BMJ Open

Secondhand-aerosol exposure from heated tobacco products among nonsmokers in Japan: its prevalence and association with respiratory symptoms—a nationwide cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065322
Article Type:	Original research
Date Submitted by the Author:	31-May-2022
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Keywords:	Asthma < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, PUBLIC HEALTH

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Study type: Original research

Secondhand-aerosol exposure from heated tobacco products among nonsmokers in Japan: its prevalence and association with respiratory symptoms—a nationwide cross-sectional study

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Counts:

Abstract: 270

Manuscript: 2,766

Figures and Tables: Four Tables and One Figure

Abstract

Objectives: To investigate the association between secondhand-aerosol exposure from heated tobacco products (HTPs) and respiratory symptoms and the prevalent of secondhand aerosols among nonsmokers.

Design: Cross sectional study.

Setting: Internet survey conducted between 8 and 26 February 2021 in Japan.

Participants: Non-smoking respondents aged 15−80 years.

Exposure: Self-reported secondhand-aerosol exposure.

Primary and secondary outcomes: We defined asthma/asthma-like symptoms as a primary outcome and persistent cough as a secondary outcome. First, we examined the association between secondhand-aerosol exposure from HTPs and respiratory symptoms (asthma attacks/asthma-like symptoms and persistent cough). The prevalence ratio (PR) and 95% confidence interval (CI) were calculated by using weighted, multivariable "modified" Poisson regression models. Second, we described the prevalence of such exposure in different environments.

Results: Of 18,839 nonsmokers, 9.8% (95% CI 8.2–11.7) and 16.7% (95% CI 14.8–18.9) of those who were exposed to secondhand aerosols reported asthma attacks/asthma-like symptoms and persistent cough, whereas 4.5% (95% CI 3.9–5.2) and 9.6% (95% CI 8.4–11.0) of those who were not, respectively. Secondhand-aerosol exposure was associated with respiratory symptoms (asthma attacks/asthma-like symptoms: PR 1.49, 95% CI 1.21–1.85; persistent cough: PR 1.44, 95% CI 1.21–1.72) after adjusting for covariates. The workplace (weighted prevalence 7.0%, 95% CI 6.4–7.6), and home (weighted prevalence 5.9%, 95% CI 5.4–6.5) were the most common indoor environments of

exposure.

Conclusion: Secondhand-aerosol exposure from HTPs was associated with both asthma attacks/asthma-like symptoms and persistent cough. In the indoor setting, such exposure was most common in the workplace and at home. These results provide policymakers with meaningful information in the regulation of HTP use for the protection of nonsmokers.

Strengths and limitations of this study

- Using a large-scale internet survey data conducted in Japan, this study clarified the association between secondhand aerosols from heated tobacco products and respiratory symptoms (asthma attacks/asthma-like symptoms and persistent cough) among nonsmokers.
- In the indoor setting, exposure of secondhand aerosols from heated tobacco products was most common in the workplace and at home.
- The findings of this study can provide policymakers with information in regulating heated tobacco product use for the protection of nonsmokers' health.
- There may be some differences between respondents and the general population.
- There may also be measurement errors because all variables were based on self-reported questionnaires.

INTRODUCTION

It is widely known that secondhand smoke (SHS) from combustible cigarettes has a harmful effect on health.[1] The detrimental effects of SHS vary, including: ear and respiratory infections, and respiratory symptoms such as asthma attacks among children; and heart disease, stroke, and lung cancer among adults.[1] SHS exposure is also associated with death among all age groups due to the diseases mentioned above. The estimated global deaths associated with SHS exposure increased from 848,702 in 2006 to 883,930 in 2016.[2] Notably, SHS exposure is harmful to nonsmokers; therefore, the Centers for Disease Control and Prevention in the United States clearly emphasize that complete protection of nonsmokers from SHS is essential for a comprehensive smoke-free policy.[1] Such a policy may reduce smoking prevalence and associated harms.[3] Taken together, the protection of nonsmokers from SHS is a relevant and established issue for healthcare professionals, public health researchers, and policymakers.

As new tobacco products, such as electronic cigarettes (e-cigarettes) and heated tobacco products (HTPs), were introduced in and spread rapidly since the early 2010s,[4,5] secondhand aerosols from such products are emerging as another public health interest associated with SHS. Secondhand aerosols from e-cigarettes are prevalent in the US and European countries,[6,7] and studies have suggested that exposure to secondhand aerosols from e-cigarettes is associated with sensory irritation or asthma attacks.[8,9] On the other hand, although secondhand aerosols from HTPs are also prevalent, especially in Japan,[5,10] there has been a lack of research on the potential association between secondhand-aerosol exposure from HTPs and health conditions. To date, only one study has revealed that inhalation of secondhand aerosols from HTPs may induce subsequent asthma-like attacks

and chest pain;[11] however, the association between such inhalation and respiratory symptoms remains unclear. In other studies, the use of HTPs was associated with upper and lower chronic respiratory diseases, such as allergic rhinitis and asthma[12]; this, in addition to the above-mentioned evidence about secondhand aerosols from e-cigarettes, led us to hypothesize that secondhand-aerosol exposure from HTPs are associated with respiratory symptoms.

Given the above evidence and our hypothesis, in this study, we aimed to investigate the cross-sectional association of secondhand-aerosol exposure from HTPs with the presence of respiratory symptoms among nonsmokers by using large-scale, internet-based survey data. Additionally, we aimed to reveal in which environments nonsmokers were typically exposed to secondhand aerosols, which is important information for the development of a comprehensive smoke-free policy.

METHODS

Data sources, Design and Setting

In this cross-sectional study, we used data from the 2021 Japan "Society and New Tobacco" Internet Survey (JASTIS). The JASTIS is a longitudinal cohort study in which a series of annual internet surveys have been performed since 2015. The survey is used to collect information about the use of tobacco products, including new tobacco products (such as HTPs and e-cigarettes) and combustible cigarettes, as well as participant demographics and socioeconomic status.[13] The online questionnaire was designed such that respondents had to answer each question before they could proceed to the next,

ensuring that all questions were answered before submission. Participants of the JASTIS were recruited via a survey panel provided by a major internet research group in Japan (Rakuten Insight).[14] The research group houses information of about 2.3 million panelists, including socioeconomic information such as education level, household income, and marital status. The survey panel were comprised of those who were initially recruited by the research group. In the 2021 JASTIS, 26,000 participants were recruited from the Japan "COVID-19 and Society" Internet Survey (JACSIS), a sister survey of JASTIS. The 2020 JACSIS, conducted between August 25 and September 30, 2020, reached 224,389 participants, sampling by gender, age, and prefecture stratification. JACSIS enrollment continued until the targeted number of respondents (n = 28,000) were reached, with *a priori* selection based on age, gender, and prefecture (based on the distribution of the general Japanese population in 2019). The participants of the 2021 JASTIS were obtained between the 8th and 26th of February 2021. Among the 2021 JASTIS participants, 87.8% (22,840/26,000) came from the 2020 JACSIS. To achieve the targeted response number in the 2021 JASTIS, we additionally recruited 3,160 participants from all respondents who previously participated in the 2015 to 2020 JASTISs. Detailed information regarding the JASTIS is described in the study profile.[13]

Inclusion and Exclusion Criteria

In this study, we included data from all the 2021 survey respondents who were nonsmokers, determined by using the following question: "Do you currently use any of the following tobacco products? (Cigarettes, roll-your-own cigarettes, Ploom Tech, Ploom Tech plus, Ploom S, IQOS, glo, glo hyper, glo sens, PULZE, electronic cigarettes containing nicotine, electronic cigarettes without nicotine, electronic cigarettes with

unknown nicotine content, cigars, little cigars, pipes, chewing tobacco, snuffing tobacco, and hookahs).” The response options were “never,” “several times in the past,” “habitually in the past,” “occasionally,” and “almost every day.” In this study, we defined nonsmokers as those who selected one of the first three options. We excluded surveys as straight-lining responses if the respondents chose the same number in answer to all questions in a set of questions. We also excluded responses in which respondents reported an amount of tobacco product use but had indicated that they had never used or were only former users of tobacco products. In addition to these exclusion criteria, we performed an attention check with the following question: "Please choose the answer second from the bottom." With this attention check, we excluded respondents who selected responses other than the second answer from the bottom.

Measurement of Exposure Variables

The exposure variable that we examined was the exposure to secondhand aerosols from HTPs over the past year. Hence, in the questionnaire, respondents were asked, “During the past year, have you knowingly inhaled aerosols from HTPs used by others?” The response options were “never,” “rarely,” “sometimes,” and “frequently.” In this study, we defined those who were exposed to secondhand aerosols from HTPs as those who selected the latter three options. In addition, we also collected information about respondents’ exposure to secondhand aerosols over the past month in the following places: at home, in the workplace, at school, in restaurants, in cafés, in bars, in casinos, in the car, and on the road, using similar questions and response options as above. We defined “indoors” as all of the above places except for “on the road,” and separately calculated the prevalence of secondhand aerosol exposure from HTPs indoors, outdoors, and overall.

Main Outcomes and Measures

In this study, we defined self-reported respiratory symptoms as outcomes. As a primary outcome, we selected asthma attacks/asthma-like symptoms, which previous studies indicated were associated with aerosols from HTPs.[11,12] As a secondary outcome, we selected non-specific persistent cough, for which a previous study indicated a possible association with e-cigarette use.[15] The JASTIS included the question, "During the past year, have you experienced any of the following conditions: asthma attacks/asthma-like symptoms or persistent cough?" The response options were "never," "rarely," "sometimes," and "frequently." We defined the presence of each respiratory symptom as a selection of any of the latter three options.

Covariates

As evidence for a relationship between secondhand aerosols and respiratory symptoms is limited, we selected the following 12 variables as potential confounding factors: age (15–29, 30–44, 45–59, or 60–80 years), sex (male or female), education status ("high school or less" or "college or more"), marital status (married, never married, or widowed/divorced), household size (living alone or living with others), household equivalent income (1st quartile, 2nd quartile, 3rd quartile, 4th quartile, or unknown/declined to answer), combustible cigarette use, HTP use, other tobacco-product use, SHS exposure over the past month, and two respiratory comorbidities: asthma and bronchitis/pneumonia.

Statistical Analysis

First, we calculated the frequency of each variable as baseline characteristics. Second, we stratified the experience of respiratory symptoms over the past year by exposure to secondhand aerosols. Third, we conducted multivariable, "modified" Poisson regression analysis with a robust estimator to estimate the prevalence ratio (PR) and confidence interval (CI) for the prevalence of each respiratory symptom. The exposure variable (exposure to secondhand aerosols from HTPs) was dichotomized, as previously noted, or included as a categorical variable (with "never" as a reference, and "rarely," "sometimes," and "frequently"). The equivalence of outcome prevalence in each category was tested by assigning a linear score by treating secondhand aerosol frequencies as an ordinal variable. Fourth, we examined the weighted prevalence of nonsmokers' exposure to secondhand aerosols from HTPs over the past month. In addition, to examine the multicollinearity of variables in the multivariable models, we evaluated the variance inflation factors in all analyses.

To account for the differences between the sociodemographic status of respondents from the survey panel and that of the Japanese general public, we used inverse-probability weighting for all analyses.[13,16] The sampling weights, which were scaled such that the total amounted to 26,000 (original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years. In this way, we adjusted for the difference between respondents in the current internet survey and the 2016 Comprehensive Survey of Living Conditions, a nationally representative survey in

Japan.[17] All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting. Statistical significance was set at $P<0.05$. The data were analyzed using "svy: tabulate" and "svy: glm" commands in STATA version 16.1 (Stata Corp., College Station, TX, USA).

Patient and public involvement

No patients or the public were involved in this study. We did not invite any patients to comment on the study design, interpretation of the results, or the readability or accuracy of the manuscript.

RESULTS

Of the 26,000 respondents, 18,839 nonsmokers were included for analyses (**Figure S1**). With inverse-probability weighting, 36.6% (95% CI 34.2–39.1) of participants were aged 60–80, 55.7% (95% CI 53.8–57.6) were female, 53.8% (95% CI 51.6–55.9) were high-school graduates or had less education, and 66.0% (95% CI 64.0–67.8) were married. Regarding smoking and SHS status, 34.0% (95% CI 32.1–36.0) were past combustible-cigarette users, 4.1% (95% CI 3.7–4.6) were past HTP users, and 9.5% (95% CI 8.7–10.4) were past users of other tobacco products. In particular, 80.3% (95% CI 79.0–81.6) of participants had been exposed to SHS in the past month (**Table 1**).

Table 1 Demographics of study participants

Characteristics	N = 18,839	n	%	Weighted %[a]	95% CI
Age	15–29	3,024	16.1	15.5	14.5–16.6
	30–44	4,205	22.3	20.4	19.3–21.5
	45–59	4,967	26.4	27.5	26.1–28.9
	60–80	6,643	35.3	36.6	34.2–39.1
Sex	Male	8,598	45.6	44.3	42.4–46.2
	Female	10,241	54.4	55.7	53.8–57.6
Education status	High school or less	5,789	30.7	53.8	51.6–55.9
	College or more	13,050	69.3	46.2	44.1–48.4
Marital status	Married	11,431	60.7	66.0	64.0–67.8
	Not married	5,670	30.1	25.1	23.6–26.7
	Widowed/divorced	1,738	9.2	8.9	7.5–10.7
Household size	Living alone	15,266	81.0	84.9	82.8–86.8
	Living with others	3,573	19.0	15.1	13.3–17.2
Household-equivalent income	1st quartile	3,816	20.3	23.0	21.5–24.6
	2nd quartile	3,874	20.6	21.5	19.7–23.5
	3rd quartile	3,716	19.7	18.4	16.9–20.1
	4th quartile	3,403	18.1	13.1	12.1–14.2
	Unknown/declined to answer	4,030	21.4	23.9	22.0–25.8
Combustible cigarette use	Never	12,822	68.1	66.0	64.1–67.9
	Past	6,017	31.9	34.0	32.1–36
HTP use	Never	18,008	95.6	95.9	95.4–96.3
	Past	831	4.4	4.1	3.7–4.6
Other tobacco product use	Never	17,035	90.4	90.5	89.6–91.3
	Past	1,804	9.6	9.5	8.7–10.4
Exposure to secondhand smoke over the past month	Absent	3,663	19.4	19.7	18.4–21.0
	Present	15,176	80.6	80.3	79.0–81.6
Asthma	Absent	18,271	97.0	96.3	95.2–97.1
	Present	568	3.0	3.7	2.9–4.8
Bronchitis or pneumonia	Absent	18,624	98.9	98.4	97.9–98.8
	Present	215	1.1	1.6	1.2–2.1

Note. CI: confidence interval, HTP: heated tobacco product.

