11.7% (n=65,
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58 185 Table 1). Furthermore, among the 365 currently pregnant women, the prevalence of ever HTP
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186 smokers was 12.6% (n=46), which did not differ from that of HTP smokers among post-
187 delivery women ($P=0.66$).

188 Among the currently pregnant women, 4.4% (4/91 participants) of the former
189 combustible cigarette smokers reported smoking HTPs during pregnancy (Table 2),
190 corresponding to 1.1% (4/365 participants) of currently pregnant women. In addition, 36.3%
191 (33/91 participants) of former combustible cigarette smokers quit HTP smoking during
192 pregnancy, corresponding to 11.5% (42/365 participants) of currently pregnant women.

193 Among the post-delivery women, the HDP incidence was higher in ever HTP smokers
194 than in never HTP smokers (13.8% [n=9] vs. 6.5% [n=35], $P=0.03$; Table 1). Similarly, the
195 incidence of LBW was higher among ever HTP smokers than among never HTP smokers
196 (18.5% [n=12] vs. 8.9% [n=44], $P=0.02$; Table 1). When stratified by combustible cigarette
197 smoking, a similar pattern was observed among never and ever combustible cigarette
198 smokers (Table 1).

199 In the regression analysis, the age-adjusted ORs for HDP and LBW were elevated in
200 ever HTP smokers (Model 1); the ORs for HDP and LBW were 2.48 (95% CI, 1.11–5.53)
201 and 2.36 (95% CI, 1.16–4.78), respectively. However, the elevated ORs were not significant
202 after adjusting for other covariates (Model 2, Figure 1). In the same regression analyses
203 (Model 2), while ever combustible cigarette smokers were not associated with perinatal
204 outcomes, the ORs of managerial workers for HDP and LBW were 3.92 (95% CI 1.16–13.2)
205 and 3.74 (95% CI 1.41–9.93), respectively.

206 In the sensitivity analyses, when stratified by combustible cigarette smoking, a similar
207 pattern was observed independently in never and ever combustible cigarette smokers (Figure
208 1). For instance, among never combustible cigarette smokers, the age-adjusted OR of HTP
209 use for LBW was 4.82 (95% CI, 1.19–19.6). A further analysis comparing 65 ever HTP
210 smokers in the post-delivery group and 411 never tobacco smokers showed similar results:

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3 211 compared with those who never smoked any form of tobacco, the age-adjusted ORs of ever
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5 212 HTP smokers for HDP and LBW were 2.56 (95% CI 1.13–5.80) and 2.52 (95% CI 1.22–
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7 213 5.20), respectively (Model 1). However, after adjusting for other covariates (Model 2), the
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9 214 ORs were not significant due to the small sample size: the ORs for HDP and LBW were 2.40
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11 215 (95% CI 0.27–21.2) and 3.59 (95% CI 0.66–19.5), respectively.
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18 218 **DISCUSSION**

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21 219 During the first wave of the COVID-19 pandemic in Japan, the incidence of HTP use among
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23 220 pregnant women exceeded 10%, and there was a suspected association of HTP use and
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25 221 perinatal risk of HDP and LBW. However, after adjusting for potential explanatory factors,
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27 222 there was no significant association, which may be due to the weak statistical power because
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29 223 of the small sample size.
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33 224 To the best of our knowledge, this is the first report of a potential association between
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35 225 HTP use and perinatal risks. Although smoking plays a controversial role,[10] recent
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37 226 evidence suggests that combustible cigarette smoking is associated with increased HDP
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39 227 risk.[11, 12] Although the biological and genetic pathways (e.g., CYP2A6 and nicotine)
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41 228 underlying the associations observed in different phenotypes of HDP (e.g., preeclampsia and
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43 229 gestational hypertension) have not been elucidated,[20] HDP is recognized as a systemic
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45 230 disease attributable to placental circulatory dysfunction.[21] In experimental research, aerosol
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47 231 from HTPs was found to damage vascular endothelial function in rats.[6] Therefore, the
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49 232 association between HDP risk and HTP use may involve acute and chronic vascular damage,
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51 233 irrespective of combustible cigarette smoking. Furthermore, as concluded in a recent
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53 234 systematic review, smoking is a strong risk factor for LBW.[22] Thus, given the fact that
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55 235 HTPs are smoking devices, our observed results are in line with established reports.
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3 236 Although HTP-related unfavorable health outcomes (e.g., acute respiratory and
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5 237 cardiovascular risks) are likely to occur,[6, 7] the impression of HTPs as a healthy alternative
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8 238 is promoted by HTP use advertisements.[5] The Japanese HTP market share accounted for
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10 239 21% of total tobacco sales in 2018, and the weak restrictions on tobacco advertisements and
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12 240 promotion in this country contribute to increased HTP use.[23] Among currently pregnant
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14 241 women, approximately 4% of former combustible cigarette smokers reported smoking HTPs
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17 242 in the present study. This result might explain the change from combustible cigarettes to HTP
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19 243 smoking during pregnancy. In a setting of weak tobacco restrictions such as Guatemala, even
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21 244 though the prevalence of HTP use is low (2.9%) among adolescents, a high prevalence is
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24 245 anticipated.[4] However, our findings imply that HTP use is not a healthy alternative.
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26 246 Evidence for unfavorable HTP-related health outcomes is still insufficient, particularly
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28 247 among reproductive age women. In addition, the impact of multidimensional factors of the
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30 248 COVID-19 pandemic (e.g., the infection, mental health, and socioeconomic factors) and the
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32 249 smoking behaviors of others (e.g., partners and family) on the association between HTP use
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35 250 and perinatal risks remains unknown. The ongoing JACSIS study may provide updates in this
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38 251 regard.