[a] The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs were based on the Wald-type test on the probability scale, which was accompanied by the robust variance estimator of the weighted proportions accounting for the inverse-probability weighting ("svy: tabulate" command in Stata)

Of 18,839 respondents, 4,402 (23.4%) were exposed to secondhand aerosols from HTPs. With inverse-probability weighting, 9.8% (95% CI 8.2–11.7) and 16.7% (95% CI 14.8–18.9) of those who were exposed to secondhand aerosols reported asthma attacks/asthma-like symptoms and persistent cough, whereas 4.5% (95% CI 3.9–5.2) and 9.6% (95% CI 8.4–11.0) of those who were not, respectively.

(**Table 2**).

Table 2 Respiratory symptoms over the past year among non-smokers classified into the experience of secondhand aerosols

Symptoms	Frequency	Secondhand aerosol (-) n = 14,437				Secondhand aerosol (+) N = 4,402			
		n	%	Weighted % [a]	95% CI	n	%	Weighted % [a]	95% CI
Asthma attacks/asthma-like symptoms	Never	13,772	95.4	95.5	94.8–96.1	4,043	91.8	90.2	88.3–91.8
	Rarely	424	2.9	2.7	2.3–3.2	211	4.8	5.6	4.5–6.8
	Sometimes	205	1.4	1.6	1.2–2.1	124	2.8	3.3	2.3–4.8
	Frequently	36	0.2	0.2	0.1–0.3	24	0.5	0.9	0.5–1.6
Persistent cough	Never	13,163	91.2	90.4	89.0–91.6	3,787	86.0	83.3	81.1–85.4
	Rarely	697	4.8	4.9	4.3–5.7	346	7.9	8.2	6.9–9.7
	Sometimes	446	3.1	3.9	2.9–5.2	224	5.1	7.1	5.6–8.9
	Frequently	131	0.9	0.8	0.6–1.1	45	1.0	1.4	0.9–2.1

Note. CI: confidence interval.

[a] The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs were based on the Wald-type test on the probability scale, which was accompanied by the robust variance estimator of the weighted proportions accounting for the inverse-probability weighting ("svy: tabulate" command in Stata).

In the multivariable analysis, exposure to secondhand aerosols was associated with both primary and secondary outcomes after adjusting for covariates using "modified" Poisson regression models (asthma attacks/asthma-like symptoms: PR 1.49, 95% CI 1.21–1.85, $P<0.001$; persistent cough: PR 1.44, 95% CI 1.21–1.72, $P<0.001$) (**Table 3**).

Table 3 Multivariable weighted Poisson regression analysis for respiratory symptoms among non-smokers

Characteristics	N = 18,839	Asthma attacks/asthma-like symptoms			Persistent cough		
		PR	95% CI	*P* value	PR	95% CI	*P* value
Exposure to secondhand aerosols	Absent		Reference			Reference	
	Present	1.49	1.21–1.85	<0.001	1.44	1.21–1.72	<0.001
Age	15–29	1.35	1.01–1.79	0.04	1.02	0.79–1.31	0.87
	30–44	1.14	0.89–1.46	0.30	1.15	0.96–1.38	0.14
	45–59		Reference			Reference	
	60–80	0.85	0.64–1.14	0.27	1.13	0.91–1.39	0.27
Sex	Male		Reference			Reference	
	Female	0.92	0.74–1.15	0.45	1.12	0.93–1.36	0.24
Education status	High school or less		Reference			Reference	
	College or more	1.04	0.86–1.26	0.69	0.92	0.74–1.15	0.47
Marital status	Married		Reference			Reference	
	Not married	1.02	0.81–1.29	0.87	0.97	0.77–1.22	0.78
	Widowed/divorced	1.60	1.03–2.46	0.04	1.39	0.93–2.08	0.11
Household size	Living alone		Reference			Reference	
	Living with others	0.85	0.61–1.19	0.34	1.14	0.8–1.61	0.47
Household-equivalent income	1st quartile		Reference			Reference	
	2nd quartile	0.81	0.61–1.07	0.14	0.90	0.67–1.21	0.49
	3rd quartile	0.88	0.62–1.24	0.47	0.77	0.56–1.06	0.11
	4th quartile	0.87	0.65–1.17	0.35	0.92	0.69–1.23	0.58
	Unknown/declined to answer	0.72	0.53–0.97	0.03	0.81	0.6–1.09	0.16
Combustible cigarette use	Never		Reference			Reference	
	Past	0.93	0.71–1.22	0.60	1.17	0.88–1.55	0.28
HTP use	Never		Reference			Reference	
	Past	1.71	1.19–2.44	0.003	1.34	1.05–1.72	0.02
Other tobacco product use	Never		Reference			Reference	
	Past	1.35	0.96–1.90	0.09	1.42	1.09–1.85	0.01
Exposure to secondhand smoke over the past month	Absent		Reference			Reference	
	Present	0.86	0.67–1.11	0.26	0.97	0.78–1.21	0.80
Asthma	Absent		Reference			Reference	
	Present	12.39	9.75–15.75	<0.001	4.12	3.13–5.42	<0.001
Bronchitis or pneumonia	Absent		Reference			Reference	
	Present	1.68	1.20–2.35	0.003	2.04	1.46–2.85	<0.001

Note. PR: prevalence ratio, CI: confidence interval, HTP: heated tobacco product.
The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting.

When examining the association of ordinal exposure variables with the outcomes, the same associations were observed (**Figure 1, Table S1**). Notably, all outcomes exhibited a nearly monotonic relationship with the frequency of exposure to secondhand aerosols (both $P<0.001$ with the linear trend test). The maximum variance inflation factor was 2.01, suggesting that there was no problematic multicollinearity in the regression models (**Table S2**).

In terms of places in which respondents were exposed to secondhand aerosols over the past month, 20.3% (95% CI 19.1–21.7) were exposed to secondhand aerosols overall, and 14.2% (95% CI 13.3–15.1) were exposed to secondhand aerosols indoors. The most common places of exposure indoors were the workplace (weighted proportion 7.0%, 95% CI 6.4–7.6) and at home (weighted proportion 5.9%, 95% CI 5.4–6.5) (**Table 4**).

Table 4 Weighted prevalence of nonsmokers' secondhand aerosol exposure from heated tobacco products in the past month

Place	N = 18,839	n	%	Weighted % [a]	95% CI
Indoors		2,801	14.9	14.2	13.3–15.1
	Home	1,088	5.8	5.9	5.4–6.5
	Workplace	1,337	7.1	7.0	6.4–7.6
	School	316	1.7	1.6	1.3–1.9
	Restaurant	841	4.5	3.4	3.1–3.8
	Café	698	3.7	2.8	2.5–3.1
	Bar	718	3.8	3.0	2.7–3.4
	Casino	353	1.9	1.7	1.5–2.0
	Car	771	4.1	4.4	3.9–5.0
Outdoors		3,023	16.0	12.9	11.9–14
Any		4,319	22.9	20.3	19.1–21.7

Note. CI: confidence interval.

[a] The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan.

All CIs were based on the Wald-type test on the probability scale, which was accompanied by the robust variance estimator of the weighted proportions accounting for the inverse-probability weighting ("svy: tabulate" command in Stata).

DISCUSSION

Using data from a large-scale, nationwide survey conducted in February 2021 in Japan, we discovered a cross-sectional association between secondhand-aerosol exposure and two respiratory symptoms (asthma attacks/asthma-like symptoms and persistent cough) after adjusting for 12 potential confounding factors. The PRs of respiratory symptoms increased as the frequency of exposure to secondhand aerosols from HTPs increased. Furthermore, the weighted prevalence of secondhand-aerosol exposure over the past month was approximately 20%, and, similar to those of SHS from combustible cigarettes and secondhand aerosols from e-cigarettes,[1,6] the workplace and home were the most common places of secondhand-aerosol exposure in indoor settings. Given these findings, many nonsmokers in Japan may be exposed to secondhand aerosols from HTPs, which may have detrimental effects on their respiratory systems.

There are several potential mechanisms by which secondhand aerosols may cause respiratory symptoms. First, in the biochemical context, aerosols from HTPs contain substantial amounts of chemical compounds such as carbonyl compounds and polycyclic aromatic hydrocarbons.[18] These chemicals damage human bronchial epithelial cells,[19] inducing asthma attacks or asthma-like symptoms. Second, in the physiological context, inhalation of the chemical compounds in aerosols from HTPs impairs respiratory function (forced expiratory volume in one second, both absolute and as a percentage of the predicted value),[20] resulting in respiratory symptoms. Finally, in the indoor environmental context, secondhand aerosols contain concentrations of harmful chemical

compounds, such as nicotine and fine particulate matter, greater than the upper limits of the range of tolerable concentrations.[21] Consequently, even nonsmokers may experience asthma attacks/asthma-like symptoms or persistent cough via the above-mentioned biochemical and physiological mechanisms after inhalation of secondhand aerosols emitted by others, especially indoors.

Although there have been studies of the prevalence of secondhand aerosols from e-cigarettes[6,7] and their association with health conditions such as asthma and lung cancer,[22,23] there have been few studies of the prevalence of exposure to secondhand aerosols from HTPs or its association with health. Tabuchi *et al.* conducted an internet survey in Japan in 2017 to investigate HTP use, the prevalence of related exposure to secondhand aerosols, and perceived symptoms from such exposure.[5] They discovered that 6.9% of nonsmoking respondents were exposed to secondhand aerosols from HTPs, and the rate of HTP use was 3.6%. In addition, Imura and Tabuchi, via an internet survey conducted in 2019, examined the cross-sectional association between exposure to secondhand aerosols and symptoms directly induced by such exposure.[11] They revealed that asthma-like attacks and chest pain were more prevalent in those who were exposed to secondhand aerosols from HTPs than to SHS from combustible cigarettes. Although those studies were informative, reports of the updated and detailed prevalence of exposure to secondhand aerosols and evaluation of its association with particular health conditions remains limited. To our knowledge, this is the first study in which the environments in which people were exposed to secondhand aerosols from HTPs were clarified and the association between such exposure and respiratory symptoms was evaluated among nonsmokers, by using nationally representative, large-scale survey data.

Our study has several limitations. First, because of this study's cross-sectional design, the temporal relationship between secondhand-aerosol exposure and respiratory symptoms was unclear, and our results cannot be used to infer causality. However, the results from this study implied a nearly monotonic relationship between the frequency of exposure to secondhand aerosols and the PR for each respiratory symptom under assessment, which is a key component in explaining causality.[24] Second, this study was based on self-report questionnaires and not all variables were measured with validated questionnaires; therefore, measurement errors may exist. However, we developed an algorithm for exclusion of responses that were unreliable or invalid, and excluded such respondents *a priori*. Third, this study is based on an internet survey; the composition of study participants may have differed from that of the general Japanese public. However, to minimize such differences, we adjusted for demographic, socioeconomic, and health-related differences between respondents in the present study and the Japanese general public by using nationally representative survey data. Finally, this study was conducted in Japan, where HTPs are more popular than in other countries;[25] therefore, our findings may not be generalizable to other countries.

In conclusion, by using data from a nationally representative survey, this study revealed that exposure to secondhand aerosols from HTPs were prevalent in 2021 in Japan. This study clarified the association between such exposure and asthma attacks/asthma-like symptoms and persistent cough among nonsmokers. Furthermore, in the indoor setting, such exposure was most common in the workplace and at home. As the number of HTP users is growing in Europe and the United States,[26,27] as well as in Japan, the threat to

nonsmokers' health due to secondhand-aerosol exposure from HTPs will increase globally. Thus, our findings provide policymakers with meaningful information in regulating HTP use for the protection of nonsmokers.

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Author contributions: All authors contributed to the conceptualization of this study. TY and TT collected data, and TY, TS, and TT developed the plan for analysis. TY analyzed the data. TY wrote the original manuscript, and all authors but TY reviewed, interpreted, critically appraised, and revised the original manuscript. All authors reviewed the final version of the manuscript and approved its submission. TY takes responsibility for the content of the manuscript, including the data and analysis.

Funding/Support: This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI grants (grant numbers 17H03589, 19K10671, 19K10446, 18H03107, 18H03062, 19H03860), the JSPS Grant-in-Aid for Young Scientists (grant number 19K19439), the Research Support Program to Apply the Wisdom of the University to tackle COVID-19 Related Emergency Problems, University of Tsukuba, and Health Labour Sciences Research Grant (grant numbers 19FA1005, 19FG2001, 19FA1012) and the Japan Agency for Medical Research and Development (AMED; grant number 2033648).

Disclaimer: The funders had no role in the study design, data collection, statistical analysis, decision to publish, or preparation of the manuscript, except for conducting the internet survey and language editing of the manuscript.

Competing interests: None to declare.

Data availability statement: The data used in this study are not available in a public repository because they contain personally identifiable or potentially sensitive participants' information. Based on the regulations for ethical guidelines in Japan, the Institutional Review Board of the Osaka International Cancer Institute has imposed restrictions on the dissemination of the data collected in this study. All data inquiries will be channeled through Takahiro Tabuchi (tabuchitak@gmail.com) to Osaka Cancer Institute Institutional Ethics Committee.

Ethics Approval

All procedures were conducted according to the ethical standards of the Declaration of Helsinki. We obtained web-based informed consent from all the respondents for use of their data from the JASTIS study in our research. A credit point known as "Epoints," which could be used for internet shopping and cash conversion, was provided to the participants as an incentive. This study was approved by the Institutional Review Board of Osaka International Cancer Institute (Number: 20084). The internet research group fully respected the Act on the Protection of Personal Information in Japan. This study followed the STROBE guidelines for cross-sectional studies.

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Figure Legends

Figure 1 Prevalence ratios of ordinal exposure variables for the outcomes

A: asthma attacks/asthma-like symptoms, B: persistent cough.

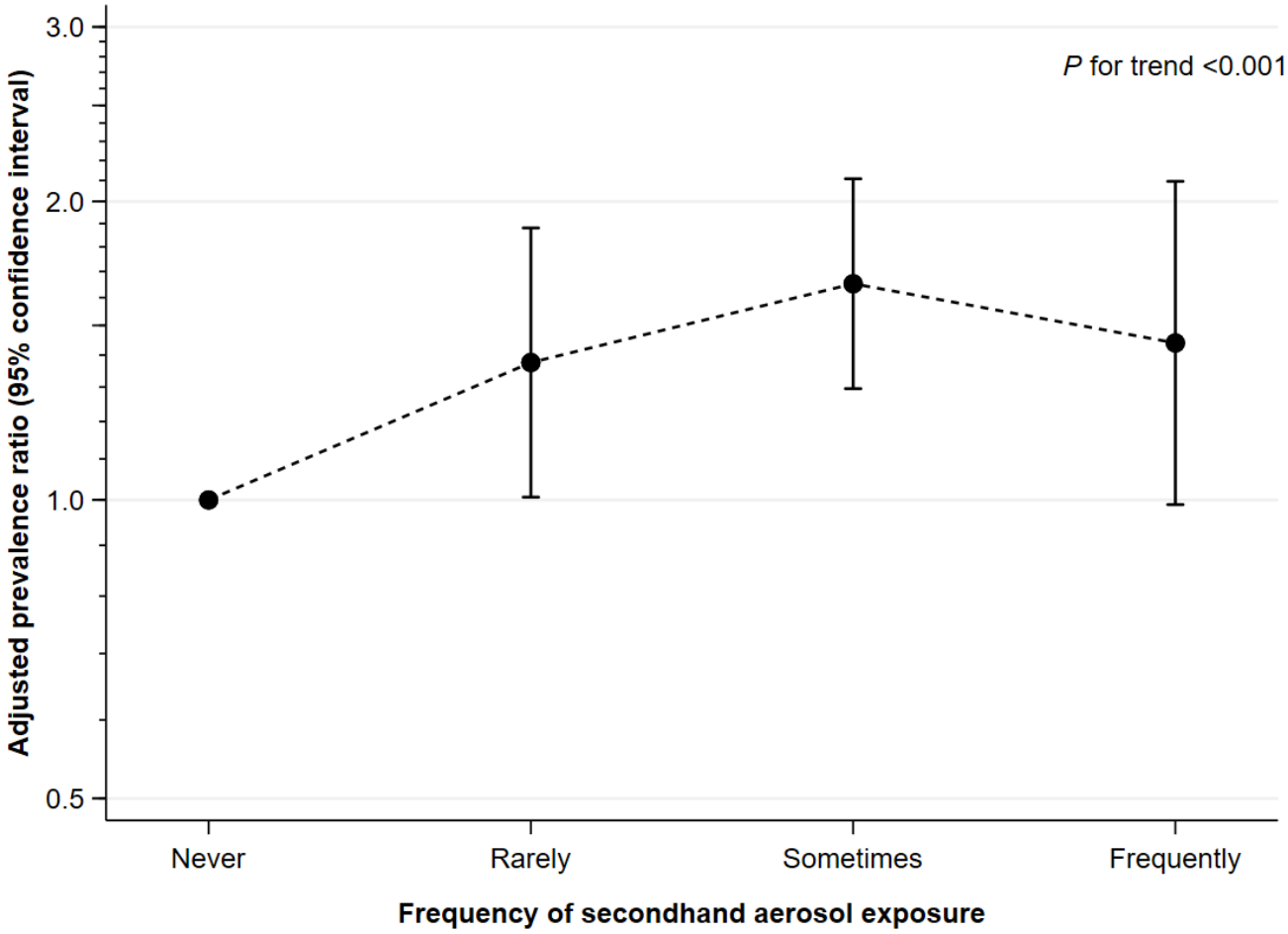
Supplemental materials:

Table S1 Multivariable Poisson regression analysis using ordinal exposure variables

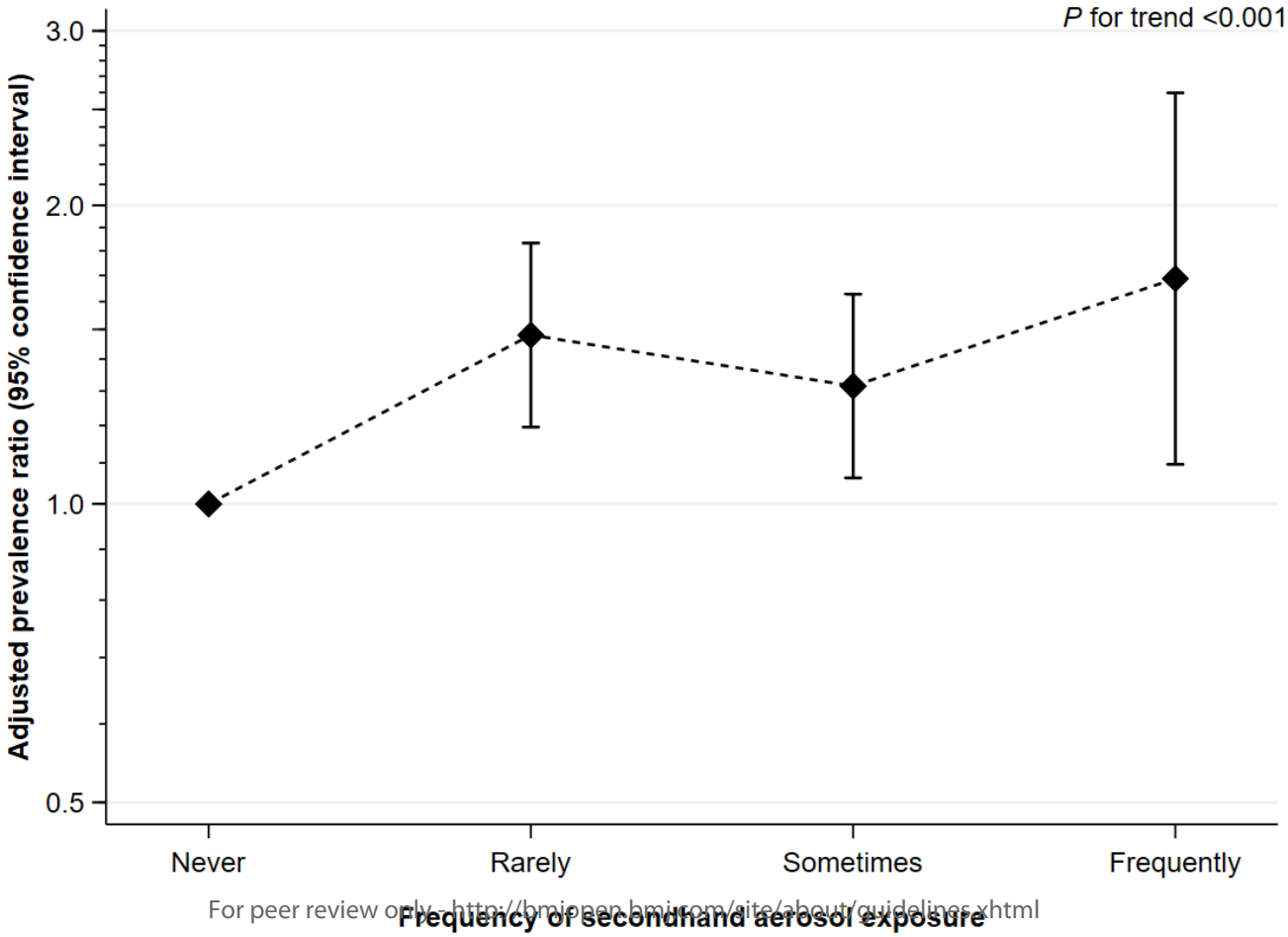
Table S2 Variance inflation factors for the evaluation of multicollinearity

Figure S1 Flow diagram of the study

A



B



Supplemental materials

Yoshioka T, Shinozaki T, Hori A, Okawa S, Nakashima K, Tabuchi T. Secondhand-aerosol exposure from heated tobacco products among nonsmokers in Japan: its prevalence and association with respiratory symptoms—a nationwide cross-sectional study

Table S1 Multivariable Poisson regression analysis using ordinal exposure variables

Characteristics	N = 18,839	Asthma/asthma-like attacks			Persistent cough		
		PR	95% CI	*P* value	PR	95% CI	*P* value
Exposure to secondhand aerosols	Never		Reference			Reference	
	Rarely	1.38	1.01–1.88	0.05	1.48	1.20–1.83	<0.001
	Sometimes	1.65	1.30–2.11	<0.001	1.31	1.06–1.63	0.01
	Frequently	1.44	0.99–2.10	0.06	1.69	1.10–2.60	0.02
Age	15–29	1.36	1.02–1.82	0.04	1.01	0.78–1.30	0.94
	30–44	1.14	0.89–1.47	0.28	1.15	0.96–1.38	0.14
	45–59		Reference			Reference	
	60–80	0.86	0.64–1.15	0.31	1.13	0.91–1.40	0.28
Sex	Male		Reference			Reference	
	Female	0.92	0.74–1.15	0.46	1.11	0.92–1.35	0.27
Education status	High school or less		Reference			Reference	
	College or more	1.04	0.85–1.27	0.70	0.93	0.74–1.16	0.50
Marital status	Married		Reference			Reference	
	Not married	1.03	0.81–1.30	0.82	0.97	0.77–1.21	0.77
	Widowed/divorced	1.61	1.04–2.48	0.03	1.39	0.93–2.07	0.11
Household size	Living alone		Reference			Reference	
	Living with others	0.84	0.60–1.19	0.33	1.14	0.81–1.61	0.47
Household-equivalent income	1st quartile		Reference			Reference	
	2nd quartile	0.81	0.62–1.07	0.14	0.89	0.66–1.21	0.46
	3rd quartile	0.89	0.63–1.26	0.51	0.76	0.56–1.05	0.10
	4th quartile	0.87	0.65–1.18	0.38	0.92	0.69–1.22	0.56
	Unknown/declined to answer	0.72	0.53–0.98	0.03	0.80	0.60–1.08	0.14
Combustible cigarette use	Never		Reference			Reference	
	Past	0.94	0.71–1.22	0.63	1.17	0.88–1.55	0.29
HTP use	Never		Reference			Reference	
	Past	1.70	1.19–2.43	0.004	1.35	1.05–1.73	0.02
Other tobacco product use	Never		Reference			Reference	
	Past	1.35	0.96–1.91	0.08	1.41	1.08–1.85	0.01
Exposure to secondhand smoke over the past month	Absent		Reference			Reference	
	Present	0.86	0.67–1.11	0.25	0.97	0.78–1.21	0.81
Asthma	Absent		Reference			Reference	
	Present	12.31	9.68–15.65	<0.001	4.13	3.14–5.42	<0.001
Bronchitis or pneumonia	Absent		Reference			Reference	
	Present	1.68	1.20–2.36	0.002	2.04	1.46–2.84	<0.001

Note. PR: prevalence ratio, CI: confidence interval, HTP: heated tobacco product.

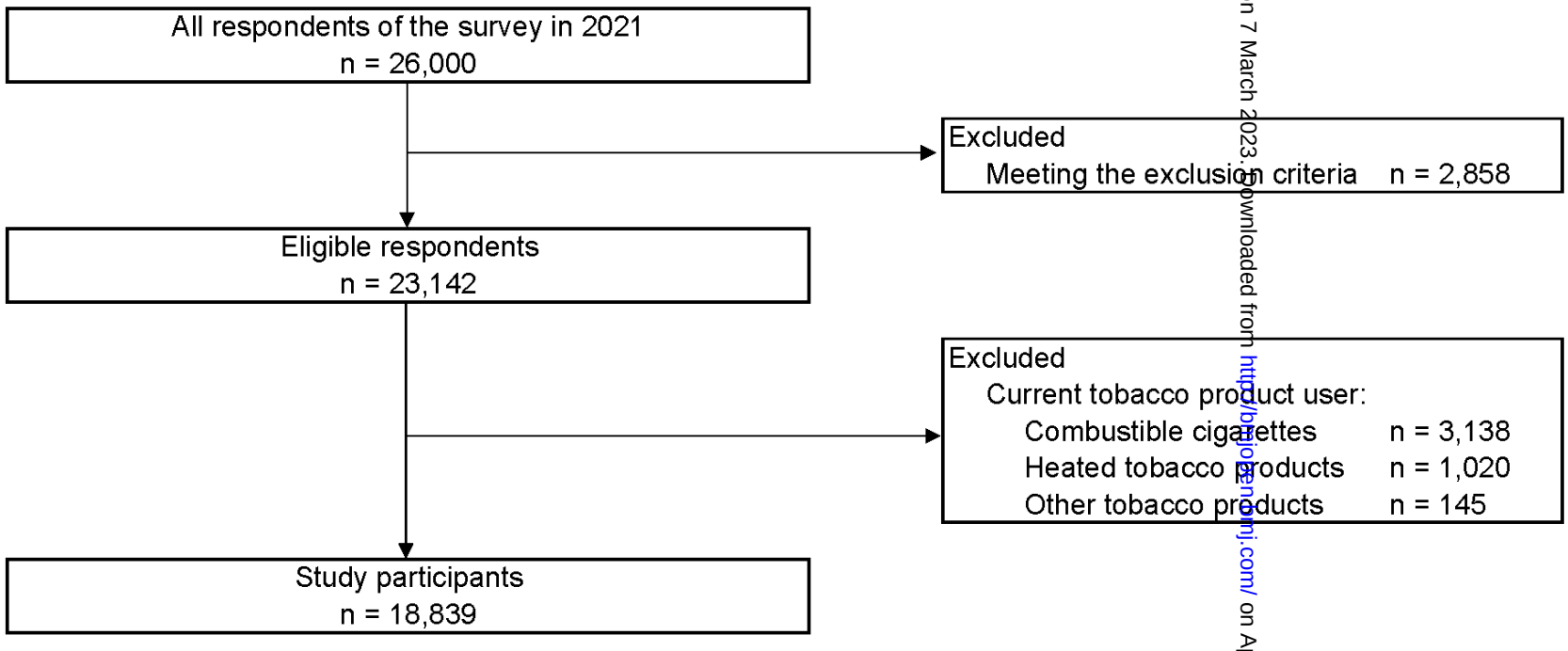
The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting.