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40 252 Our study has limitations. First, this web-based, self-reported, cross-sectional study had
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42 253 a small sample size, which may thus involve a selection bias and weak statistical precision,
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44 254 and it cannot provide an explanation of the causal mechanisms between HTP use and
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47 255 perinatal risks. Due to the lack of information on HTP smoking during pregnancy, the direct
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49 256 impact of HTP smoking on pregnancy outcomes could not be assessed. Furthermore, details
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51 257 on the participants' medical histories including relevant comorbidities, and detailed smoking
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54 258 information such as smoking intensity and duration of smoking abstinence were not
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56 259 available. In addition, electronic cigarette use was not assessed. However, the prevalences of
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58 260 HDP and HTP smokers were mostly parallel to the general population in Japan.[2, 3, 16] The
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3 261 incidence of HTP use did not differ between post-delivery and currently pregnant women in
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5 262 our study. Second, recall and reporting bias of HTP use could not be discarded, as suggested
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8 263 in a study on combustible cigarette and electronic cigarette smoking.[4] Because self-report-
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10 264 based smoking status among pregnant women tends to misclassify ever smokers as never
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12 265 smokers,[24] our estimates might be biased toward the null. Third, the perinatal clinical
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14 266 information was self-reported and not based on medical charts, thereby limiting the precision
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17 267 of the results. However, all participants were asked to base their responses on information in
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19 268 their Maternal and Child Health Handbooks, a well-established home-based maternal and
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21 269 neonatal record during pregnancy.[18] Therefore, this limitation might not have affected our
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24 270 results, or at least not largely. Despite these limitations, all HTPs that were available during
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26 271 the study period were assessed. This is the first report on the status of HTP use among
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28 272 pregnant women in Japan, and it highlights the potentially elevated maternal and neonatal
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31 273 risks associated with HTP use. Additionally, to date, besides the present study, no other
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33 274 human studies have assessed the potential effect of the maternal use of new tobacco products
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35 275 (i.e., e-cigarettes and HTPs) on perinatal health.[25] Therefore, our findings shed light and
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37 276 motivate further investigations to assess the life-threatening perinatal risks associated with
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40 277 new tobacco products.

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42 278 In conclusion, the incidence of HTP use seems to exceed 10% among pregnant women,
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44 279 and HTP smoking may be associated with increased maternal and neonatal risks in Japan.
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47 280 Undoubtedly, smoking in reproductive age women can cause unfavorable perinatal
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49 281 outcomes.[26] Hence, efforts should be made to investigate the risk of HTP use in
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51 282 reproductive age women, to prevent life-threatening perinatal complications and deaths.
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4
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11
12 289 JP18K17351).

14
15 290 **Data availability statement:** The data that support the findings of this study are available on
16
17 291 reasonable request. However, restrictions apply to the availability of these data due to
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19 292 personal identification; research data are not shared. If any person wishes to verify our data,
20
21 293 they are most welcome to contact the corresponding author.

23
24 294 **Conflict of interest:** The authors declare no potential conflicts of interest.

25
26 295 **Author contributions:** MZ and TT designed the study. TT supervised the study. MZ, YH,
27
28 296 and SO developed the methodology. SO, AH, and TT created the dataset. MZ and YH
29
30 297 analyzed the data. MZ and YH wrote the first draft of the manuscript. SO, AH, GK, and TT
31
32 298 commented on the manuscript. All authors read and approved the final version.

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34 299 **Ethics approval:** The study was approved by the Institutional Review Board of the Osaka
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36 300 International Cancer Institute approved the study (Protocol Number 20084).