Table S2 Variance inflation factors for the evaluation of multicollinearity

Characteristics	N = 18,839	VIF
Exposure to secondhand aerosols	Absent	Reference
	Present	1.07
Age	15–29	1.78
	30–44	1.49
	45–59	Reference
	60–80	1.68
Sex	Male	Reference
	Female	1.19
Education status	High school or less	Reference
	College or more	1.06
Marital status	Married	Reference
	Not married	2.01
	Widowed/divorced	1.31
Household size	Living alone	Reference
	Living with others	1.48
Household-equivalent income	1st quartile	Reference
	2nd quartile	1.63
	3rd quartile	1.65
	4th quartile	1.68
	Unanswered	1.66
Combustible cigarette use	Never	Reference
	Past	1.40
HTP use	Never	Reference
	Past	1.19
Other tobacco product use	Never	Reference
	Past	1.31
Exposure to secondhand smoke over the past month	Absent	Reference
	Present	1.03
Asthma	Absent	Reference
	Present	1.09
Bronchitis or pneumonia	Absent	Reference
	Present	1.10
Mean		1.41

Note. VIF: variance inflation factor, CI: confidence interval, HTP: heated tobacco products.

Figure S1 Flow diagram of the study



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1,3-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	#7
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#7,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	#8,9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#9,10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#9,10
Bias	9	Describe any efforts to address potential sources of bias	#11-12
Study size	10	Explain how the study size was arrived at	#7,8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#11,12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#11,12
		(*b*) Describe any methods used to examine subgroups and interactions	#11
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	#7,8
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#12
		(b) Give reasons for non-participation at each stage	#12, Figure S1
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#13,14
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	#14, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#16, Table 1-4
		(*b*) Report category boundaries when continuous variables were categorized	#16, Table 1-4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 1
Discussion			
Key results	18	Summarise key results with reference to study objectives	#19
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	#20,21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	#21
Other information			
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	#23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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

Association between exposure to secondhand aerosol from heated tobacco products and respiratory symptoms among current nonsmokers in Japan

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065322.R1
Article Type:	Original research
Date Submitted by the Author:	18-Nov-2022
Complete List of Authors:	Yoshioka, Takashi; Keio University, Department of Preventive Medicine and Public Health Shinozaki, Tomohiro; Tokyo University of Science, Department of Information and Computer Technology, Faculty of Engineering Hori, Ai; University of Tsukuba, Department of Global Public Health Okawa, Sumiyo; Kokuritsu Kokusai Iryo Kenkyu Center Kenkyujo Nakashima, Kei; Kameda Medical Center, Department of Pulmonary Medicine Tabuchi, Takahiro; Osaka Kokusai Gan Center, Cancer Control Center
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Health policy, Respiratory medicine, Public health
Keywords:	Asthma < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, PUBLIC HEALTH

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Study type: Original research

Association between exposure to secondhand aerosol from heated tobacco products and respiratory symptoms among current nonsmokers in Japan

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Counts:

Abstract: 216

Manuscript: 3,487

Figures and Tables: Three Tables and One Figure

Abstract

Objectives: To investigate the association between secondhand-aerosol exposure from heated tobacco products (HTPs) and respiratory symptoms among current nonsmokers.

Design: Cross sectional study.

Setting: Internet survey conducted between 8 and 26 February 2021 in Japan.

Participants: Non-smoking respondents at the survey aged 15−80 years.

Exposure: Self-reported secondhand-aerosol exposure.

Primary and secondary outcomes: We defined asthma/asthma-like symptoms as a primary outcome and persistent cough as a secondary outcome. We examined the association between secondhand-aerosol exposure from HTPs and respiratory symptoms (asthma attacks/asthma-like symptoms and persistent cough). The prevalence ratio (PR) and 95% confidence interval (CI) were calculated by using weighted, multivariable "modified" Poisson regression models.

Results: Of 18,839 current nonsmokers, 9.8% (95% CI 8.2–11.7) and 16.7% (95% CI 14.8–18.9) of those who were exposed to secondhand aerosols reported asthma attacks/asthma-like symptoms and persistent cough, whereas 4.5% (95% CI 3.9–5.2) and 9.6% (95% CI 8.4–11.0) of those who were not, respectively. Secondhand-aerosol exposure was associated with respiratory symptoms (asthma attacks/asthma-like symptoms: PR 1.49, 95% CI 1.21–1.85; persistent cough: PR 1.44, 95% CI 1.21–1.72) after adjusting for covariates.

Conclusion: Secondhand-aerosol exposure from HTPs was associated with both asthma attacks/asthma-like symptoms and persistent cough. These results provide policymakers with meaningful information in the regulation of HTP use for the protection of current

nonsmokers.

Strengths and limitations of this study

- This study used large-scale internet survey data with sampling weights from a nationally representative survey in Japan.
- This study focused on current nonsmokers that are the most important population for tobacco control policy but are currently underexamined.
- There may be some differences between respondents and the general population.
- There may also be measurement errors because all variables were based on self-reported questionnaires.

INTRODUCTION

It is widely known that secondhand smoke (SHS) from combustible cigarettes has a harmful effect on health [1]. The detrimental effects of SHS vary, including: ear and respiratory infections, and respiratory symptoms such as asthma attacks among children; and heart disease, stroke, and lung cancer among adults [1]. SHS exposure is also associated with death among all age groups due to the diseases mentioned above. The estimated global deaths associated with SHS exposure increased from 848,702 in 2006 to 883,930 in 2016 [2]. Notably, SHS exposure is harmful to current nonsmokers; therefore, the Centers for Disease Control and Prevention in the United States clearly emphasize that complete protection of nonsmokers from SHS is essential for a comprehensive smoke-free policy [1]. Such a policy may reduce smoking prevalence and associated harms [3]. Taken together, the protection of nonsmokers from SHS is a relevant and established issue for healthcare professionals, public health researchers, and policymakers.

As new tobacco products, such as electronic cigarettes (e-cigarettes) and heated tobacco products (HTPs), were introduced in and spread rapidly since the early 2010s [4,5], secondhand aerosols from such products are emerging as another public health interest associated with SHS. Secondhand aerosols from e-cigarettes are prevalent in the US and European countries [6,7]. In the United States, middle and high school students have been exposed to secondhand aerosols from e-cigarettes, with an increasing trend (approximately 25% in 2015 and 33.2% in 2018) [7–9]. In the TackSHS survey that included nationally representative samples aged 15 years in 12 European countries, 16.0% of respondents experienced secondhand aerosols from e-cigarettes [6].

Secondhand aerosols from heated tobacco products (HTPs) have also been prevalent, especially in Japan, which has the most fertile market for HTPs [5].

In recent studies, associations of secondhand aerosol from e-cigarettes with negative respiratory outcomes were observed. For example, there was a cross-sectional association between secondhand aerosol from e-cigarettes and asthma symptoms in youth aged 11-17 years in Florida, the United States [10]. Outside the United States, a similar cross-sectional study was conducted in Kuwait and the same association was observed [11]. In addition, a recent study showed that exposure to secondhand aerosol from e-cigarettes was longitudinally associated with bronchitic symptoms among young adults [12]. Compared to secondhand aerosol from e-cigarettes, evidence regarding negative respiratory outcomes by secondhand aerosols from heated tobacco products is scarce. To our knowledge, only one study in Japan examined the association between exposure to secondhand aerosol from HTPs and respiratory symptoms immediately after inhalation [13].

Despite the current evidence, it remains unclear whether exposure to secondhand aerosol from HTPs is associated with chronic to subacute respiratory symptoms. Moreover, it is also unclear whether such an association is observed among current nonsmokers in whom the smoke-free policy is really interested [1].

Given the above evidence, in this study, we aimed to investigate the cross-sectional association of secondhand-aerosol exposure from HTPs with the presence of respiratory symptoms among current nonsmokers by using large-scale, internet-based survey data.

METHODS

Data sources, Design and Setting

In this cross-sectional study, we used data from the 2021 Japan "Society and New Tobacco" Internet Survey (JASTIS). The JASTIS is a longitudinal cohort study in which a series of annual internet surveys have been performed since 2015. The survey is used to collect information about the use of tobacco products, including new tobacco products (such as HTPs and e-cigarettes) and combustible cigarettes, as well as participant demographics and socioeconomic status [14]. The online questionnaire was designed such that respondents had to answer each question before they could proceed to the next, ensuring that all questions were answered before submission. Participants of the JASTIS were recruited via a survey panel provided by a major internet research group in Japan (Rakuten Insight) [15]. The research group houses information of about 2.3 million panelists, including socioeconomic information such as education level, household income, and marital status. The survey panel were comprised of those who were initially recruited by the research group. In the 2021 JASTIS, 26,000 participants were recruited from the Japan "COVID-19 and Society" Internet Survey (JACSIS), a sister survey of JASTIS. The participants of the 2021 JASTIS were obtained between the 8th and 26th of February 2021. Among the 2021 JASTIS participants, 87.8% (22,840/26,000) came from the 2020 JACSIS. To achieve the targeted response number in the 2021 JASTIS, we additionally recruited 3,160 participants from all respondents who previously participated in the 2015 to 2020 JASTISs. Detailed information regarding the JASTIS is described in the study profile [14].

Inclusion and Exclusion Criteria

In this study, we included data from all the 2021 survey respondents who were current nonsmokers, determined by using the following question: “Do you currently use any of the following tobacco products? (Cigarettes, roll-your-own cigarettes, Ploom Tech, Ploom Tech plus, Ploom S, IQOS, glo, glo hyper, glo sens, PULZE, electronic cigarettes containing nicotine, electronic cigarettes without nicotine, electronic cigarettes with unknown nicotine content, cigars, little cigars, pipes, chewing tobacco, snuffing tobacco, and hookahs).” The response options were “never,” “several times in the past,” “habitually in the past,” “occasionally,” and “almost every day.” In this study, we defined current nonsmokers as those who selected one of the first three options. We excluded surveys as straight-lining responses if the respondents chose the same number in answer to all questions in a set of questions. We also excluded responses in which respondents reported an amount of tobacco product use but had indicated that they had never used or were only former users of tobacco products. In addition to these exclusion criteria, we performed an attention check with the following question: "Please choose the answer second from the bottom." With this attention check, we excluded respondents who selected responses other than the second answer from the bottom.

Measurement of Exposure Variables

The exposure variable that we examined was the exposure to secondhand aerosols from HTPs over the past year. Hence, in the questionnaire, respondents were asked, “During the past 12 months, have you knowingly inhaled aerosols from HTPs when someone used HTPs in your presence?” The response options were “never,” “rarely,” “sometimes,” and “frequently.” In this study, we defined those who were exposed to secondhand aerosols

from HTPs as those who selected the latter three options

Main Outcomes and Measures

In this study, we defined self-reported respiratory symptoms as outcomes. As a primary outcome, we selected asthma attacks/asthma-like symptoms, which previous studies indicated were associated with aerosols from HTPs [13,16]. As a secondary outcome, we selected non-specific persistent cough, for which a previous study indicated a possible association with e-cigarette use [17]. The JASTIS included the question, "During the past 12 months, have you experienced any of the following conditions: asthma attacks/asthma-like symptoms or persistent cough?" The response options were "never," "rarely," "sometimes," and "frequently." We defined the presence of each respiratory symptom as a selection of any of the latter three options.

Covariates

As evidence for a relationship between secondhand aerosols and respiratory symptoms is limited, we selected the following 12 variables as potential confounding factors: age groups based on the definition from a previous study (15–29, 30–44, 45–59, or 60–80 years) [18], sex (male or female), education status ("high school or less" or "college or more"), marital status (married, never married, or widowed/divorced), household size (living alone or living with others), household equivalent income (1st quartile, 2nd quartile, 3rd quartile, 4th quartile, or unknown/declined to answer), combustible cigarette use, HTP use, other tobacco-product use, SHS exposure over the past month, and two respiratory comorbidities: asthma and bronchitis/pneumonia. Out of these confounding factors, age, sex, income, past combustible cigarette, HTP, or other tobacco product use,

SHS exposure, respiratory comorbidities were selected from previous studies regarding secondhand aerosols from e-cigarettes [10,11]. The others, *e.g.*, education and marital status, were also defined as confounding factors, based on a previous study regarding secondhand aerosols from heated tobacco products and socioeconomic inequality [19].

Statistical Analysis

First, we calculated the frequency of each variable as baseline characteristics. Second, we stratified the experience of respiratory symptoms over the past year by exposure to secondhand aerosols. Third, we conducted multivariable, "modified" Poisson regression analysis with a robust estimator to estimate the prevalence ratio (PR) and confidence interval (CI) for the prevalence of each respiratory symptom. The exposure variable (exposure to secondhand aerosols from HTPs) was dichotomized, as previously noted, or included as a categorical variable (with "never" as a reference, and "rarely," "sometimes," and "frequently"). The equivalence of outcome prevalence in each category was tested by assigning a linear score by treating secondhand aerosol frequencies as an ordinal variable. In addition, to examine the multicollinearity of variables in the multivariable models, we evaluated the variance inflation factors in all analyses.

We also conducted a sensitivity analysis using a parsimonious model. We constructed a weighted multivariable "modified" Poisson model to examine the consistency of the results for our main analysis. In the model, we selected all the confounding factors with a minimal set of classifications from previous studies [10,11]. The selected variables are as follows: age (15–29 or 30–), sex (male or female), education ("high school or less" or "college or more"), income (lower half or upper half or unknown/declined to answer),

past combustible cigarette use (never or past), past HTP use (never or past), SHS (absent or present), and asthma (absent or present).

To account for the differences between the sociodemographic status of respondents from the survey panel and that of the Japanese general public, we used inverse-probability weighting for all analyses [14,20]. The sampling weights, which were scaled such that the total amounted to 26,000 (original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years. In this way, we adjusted for the difference between respondents in the current internet survey and the 2016 Comprehensive Survey of Living Conditions, a nationally representative survey in Japan [21]. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting. Statistical significance was set at $P<0.05$. The data were analyzed using "svy: tabulate" and "svy: glm" commands in STATA version 16.1 (Stata Corp., College Station, TX, USA).

Patient and public involvement

No patients or the public were involved in this study. We did not invite any patients to comment on the study design, interpretation of the results, or the readability or accuracy of the manuscript.

RESULTS

Of the 26,000 respondents, 18,839 current nonsmokers were included for analyses (**Figure S1**). With inverse-probability weighting, 36.6% (95% CI 34.2–39.1) of participants were aged 60–80, 55.7% (95% CI 53.8–57.6) were female, 53.8% (95% CI 51.6–55.9) were high-school graduates or had less education, and 66.0% (95% CI 64.0–67.8) were married. Regarding smoking and SHS status, 34.0% (95% CI 32.1–36.0) were past combustible-cigarette users, 4.1% (95% CI 3.7–4.6) were past HTP users, and 9.5% (95% CI 8.7–10.4) were past users of other tobacco products. In particular, 80.3% (95% CI 79.0–81.6) of participants had been exposed to SHS in the past month (**Table 1**).

Table 1 Demographics of study participants

Characteristics	N = 18,839	n	%	Weighted %[a]	95% CI
Age	15–29	3,024	16.1	15.5	14.5–16.6
	30–44	4,205	22.3	20.4	19.3–21.5
	45–59	4,967	26.4	27.5	26.1–28.9
	60–80	6,643	35.3	36.6	34.2–39.1
Sex	Male	8,598	45.6	44.3	42.4–46.2
	Female	10,241	54.4	55.7	53.8–57.6
Education status	High school or less	5,789	30.7	53.8	51.6–55.9
	College or more	13,050	69.3	46.2	44.1–48.4
Marital status	Married	11,431	60.7	66.0	64.0–67.8
	Not married	5,670	30.1	25.1	23.6–26.7
	Widowed/divorced	1,738	9.2	8.9	7.5–10.7
Household size	Living alone	15,266	81.0	84.9	82.8–86.8
	Living with others	3,573	19.0	15.1	13.3–17.2
Household-equivalent income	1st quartile	3,816	20.3	23.0	21.5–24.6
	2nd quartile	3,874	20.6	21.5	19.7–23.5
	3rd quartile	3,716	19.7	18.4	16.9–20.1
	4th quartile	3,403	18.1	13.1	12.1–14.2
	Unknown/declined to answer	4,030	21.4	23.9	22.0–25.8
Combustible cigarette use	Never	12,822	68.1	66.0	64.1–67.9
	Past	6,017	31.9	34.0	32.1–36
HTP use	Never	18,008	95.6	95.9	95.4–96.3
	Past	831	4.4	4.1	3.7–4.6
Other tobacco product use	Never	17,035	90.4	90.5	89.6–91.3
	Past	1,804	9.6	9.5	8.7–10.4
Exposure to secondhand smoke over the past month	Absent	3,663	19.4	19.7	18.4–21.0
	Present	15,176	80.6	80.3	79.0–81.6
Asthma	Absent	18,271	97.0	96.3	95.2–97.1
	Present	568	3.0	3.7	2.9–4.8
Bronchitis or pneumonia	Absent	18,624	98.9	98.4	97.9–98.8
	Present	215	1.1	1.6	1.2–2.1
Exposure to secondhand aerosol from HTPs over the past 12 months	Absent	14,437	76.6	77.4	75.9–78.9
	Present	4,402	23.4	22.6	21.1–24.1

Note. CI: confidence interval, HTP: heated tobacco product.

[a] The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs were based on the Wald-type test on the probability scale, which was

accompanied by the robust variance estimator of the weighted proportions accounting for the inverse-probability weighting ("svy: tabulate" command in Stata)

Of 18,839 respondents, 4,402 (23.4%) were exposed to secondhand aerosols from HTPs. With inverse-probability weighting, 9.8% (95% CI 8.2–11.7) and 16.7% (95% CI 14.8–18.9) of those who were exposed to secondhand aerosols reported asthma attacks/asthma-like symptoms and persistent cough, whereas 4.5% (95% CI 3.9–5.2) and 9.6% (95% CI 8.4–11.0) of those who were not, respectively.

(**Table 2**).

Table 2 Respiratory symptoms over the past year among non-smokers classified into the experience of secondhand aerosols

Symptoms	Frequency	Secondhand aerosol (-) n = 14,437				Secondhand aerosol (+) N = 4,402			
		n	%	Weighted % [a]	95% CI	n	%	Weighted % [a]	95% CI
Asthma attacks/asthma-like symptoms	Never	13,772	95.4	95.5	94.8–96.1	4,043	91.8	90.2	88.3–91.8
	Rarely	424	2.9	2.7	2.3–3.2	211	4.8	5.6	4.5–6.8
	Sometimes	205	1.4	1.6	1.2–2.1	124	2.8	3.3	2.3–4.8
	Frequently	36	0.2	0.2	0.1–0.3	24	0.5	0.9	0.5–1.6
Persistent cough	Never	13,163	91.2	90.4	89.0–91.6	3,787	86.0	83.3	81.1–85.4
	Rarely	697	4.8	4.9	4.3–5.7	346	7.9	8.2	6.9–9.7
	Sometimes	446	3.1	3.9	2.9–5.2	224	5.1	7.1	5.6–8.9
	Frequently	131	0.9	0.8	0.6–1.1	45	1.0	1.4	0.9–2.1

Note. CI: confidence interval.

[a] The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs were based on the Wald-type test on the probability scale, which was accompanied by the robust variance estimator of the weighted proportions accounting for the inverse-probability weighting ("svy: tabulate" command in Stata).

In the multivariable analysis, exposure to secondhand aerosols was associated with both primary and secondary outcomes after adjusting for covariates using "modified" Poisson regression models (asthma attacks/asthma-like symptoms: PR 1.49, 95% CI 1.21–1.85, $P<0.001$; persistent cough: PR 1.44, 95% CI 1.21–1.72, $P<0.001$) (**Table 3**).

Table 3 Multivariable weighted Poisson regression analysis for respiratory symptoms among non-smokers

Characteristics	N = 18,839	Asthma attacks/asthma-like symptoms			Persistent cough		
		PR	95% CI	*P* value	PR	95% CI	*P* value
Exposure to secondhand aerosols	Absent		Reference			Reference	
	Present	1.49	1.21–1.85	<0.001	1.44	1.21–1.72	<0.001
Age	15–29	1.35	1.01–1.79	0.04	1.02	0.79–1.31	0.87
	30–44	1.14	0.89–1.46	0.30	1.15	0.96–1.38	0.14
	45–59		Reference			Reference	
	60–80	0.85	0.64–1.14	0.27	1.13	0.91–1.39	0.27
Sex	Male		Reference			Reference	
	Female	0.92	0.74–1.15	0.45	1.12	0.93–1.36	0.24
Education status	High school or less		Reference			Reference	
	College or more	1.04	0.86–1.26	0.69	0.92	0.74–1.15	0.47
Marital status	Married		Reference			Reference	
	Not married	1.02	0.81–1.29	0.87	0.97	0.77–1.22	0.78
	Widowed/divorced	1.60	1.03–2.46	0.04	1.39	0.93–2.08	0.11
Household size	Living alone		Reference			Reference	
	Living with others	0.85	0.61–1.19	0.34	1.14	0.8–1.61	0.47
Household-equivalent income	1st quartile		Reference			Reference	
	2nd quartile	0.81	0.61–1.07	0.14	0.90	0.67–1.21	0.49
	3rd quartile	0.88	0.62–1.24	0.47	0.77	0.56–1.06	0.11
	4th quartile	0.87	0.65–1.17	0.35	0.92	0.69–1.23	0.58
	Unknown/declined to answer	0.72	0.53–0.97	0.03	0.81	0.6–1.09	0.16
Combustible cigarette use	Never		Reference			Reference	
	Past	0.93	0.71–1.22	0.60	1.17	0.88–1.55	0.28
HTP use	Never		Reference			Reference	
	Past	1.71	1.19–2.44	0.003	1.34	1.05–1.72	0.02
Other tobacco product use	Never		Reference			Reference	
	Past	1.35	0.96–1.90	0.09	1.42	1.09–1.85	0.01
Exposure to secondhand smoke over the past month	Absent		Reference			Reference	
	Present	0.86	0.67–1.11	0.26	0.97	0.78–1.21	0.80
Asthma	Absent		Reference			Reference	
	Present	12.39	9.75–15.75	<0.001	4.12	3.13–5.42	<0.001
Bronchitis or pneumonia	Absent		Reference			Reference	
	Present	1.68	1.20–2.35	0.003	2.04	1.46–2.85	<0.001

Note. PR: prevalence ratio, CI: confidence interval, HTP: heated tobacco product.
The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting.

When examining the association of ordinal exposure variables with the outcomes, the same associations were observed (**Figure 1, Table S1**). Notably, all outcomes exhibited a nearly monotonic relationship with the frequency of exposure to secondhand aerosols (both $P<0.001$ with the linear trend test). The maximum variance inflation factor was 2.01, suggesting that there was no problematic multicollinearity in the regression models (**Table S2**).

The results of the sensitivity analysis were shown in **Table S3**. Consistent associations between exposure to secondhand aerosols from HTPs and two outcomes were observed (Asthma attacks/asthma-like symptoms, PR 1.64, 95% CI 1.31–2.04, $P<0.001$; persistent cough, PR 1.48, 95% CI 1.22–1.79, $P<0.001$).

DISCUSSION

Using data from a large-scale, nationwide survey conducted in February 2021 in Japan, we discovered a cross-sectional association between secondhand-aerosol exposure and two respiratory symptoms (asthma attacks/asthma-like symptoms and persistent cough) after adjusting for 12 potential confounding factors. The PRs of respiratory symptoms increased as the frequency of exposure to secondhand aerosols from HTPs increased. Furthermore, the weighted prevalence of secondhand-aerosol exposure over the past month was approximately 20%, and, similar to those of SHS from combustible cigarettes and secondhand aerosols from e-cigarettes [1,6]. Given these findings, many current nonsmokers in Japan may be exposed to secondhand aerosols from HTPs, which may have detrimental effects on their respiratory systems.

There are several potential mechanisms by which secondhand aerosols may cause respiratory symptoms. First, in the biochemical context, aerosols from HTPs contain substantial amounts of chemical compounds such as carbonyl compounds and polycyclic aromatic hydrocarbons [22]. These chemicals damage human bronchial epithelial cells [23], inducing asthma attacks or asthma-like symptoms. Second, in the physiological context, inhalation of the chemical compounds in aerosols from HTPs impairs respiratory function (forced expiratory volume in one second, both absolute and as a percentage of the predicted value) [24], resulting in respiratory symptoms. Finally, in the indoor environmental context, secondhand aerosols contain concentrations of harmful chemical compounds, such as nicotine and fine particulate matter, greater than the upper limits of the range of tolerable concentrations [25]. Consequently, even current nonsmokers may

experience asthma attacks/asthma-like symptoms or persistent cough via the above-mentioned biochemical and physiological mechanisms after inhalation of secondhand aerosols emitted by others, especially indoors.

Secondhand aerosols from e-cigarettes have already been an emerging public health threat. A study by Bayly *et al.* presented a cross-sectional association between exposure to secondhand aerosol from e-cigarettes and asthma attacks in youth aged 11–17 years (n = 11,830) in the United States [10]. In the study, both secondhand aerosol from e-cigarettes and SHS were associated with asthma attacks in the multivariable logistic regression model; however, the estimated odds ratio in SHS was smaller than that in secondhand aerosols (SHS, odds ratio [OR] 1.19, 95% CI 1.05–1.35; and secondhand aerosol rom e-cigarettes, OR 1.27, 95% CI 1.11–1.47). Although the study adjusted for numerous confounding factors including various patterns of tobacco product use, there was an important limitation regarding inconsistent time frames of the measurements, *i.e.*, the time frame of the exposure was past 30 days and that of the outcome was 12 months. Such an inconsistent time frame may imply an increased risk of the reverse relationship between exposure to secondhand aerosol from e-cigarettes and asthma attacks. Another study by Alnajem *et al.* also showed a cross-sectional association between secondhand aerosol exposure from e-cigarettes in the past 7 days and respiratory symptoms in the past 12 months among schoolchildren aged 16–19 years in Kuwait [11]. In that study, frequent secondhand aerosol exposure was associated with an increased risk of wheeze (PR 1.30, 95% CI 1.04–1.59), asthma (PR 1.56, 95% CI 1.13–2.16), and uncontrolled asthma symptoms (PR 1.88, 95% CI 1.35–2.62). However, like the study by Bayly *et al.*, the same limitation for time frame was observed (7 days for the exposure and 12 months for