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3 377 **FIGURE LEGEND**
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5 378 **Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive**
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8 379 **disorders of pregnancy and low birth weight, compared with never heated tobacco**
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10 380 **product smokers.** Age was adjusted in Model 1, and other covariates (combustible cigarette
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12 381 smoking, educational attainment, occupation, household income, and comorbidity) were
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14 382 additionally adjusted in Model 2. The samples for each analysis in Model 2 were as follows:
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16 383 n=494 (overall), n=370 (never combustible cigarette smokers), and n=124 (ever combustible
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18 384 cigarette smokers) for hypertensive disorders of pregnancy; and n=478 (overall), n=310
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20 385 (never combustible cigarette smokers), and n=118 (ever combustible cigarette smokers) for
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22 386 low birth weight. Abbreviations: HTP, heated tobacco products; OR, Odds ratio.
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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	<i>n</i> =493	<i>n</i> =65	<i>n</i> =319	<i>n</i> =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	<i>n</i> =436	<i>n</i> =58	<i>n</i> =263	<i>n</i> =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	<i>n</i> =411	<i>n</i> =10	<i>n</i> =265	<i>n</i> =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	<i>n</i> =361	<i>n</i> =9	<i>n</i> =219	<i>n</i> =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	<i>n</i> =82	<i>n</i> =55	<i>n</i> =54	<i>n</i> =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	<i>n</i> =75	<i>n</i> =49	<i>n</i> =44	<i>n</i> =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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394 **Table 2. Smoking status and use of heated tobacco products cross-classified according**
 395 **to combustible cigarette smoking status**

Characteristics	HTP smoking status			
	Never	Former	Current	Total
Post-delivery women, <i>total</i>	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, <i>total</i>	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%)

396 Abbreviation: HTP, heated tobacco product.

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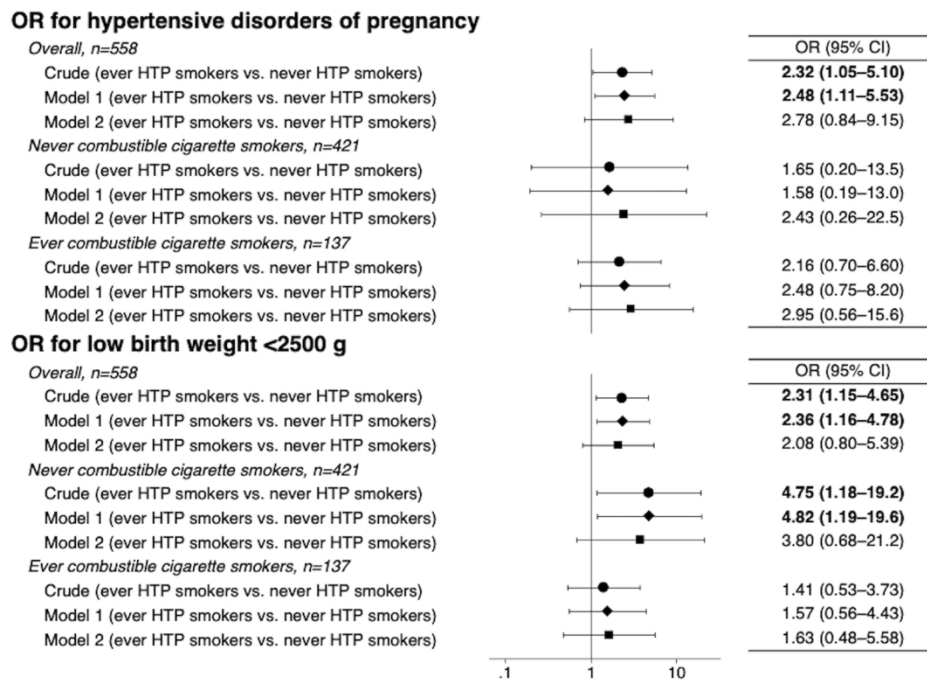


Figure 1. Odds ratio of ever heated tobacco product smokers with hypertensive disorders of pregnancy and low birth weight, compared with never heated tobacco product smokers. Age was adjusted in Model 1, and other covariates (combustible cigarette smoking, educational attainment, occupation, household 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)

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 an 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)

1	Time/Date	In what timeframe were the data collected?	P5
2	Randomization of items or questionnaires	To prevent biases items can be randomized or alternated.	Not used
3	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
4	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
5	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
6	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
7	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
8	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
9	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
10	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
11	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

1	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".)	
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6	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
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11	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
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18	Log file analysis	Indicate whether other techniques to analyze the log file for identification of multiple entries were used. If so, please describe.	P5
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21	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
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25	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
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27			
28	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
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32	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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36 This checklist has been modified from Eysenbach G. Improving the quality of Web surveys: the Checklist for Reporting Results of Internet E-Surveys (CHERRIES). J Med Internet Res. 2004 Sep 29;6(3):e34 [erratum in J Med Internet Res. 2012; 14(1): e8.]. Article available at
37 <https://www.jmir.org/2004/3/e34/>; erratum available <https://www.jmir.org/2012/1/e8/>. Copyright ©Gunther Eysenbach. Originally published in the
38 [Journal of Medical Internet](https://www.jmir.org/2004/3/e34/) Research, 29.9.2004 and 04.01.2012.
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