the outcome). A. recent study by Islam *et al.* showed the longitudinal association between exposure to e-cigarette secondhand aerosols and bronchitic symptoms (OR 1.40, 95% CI 1.06–1.84) and shortness of breath (OR 1.53, 95% CI 1.06–2.21) among young adults (average age, 17.3 years; n = 2,090) in the United States [12]. Although these studies are informative, they commonly focus on e-cigarettes and a specific population (adolescents and young adults). There have been few studies on the association of exposure to secondhand aerosol from HTPs with respiratory outcomes. To date, we could find only one study by Imura and Tabuchi, via an internet survey conducted in 2019, which examined the cross-sectional association between exposure to secondhand aerosols and symptoms directly induced by such exposure [13]. They revealed that asthma-like attacks and chest pain were more prevalent in those who were exposed to secondhand aerosols from HTPs than to SHS from combustible cigarettes. Although this study is informative, evaluation of its association with subacute to chronic respiratory symptoms remains limited. Thus, we examined the association between exposure to secondhand aerosols from HTPs and asthma attacks/asthma-like symptoms and persistent cough. When designing this study, we used the same frame for the measurement of the exposure and outcomes (past 12 months) to compensate for the previous cross-sectional studies. The associations were mostly consistent with the previous studies regarding secondhand aerosols from e-cigarettes. However, there were some inconsistent estimates, *e.g.*, the association between SHS and respiratory outcomes was not observed. Nevertheless, as noted above, a previous study showed that the odds ratio of SHS for asthma was smaller than that of secondhand aerosols from e-cigarettes [10]. The phenomenon that the odds or prevalence ratios in SHS were lower than those in secondhand aerosols from HTPs might be induced by the different time frames of measurements for SHS (30 days) and

outcomes (12 months) both in this study and a previous study. Moreover, when stratified by exposure to SHS, the associations of exposure to secondhand aerosol from HTPs with both asthma attacks/asthma-like symptoms and persistent cough were consistently observed among the exposure to SHS group in our data (asthma attacks/asthma-like symptoms, PR 1.53, 95% CI 1.21–1.93; persistent cough, PR 1.44, 95% CI 1.19–1.74). Therefore, we believe that our results were not discrepant from the previous studies. Notably, the strength of this study is that we focused on current nonsmokers whom most policymakers have interested [1], and used consistent time frames for the measurements of the exposure and outcomes. To our knowledge, this is the first study in which the environments in which people were exposed to secondhand aerosols from HTPs were clarified and the association between such exposure and respiratory symptoms was evaluated among current nonsmokers, by using nationally representative, large-scale survey data. As the number of HTP users is growing in Europe and the United States [26,27], as well as in Japan, the threat to current nonsmokers' health due to secondhand-aerosol exposure from HTPs will increase globally. Thus, our findings provide policymakers with meaningful information in regulating HTP use for the protection of current nonsmokers. In addition, we believe our results will contribute to longitudinal epidemiological studies, biological studies for the relationship between respiratory systems and toxic effects of aerosols from HTPs, environmental studies that examined the chemical pounds from HTP aerosols, and so on.

Our study has several limitations. First, because of this study's cross-sectional design, the temporal relationship between secondhand-aerosol exposure and respiratory symptoms was unclear, and our results cannot be used to infer causality. However, the results from

this study implied a nearly monotonic relationship between the frequency of exposure to secondhand aerosols and the PR for each respiratory symptom under assessment, which is a key component in explaining causality [28]. Second, this study was based on self-report questionnaires and not all variables were measured with validated questionnaires; therefore, measurement errors may exist. However, we developed an algorithm for exclusion of responses that were unreliable or invalid, and excluded such respondents *a priori*. Moreover, our questionnaire for exposure variables clearly assumed that someone used HTPs in the respondents' presence. In combination with the high prevalence of HTP use in 2020 Japan [29], we believe that our questionnaire for exposure had substantial sensitivity. Third, this study is based on an internet survey; the composition of study participants may have differed from that of the general Japanese public. However, to minimize such differences, we adjusted for demographic, socioeconomic, and health-related differences between respondents in the present study and the Japanese general public by using nationally representative survey data. Finally, this study was conducted in Japan, where HTPs are more popular than in other countries [30]; therefore, our findings may not be generalizable to other countries.

In conclusion, by using data from a nationally representative survey, this study revealed that exposure to secondhand aerosols from HTPs were prevalent in 2021 in Japan. This study clarified the association between such exposure and asthma attacks/asthma-like symptoms and persistent cough among current nonsmokers. Our results will provide policymakers with meaningful information for a smoke-free policy. Also, we can provide good evidence to make progress in future research in relation to respiratory diseases induced by secondhand aerosol from HTPs.

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Author contributions: TY, TS, AH, KN, SO and TT contributed to the conceptualization of this study. TY and TT collected data, and TY, TS, and TT developed the plan for analysis. TY analyzed the data. TY wrote the original manuscript, and TS, AH, KN, SO, and TT reviewed, interpreted, critically appraised, and revised the original manuscript. TY, TS, AH, KN, SO, and TT reviewed the final version of the manuscript and approved its submission. TY takes responsibility for the content of the manuscript, including the data and analysis.

Funding/Support: This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI grants (grant numbers 17H03589, 19K10671, 19K10446, 18H03107, 18H03062, 19H03860), the JSPS Grant-in-Aid for Young Scientists (grant number 19K19439), the Research Support Program to Apply the Wisdom of the University to tackle COVID-19 Related Emergency Problems, University of Tsukuba, and Health Labour Sciences Research Grant (grant numbers 19FA1005, 19FG2001, 19FA1012) and the Japan Agency for Medical Research and Development (AMED; grant number 2033648). We acknowledge the support by National Institute of Public Health for the article publishing charge.

Disclaimer: The funders had no role in the study design, data collection, statistical analysis, decision to publish, or preparation of the manuscript, except for conducting the internet survey, language editing of the manuscript, and the article publishing charge.

Competing interests: None to declare.

Data availability statement: The data used in this study are not available in a public repository because they contain personally identifiable or potentially sensitive participants' information. Based on the regulations for ethical guidelines in Japan, the Institutional Review Board of the Osaka International Cancer Institute has imposed restrictions on the dissemination of the data collected in this study. All data inquiries will be channeled through Takahiro Tabuchi (tabuchitak@gmail.com) to Osaka Cancer Institute Institutional Ethics Committee.

Ethics Approval

All procedures were conducted according to the ethical standards of the Declaration of Helsinki. We obtained web-based informed consent from all the respondents for use of their data from the JASTIS study in our research. A credit point known as "Epoints," which could be used for internet shopping and cash conversion, was provided to the participants as an incentive. This study was approved by the Institutional Review Board of Osaka International Cancer Institute (Number: 20084). The internet research group fully respected the Act on the Protection of Personal Information in Japan. This study followed the STROBE guidelines for cross-sectional studies.

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Figure Legends

Figure 1 Prevalence ratios of ordinal exposure variables for the outcomes

A: asthma attacks/asthma-like symptoms, B: persistent cough.

Supplemental materials:

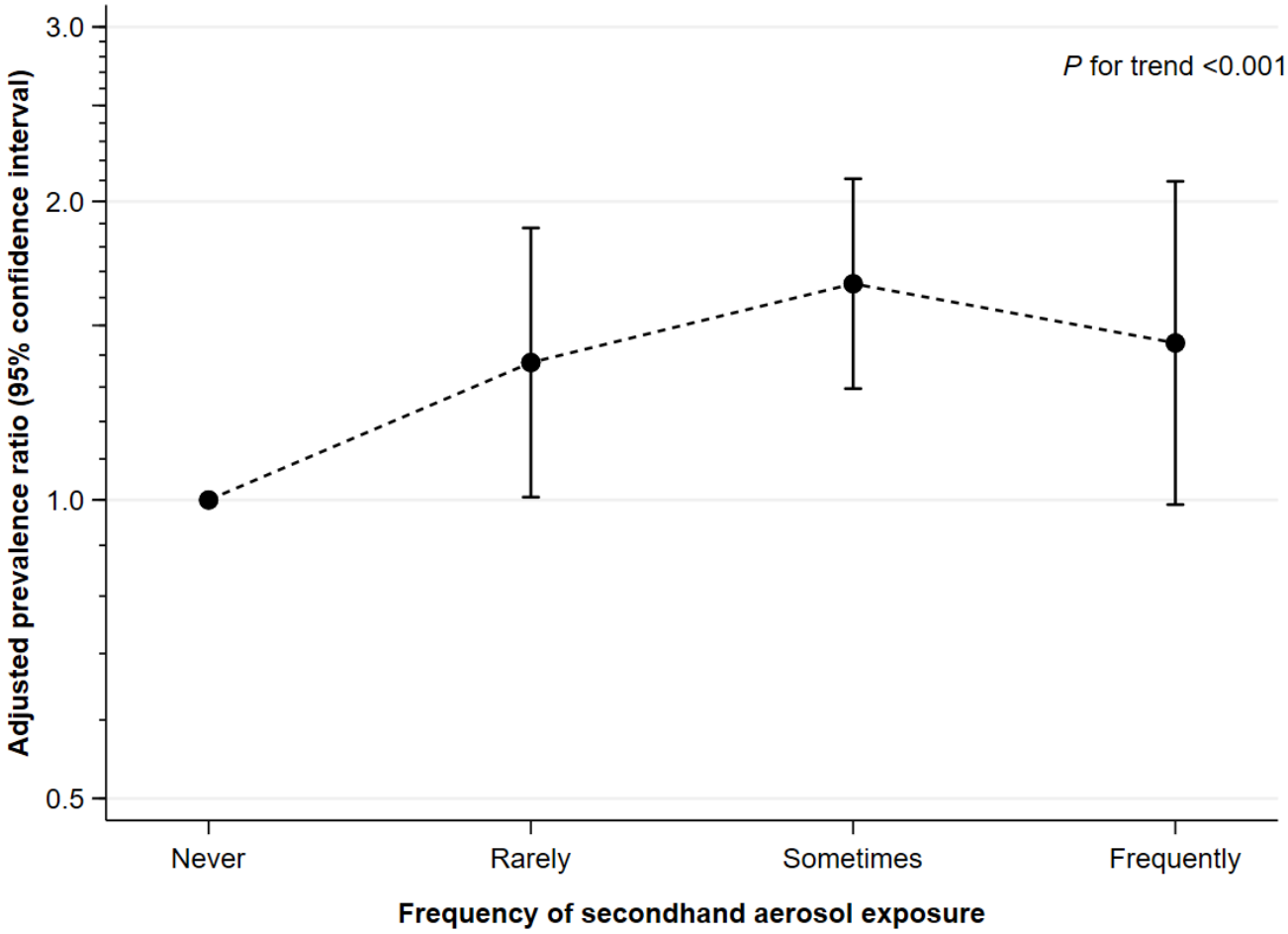
Table S1 Multivariable Poisson regression analysis using ordinal exposure variables

Table S2 Variance inflation factors for the evaluation of multicollinearity

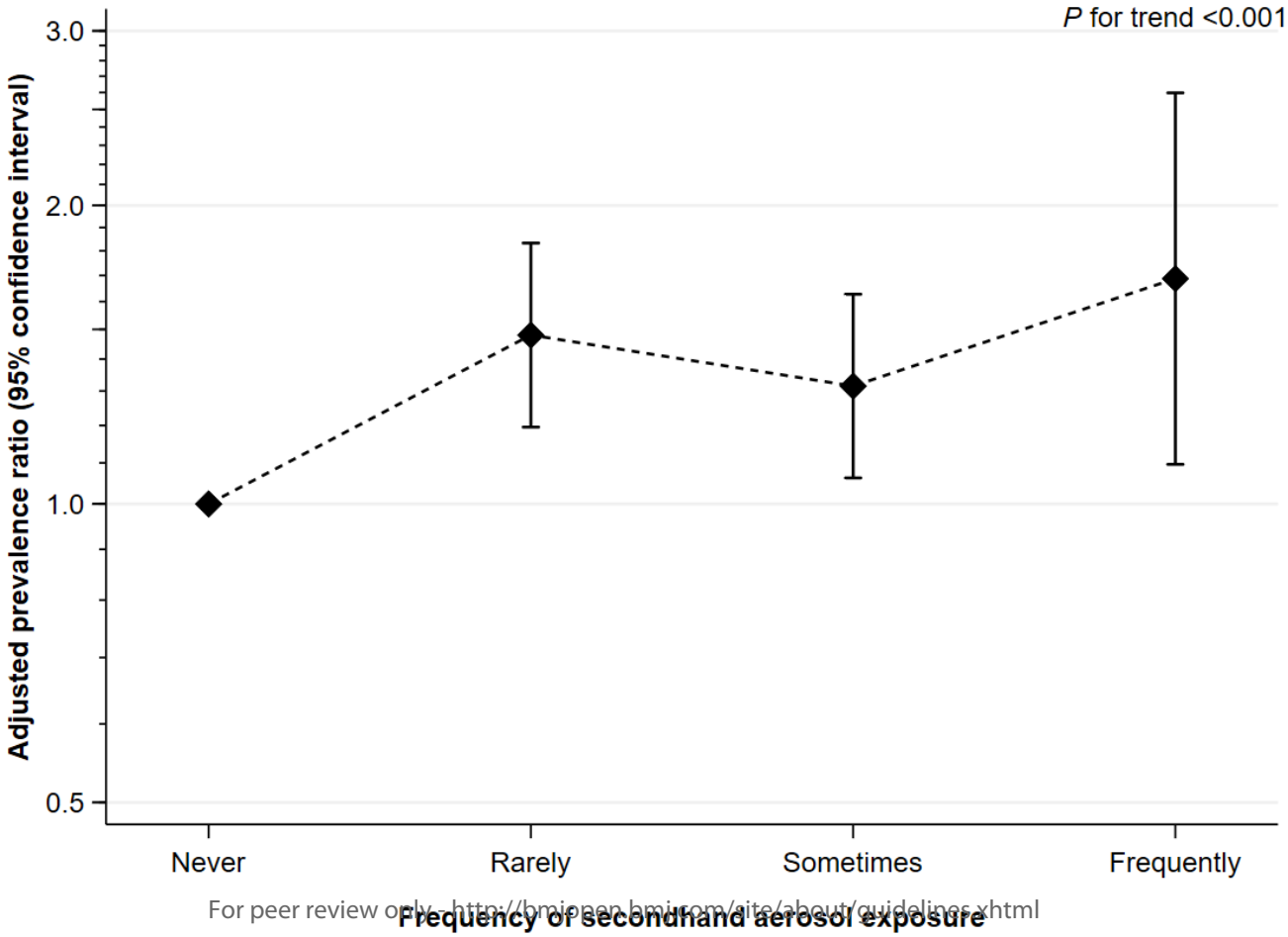
Table S3 Multivariable Poisson regression analysis based on a parsimonious model

Figure S1 Flow diagram of the study

A



B



Supplemental materials

Yoshioka T, Shinozaki T, Hori A, Okawa S, Nakashima K, Tabuchi T. Association between exposure to secondhand-aerosol from heated tobacco products and respiratory symptoms among current nonsmokers in Japan

Table S1 Multivariable Poisson regression analysis using ordinal exposure variables

Characteristics	N = 18,839	Asthma/asthma-like attacks			Persistent cough		
		PR	95% CI	*P* value	PR	95% CI	*P* value
Exposure to secondhand aerosols	Never		Reference			Reference	
	Rarely	1.38	1.01–1.88	0.05	1.48	1.20–1.83	<0.001
	Sometimes	1.65	1.30–2.11	<0.001	1.31	1.06–1.63	0.01
	Frequently	1.44	0.99–2.10	0.06	1.69	1.10–2.60	0.02
Age	15–29	1.36	1.02–1.82	0.04	1.01	0.78–1.30	0.94
	30–44	1.14	0.89–1.47	0.28	1.15	0.96–1.38	0.14
	45–59		Reference			Reference	
	60–80	0.86	0.64–1.15	0.31	1.13	0.91–1.40	0.28
Sex	Male		Reference			Reference	
	Female	0.92	0.74–1.15	0.46	1.11	0.92–1.35	0.27
Education status	High school or less		Reference			Reference	
	College or more	1.04	0.85–1.27	0.70	0.93	0.74–1.16	0.50
Marital status	Married		Reference			Reference	
	Not married	1.03	0.81–1.30	0.82	0.97	0.77–1.21	0.77
	Widowed/divorced	1.61	1.04–2.48	0.03	1.39	0.93–2.07	0.11
Household size	Living alone		Reference			Reference	
	Living with others	0.84	0.60–1.19	0.33	1.14	0.81–1.61	0.47
Household-equivalent income	1st quartile		Reference			Reference	
	2nd quartile	0.81	0.62–1.07	0.14	0.89	0.66–1.21	0.46
	3rd quartile	0.89	0.63–1.26	0.51	0.76	0.56–1.05	0.10
	4th quartile	0.87	0.65–1.18	0.38	0.92	0.69–1.22	0.56
	Unknown/declined to answer	0.72	0.53–0.98	0.03	0.80	0.60–1.08	0.14
Combustible cigarette use	Never		Reference			Reference	
	Past	0.94	0.71–1.22	0.63	1.17	0.88–1.55	0.29
HTP use	Never		Reference			Reference	
	Past	1.70	1.19–2.43	0.004	1.35	1.05–1.73	0.02
Other tobacco product use	Never		Reference			Reference	
	Past	1.35	0.96–1.91	0.08	1.41	1.08–1.85	0.01
Exposure to secondhand smoke over the past month	Absent		Reference			Reference	
	Present	0.86	0.67–1.11	0.25	0.97	0.78–1.21	0.81
Asthma	Absent		Reference			Reference	
	Present	12.31	9.68–15.65	<0.001	4.13	3.14–5.42	<0.001
Bronchitis or pneumonia	Absent		Reference			Reference	
	Present	1.68	1.20–2.36	0.002	2.04	1.46–2.84	<0.001

Note. PR: prevalence ratio, CI: confidence interval, HTP: heated tobacco product.

The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting.

Table S2 Variance inflation factors for the evaluation of multicollinearity

Characteristics	N = 18,839	VIF
Exposure to secondhand aerosols	Absent	Reference
	Present	1.07
Age	15–29	1.78
	30–44	1.49
	45–59	Reference
	60–80	1.68
Sex	Male	Reference
	Female	1.19
Education status	High school or less	Reference
	College or more	1.06
Marital status	Married	Reference
	Not married	2.01
	Widowed/divorced	1.31
Household size	Living alone	Reference
	Living with others	1.48
Household-equivalent income	1st quartile	Reference
	2nd quartile	1.63
	3rd quartile	1.65
	4th quartile	1.68
	Unanswered	1.66
Combustible cigarette use	Never	Reference
	Past	1.40
HTP use	Never	Reference
	Past	1.19
Other tobacco product use	Never	Reference
	Past	1.31
Exposure to secondhand smoke over the past month	Absent	Reference
	Present	1.03
Asthma	Absent	Reference
	Present	1.09
Bronchitis or pneumonia	Absent	Reference
	Present	1.10
Mean		1.41

Note. VIF: variance inflation factor, CI: confidence interval, HTP: heated tobacco products.

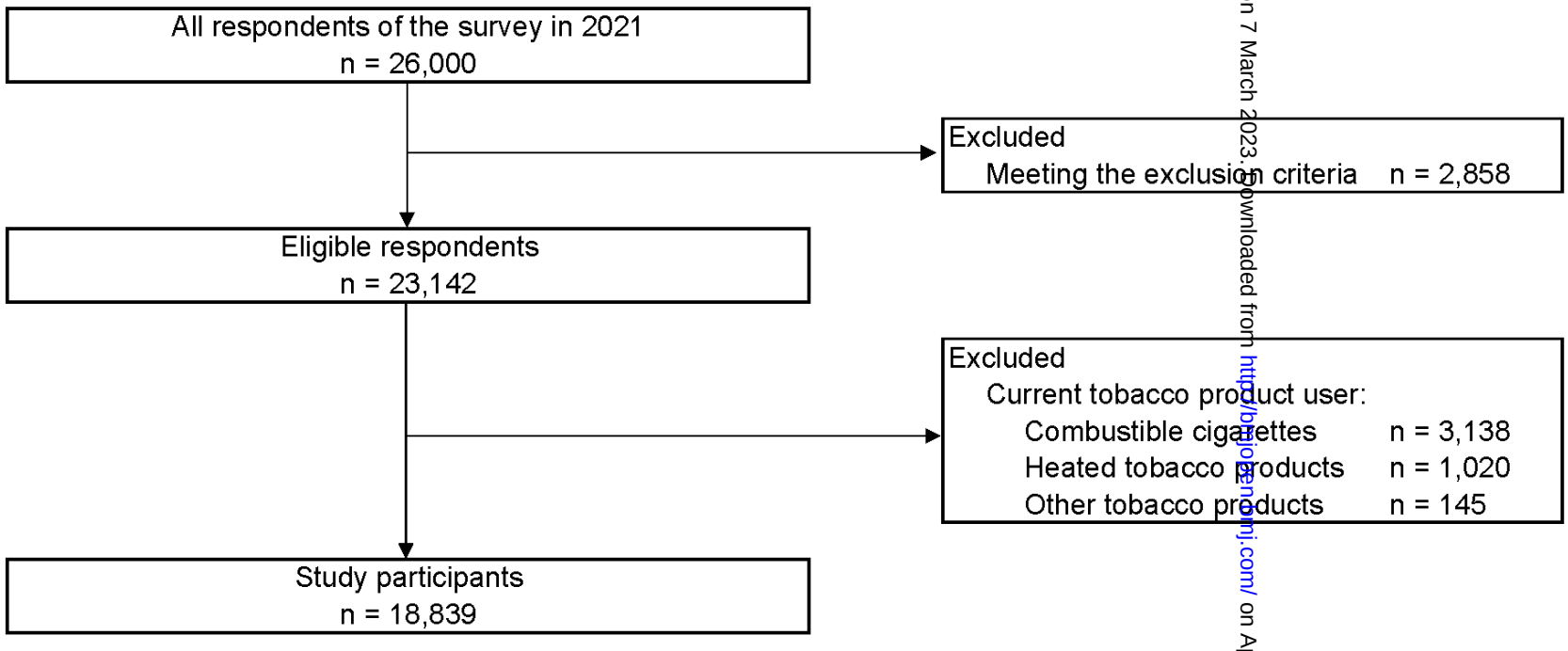
Table S3 Multivariable Poisson regression analysis based on a parsimonious model

Characteristics	N = 18,839	Asthma attacks/asthma-like symptoms			Persistent cough		
		PR	(95% CI)	P value	PR	(95% CI)	P value
Exposure to secondhand aerosols from HTPs	Absent		Reference			Reference	
	Present	1.64	(1.31-2.04)	<0.001	1.48	(1.22-1.79)	<0.001
Age	15–29	1.30	(1.04-1.64)	0.02	0.89	(0.74-1.08)	0.23
	30–80		Reference			Reference	
Sex	Male		Reference			Reference	
	Female	0.88	(0.70-1.11)	0.29	1.06	(0.84-1.34)	0.60
Education status	High school or less		Reference			Reference	
	College or more	0.99	(0.81-1.22)	0.96	0.89	(0.71-1.12)	0.33
Household-equivalent income	Lower half		Reference			Reference	
	Upper half	0.93	(0.72-1.19)	0.56	0.81	(0.64-1.03)	0.09
	Unknown/declined to answer	0.76	(0.58-0.99)	0.04	0.80	(0.62-1.03)	0.08
Combustible cigarette use	Never		Reference			Reference	
	Past	0.94	(0.71-1.26)	0.69	1.26	(0.93-1.71)	0.13
HTP use	Never		Reference			Reference	
	Past	2.05	(1.48-2.84)	<0.001	1.54	(1.17-2.02)	<0.001
Exposure to secondhand smoke over the past month	Absent		Reference			Reference	
	Present	0.84	(0.64-1.11)	0.22	0.99	(0.79-1.24)	0.92
Asthma	Absent		Reference			Reference	
	Present	14.64	(11.63-18.42)	<0.001	5.23	(4.05-6.76)	<0.001

Note. PR: prevalence ratio, CI: confidence interval, HTP: heated tobacco product.

The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting.

Figure S1 Flow diagram of the study



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	#6
Methods			
Study design	4	Present key elements of study design early in the paper	#7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	#8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#7-10
Bias	9	Describe any efforts to address potential sources of bias	#11
Study size	10	Explain how the study size was arrived at	#7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#10-11
		(*b*) Describe any methods used to examine subgroups and interactions	#10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	#7
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#12
		(b) Give reasons for non-participation at each stage	#12, Figure S1
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#12
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	#15, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#17, Table 1-3
		(*b*) Report category boundaries when continuous variables were categorized	#17, Table 1-3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 1, #19, Table S3
Discussion			
Key results	18	Summarise key results with reference to study objectives	#20
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	#23,24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#21-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	#24
Other information			
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	#25

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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

Association between exposure to secondhand aerosol from heated tobacco products and respiratory symptoms among current nonsmokers in Japan: a cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065322.R2
Article Type:	Original research
Date Submitted by the Author:	02-Feb-2023
Complete List of Authors:	Yoshioka, Takashi; Keio University, Department of Preventive Medicine and Public Health Shinozaki, Tomohiro; Tokyo University of Science, Department of Information and Computer Technology, Faculty of Engineering Hori, Ai; University of Tsukuba, Department of Global Public Health Okawa, Sumiyo; Kokuritsu Kokusai Iryo Kenkyu Center Kenkyujo Nakashima, Kei; Kameda Medical Center, Department of Pulmonary Medicine Tabuchi, Takahiro; Osaka Kokusai Gan Center, Cancer Control Center
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Health policy, Respiratory medicine, Public health
Keywords:	Asthma < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, PUBLIC HEALTH

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Study type: Original research

Association between exposure to secondhand aerosol from heated tobacco products and respiratory symptoms among current nonsmokers in Japan: a cross-sectional study

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Counts:

Abstract: 216

Manuscript: 3,487

Figures and Tables: Four Tables and One Figure

Abstract

Objectives: To investigate the association between secondhand-aerosol exposure from heated tobacco products (HTPs) and respiratory symptoms among current nonsmokers.

Design: Cross sectional study.

Setting: Internet survey conducted between 8 and 26 February 2021 in Japan.

Participants: Non-smoking respondents at the survey aged 15–80 years.

Exposure: Self-reported secondhand-aerosol exposure.

Primary and secondary outcomes: We defined asthma/asthma-like symptoms as a primary outcome and persistent cough as a secondary outcome. We examined the association between secondhand-aerosol exposure from HTPs and respiratory symptoms (asthma attacks/asthma-like symptoms and persistent cough). The prevalence ratio (PR) and 95% confidence interval (CI) were calculated by using weighted, multivariable "modified" Poisson regression models.

Results: Of 18,839 current nonsmokers, 9.8% (95% CI 8.2–11.7) and 16.7% (95% CI 14.8–18.9) of those who were exposed to secondhand aerosols reported asthma attacks/asthma-like symptoms and persistent cough, whereas 4.5% (95% CI 3.9–5.2) and 9.6% (95% CI 8.4–11.0) of those who were not, respectively. Secondhand-aerosol exposure was associated with respiratory symptoms (asthma attacks/asthma-like symptoms: PR 1.49, 95% CI 1.21–1.85; persistent cough: PR 1.44, 95% CI 1.21–1.72) after adjusting for covariates.

Conclusion: Secondhand-aerosol exposure from HTPs was associated with both asthma attacks/asthma-like symptoms and persistent cough. These results provide policymakers with meaningful information in the regulation of HTP use for the protection of current nonsmokers.

Strengths and limitations of this study

- This study used large-scale internet survey data with sampling weights from a nationally representative survey in Japan.
- This study focused on current nonsmokers that are the most important population for tobacco control policy but are currently underexamined.
- There may be some differences between respondents and the general population.
- There may also be measurement errors because all variables were based on self-reported questionnaires.

INTRODUCTION

It is widely known that secondhand smoke (SHS) from combustible cigarettes has a harmful effect on health [1]. The detrimental effects of SHS vary, including: ear and respiratory infections, and respiratory symptoms such as asthma attacks among children; and heart disease, stroke, and lung cancer among adults [1]. SHS exposure is also associated with death among all age groups due to the diseases mentioned above. The estimated global deaths associated with SHS exposure increased from 848,702 in 2006 to 883,930 in 2016 [2]. Notably, SHS exposure is harmful to current nonsmokers; therefore, the Centers for Disease Control and Prevention in the United States clearly emphasize that complete protection of nonsmokers from SHS is essential for a comprehensive smoke-free policy [1]. Such a policy may reduce smoking prevalence and associated harms [3]. Taken together, the protection of nonsmokers from SHS is a relevant and established issue for healthcare professionals, public health researchers, and policymakers.

As new tobacco products, such as electronic cigarettes (e-cigarettes) and heated tobacco products (HTPs), were introduced in and spread rapidly since the early 2010s [4,5], secondhand aerosols from such products are emerging as another public health interest associated with SHS. Secondhand aerosols from e-cigarettes are prevalent in the US and European countries [6,7]. In the United States, middle and high school students have been exposed to secondhand aerosols from e-cigarettes, with an increasing trend (approximately 25% in 2015 and 33.2% in 2018) [7–9]. In the TackSHS survey that included nationally representative samples aged 15 years in 12 European countries, 16.0% of respondents experienced secondhand aerosols from e-cigarettes [6].

Secondhand aerosols from heated tobacco products (HTPs) have also been prevalent, especially in Japan, which has the most fertile market for HTPs [5].

In recent studies, associations of secondhand aerosol from e-cigarettes with negative respiratory outcomes were observed. For example, there was a cross-sectional association between secondhand aerosol from e-cigarettes and asthma symptoms in youth aged 11-17 years in Florida, the United States [10]. Outside the United States, a similar cross-sectional study was conducted in Kuwait and the same association was observed [11]. In addition, a recent study showed that exposure to secondhand aerosol from e-cigarettes was longitudinally associated with bronchitic symptoms among young adults [12]. Compared to secondhand aerosol from e-cigarettes, evidence regarding negative respiratory outcomes by secondhand aerosols from heated tobacco products is scarce. To our knowledge, only one study in Japan examined the association between exposure to secondhand aerosol from HTPs and respiratory symptoms immediately after inhalation [13].

Despite the current evidence, it remains unclear whether exposure to secondhand aerosol from HTPs is associated with chronic to subacute respiratory symptoms. Moreover, it is also unclear whether such an association is observed among current nonsmokers in whom the smoke-free policy is really interested [1].

Given the above evidence, in this study, we aimed to investigate the cross-sectional association of secondhand-aerosol exposure from HTPs with the presence of respiratory symptoms among current nonsmokers by using large-scale, internet-based survey data.

METHODS

Data sources, Design and Setting

In this cross-sectional study, we used data from the 2021 Japan "Society and New Tobacco" Internet Survey (JASTIS). The JASTIS is a longitudinal cohort study in which a series of annual internet surveys have been performed since 2015. The survey is used to collect information about the use of tobacco products, including new tobacco products (such as HTPs and e-cigarettes) and combustible cigarettes, as well as participant demographics and socioeconomic status [14]. The online questionnaire was designed such that respondents had to answer each question before they could proceed to the next, ensuring that all questions were answered before submission. Participants of the JASTIS were recruited via a survey panel provided by a major internet research group in Japan (Rakuten Insight) [15]. The research group houses information of about 2.3 million panelists, including socioeconomic information such as education level, household income, and marital status. The survey panel were comprised of those who were initially recruited by the research group. In the 2021 JASTIS, 26,000 participants were recruited from the Japan "COVID-19 and Society" Internet Survey (JACSIS), a sister survey of JASTIS. The participants of the 2021 JASTIS were obtained between the 8th and 26th of February 2021. Among the 2021 JASTIS participants, 87.8% (22,840/26,000) came from the 2020 JACSIS. To achieve the targeted response number in the 2021 JASTIS, we additionally recruited 3,160 participants from all respondents who previously participated in the 2015 to 2020 JASTISs. Detailed information regarding the JASTIS is described in the study profile [14].

Inclusion and Exclusion Criteria

In this study, we included data from all the 2021 survey respondents who were current nonsmokers, determined by using the following question: “Do you currently use any of the following tobacco products? (Cigarettes, roll-your-own cigarettes, Ploom Tech, Ploom Tech plus, Ploom S, IQOS, glo, glo hyper, glo sens, PULZE, electronic cigarettes containing nicotine, electronic cigarettes without nicotine, electronic cigarettes with unknown nicotine content, cigars, little cigars, pipes, chewing tobacco, snuffing tobacco, and hookahs).” The response options were “never,” “several times in the past,” “habitually in the past,” “occasionally,” and “almost every day.” In this study, we defined current nonsmokers as those who selected one of the first three options. We excluded surveys as straight-lining responses if the respondents chose the same number in answer to all questions in a set of questions. We also excluded responses in which respondents reported an amount of tobacco product use but had indicated that they had never used or were only former users of tobacco products. In addition to these exclusion criteria, we performed an attention check with the following question: "Please choose the answer second from the bottom." With this attention check, we excluded respondents who selected responses other than the second answer from the bottom.

Measurement of Exposure Variables

The exposure variable that we examined was the exposure to secondhand aerosols from HTPs over the past year. Hence, in the questionnaire, respondents were asked, “During the past 12 months, have you knowingly inhaled aerosols from HTPs when someone used HTPs in your presence?” The response options were “never,” “rarely,” “sometimes,” and “frequently.” In this study, we defined those who were exposed to secondhand aerosols from HTPs as those who selected the latter three options

Main Outcomes and Measures

In this study, we defined self-reported respiratory symptoms as outcomes. As a primary outcome, we selected asthma attacks/asthma-like symptoms, which previous studies indicated were associated with aerosols from HTPs [13,16]. As a secondary outcome, we selected non-specific persistent cough, for which a previous study indicated a possible association with e-cigarette use [17]. The JASTIS included the question, "During the past 12 months, have you experienced any of the following conditions: asthma attacks/asthma-like symptoms or persistent cough?" The response options were "never," "rarely," "sometimes," and "frequently." We defined the presence of each respiratory symptom as a selection of any of the latter three options.

Covariates

As evidence for a relationship between secondhand aerosols and respiratory symptoms is limited, we selected the following 12 variables as potential confounding factors: age groups based on the definition from a previous study (15–29, 30–44, 45–59, or 60–80 years) [18], sex (male or female), education status ("high school or less" or "college or more"), marital status (married, never married, or widowed/divorced), household size (living alone or living with others), equivalent household income (1st quartile, 2nd quartile, 3rd quartile, 4th quartile, or unknown/declined to answer), combustible cigarette use, HTP use, other tobacco-product use, SHS exposure over the past month, and two respiratory comorbidities: asthma and bronchitis/pneumonia. Out of these confounding factors, age, sex, income, past combustible cigarette, HTP, or other tobacco product use, SHS exposure, respiratory comorbidities were selected from previous studies regarding

secondhand aerosols from e-cigarettes [10,11]. The others, *e.g.*, education and marital status, were also defined as confounding factors, based on a previous study regarding secondhand aerosols from heated tobacco products and socioeconomic inequality [19].

Statistical Analysis

First, we calculated the frequency of each variable as baseline characteristics. Second, we stratified the experience of respiratory symptoms over the past year by exposure to secondhand aerosols. Third, we conducted multivariable, "modified" Poisson regression analysis with a robust estimator to estimate the prevalence ratio (PR) and confidence interval (CI) for the prevalence of each respiratory symptom. The exposure variable (exposure to secondhand aerosols from HTPs) was dichotomized, as previously noted, or included as a categorical variable (with "never" as a reference, and "rarely," "sometimes," and "frequently"). The equivalence of outcome prevalence in each category was tested by assigning a linear score by treating secondhand aerosol frequencies as an ordinal variable. In addition, to examine the multicollinearity of variables in the multivariable models, we evaluated the variance inflation factors in all analyses.

We also conducted a sensitivity analysis using a parsimonious model. We constructed a weighted multivariable "modified" Poisson model to examine the consistency of the results for our main analysis. In the model, we selected all the confounding factors with a minimal set of classifications from previous studies [10,11]. The selected variables are as follows: age (15–29 or 30–), sex (male or female), education ("high school or less" or "college or more"), income (lower half or upper half or unknown/declined to answer), past combustible cigarette use (never or past), past HTP use (never or past), SHS (absent

or present), and asthma (absent or present).

To account for the differences between the sociodemographic status of respondents from the survey panel and that of the Japanese general public, we used inverse-probability weighting for all analyses [14,20]. The sampling weights, which were scaled such that the total amounted to 26,000 (original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years. In this way, we adjusted for the difference between respondents in the current internet survey and the 2016 Comprehensive Survey of Living Conditions, a nationally representative survey in Japan [21]. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting. Statistical significance was set at $P<0.05$. The data were analyzed using "svy: tabulate" and "svy: glm" commands in STATA version 16.1 (Stata Corp., College Station, TX, USA).

Patient and public involvement

No patients or the public were involved in this study. We did not invite any patients to comment on the study design, interpretation of the results, or the readability or accuracy of the manuscript.

RESULTS

Of the 26,000 respondents, 18,839 current nonsmokers were included for analyses (**Figure S1**). With inverse-probability weighting, 36.6% (95% CI 34.2–39.1) of participants were aged 60–80, 55.7% (95% CI 53.8–57.6) were female, 53.8% (95% CI 51.6–55.9) were high-school graduates or had less education, and 66.0% (95% CI 64.0–67.8) were married. Regarding smoking and SHS status, 34.0% (95% CI 32.1–36.0) were past combustible-cigarette users, 4.1% (95% CI 3.7–4.6) were past HTP users, and 9.5% (95% CI 8.7–10.4) were past users of other tobacco products. In particular, 80.3% (95% CI 79.0–81.6) of participants had been exposed to SHS in the past month (**Table 1**).

Table 1 Demographics of study participants

Characteristics	N = 18,839	n	%	Weighted %[a]	95% CI
Age	15–29	3,024	16.1	15.5	14.5–16.6
	30–44	4,205	22.3	20.4	19.3–21.5
	45–59	4,967	26.4	27.5	26.1–28.9
	60–80	6,643	35.3	36.6	34.2–39.1
Sex	Male	8,598	45.6	44.3	42.4–46.2
	Female	10,241	54.4	55.7	53.8–57.6
Education status	High school or less	5,789	30.7	53.8	51.6–55.9
	College or more	13,050	69.3	46.2	44.1–48.4
Marital status	Married	11,431	60.7	66.0	64.0–67.8
	Not married	5,670	30.1	25.1	23.6–26.7
	Widowed/divorced	1,738	9.2	8.9	7.5–10.7
Household size	Living alone	15,266	81.0	84.9	82.8–86.8
	Living with others	3,573	19.0	15.1	13.3–17.2
Equivalent household income	1st quartile	3,816	20.3	23.0	21.5–24.6
	2nd quartile	3,874	20.6	21.5	19.7–23.5
	3rd quartile	3,716	19.7	18.4	16.9–20.1
	4th quartile	3,403	18.1	13.1	12.1–14.2
	Unknown/declined to answer	4,030	21.4	23.9	22.0–25.8
Combustible cigarette use	Never	12,822	68.1	66.0	64.1–67.9
	Past	6,017	31.9	34.0	32.1–36
HTP use	Never	18,008	95.6	95.9	95.4–96.3
	Past	831	4.4	4.1	3.7–4.6
Other tobacco product use	Never	17,035	90.4	90.5	89.6–91.3
	Past	1,804	9.6	9.5	8.7–10.4
Exposure to secondhand smoke over the past month	Absent	3,663	19.4	19.7	18.4–21.0
	Present	15,176	80.6	80.3	79.0–81.6
Asthma	Absent	18,271	97.0	96.3	95.2–97.1
	Present	568	3.0	3.7	2.9–4.8

Bronchitis or pneumonia	Absent	18,624	98.9	98.4	97.9–98.8
	Present	215	1.1	1.6	1.2–2.1
Exposure to secondhand aerosol from HTPs over the past 12 months	Absent	14,437	76.6	77.4	75.9–78.9
	Present	4,402	23.4	22.6	21.1–24.1

Note. CI: confidence interval, HTP: heated tobacco product.

[a] The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs were based on the Wald-type test on the probability scale, which was accompanied by the robust variance estimator of the weighted proportions accounting for the inverse-probability weighting ("svy: tabulate" command in Stata)

Of 18,839 respondents, 4,402 (23.4%) were exposed to secondhand aerosols from HTPs. With inverse-probability weighting, 9.8% (95% CI 8.2–11.7) and 16.7% (95% CI 14.8–18.9) of those who were exposed to secondhand aerosols reported asthma attacks/asthma-like symptoms and persistent cough, whereas 4.5% (95% CI 3.9–5.2) and 9.6% (95% CI 8.4–11.0) of those who were not, respectively.

(**Table 2**).

Table 2 Respiratory symptoms over the past year among non-smokers classified into the experience of secondhand aerosols

Symptoms	Frequency		Secondhand aerosol (-) n = 14,437					Secondhand aerosol (+) N = 4,402			
			n	%	Weighted % [a]	95% CI		n	%	Weighted % [a]	95% CI
Asthma attacks/asthma-like symptoms	Never		13,772	95.4	95.5	94.8–96.1		4,043	91.8	90.2	88.3–91.8
	Rarely		424	2.9	2.7	2.3–3.2		211	4.8	5.6	4.5–6.8
	Sometimes		205	1.4	1.6	1.2–2.1		124	2.8	3.3	2.3–4.8
	Frequently		36	0.2	0.2	0.1–0.3		24	0.5	0.9	0.5–1.6
Persistent cough	Never		13,163	91.2	90.4	89.0–91.6		3,787	86.0	83.3	81.1–85.4
	Rarely		697	4.8	4.9	4.3–5.7		346	7.9	8.2	6.9–9.7
	Sometimes		446	3.1	3.9	2.9–5.2		224	5.1	7.1	5.6–8.9
	Frequently		131	0.9	0.8	0.6–1.1		45	1.0	1.4	0.9–2.1

Note. CI: confidence interval.

[a] The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs were based on the Wald-type test on the probability scale, which was accompanied by the robust variance estimator of the weighted proportions accounting for the inverse-probability weighting ("svy: tabulate" command in Stata).

In the multivariable analysis, exposure to secondhand aerosols was associated with both primary and secondary outcomes after adjusting for covariates using "modified" Poisson regression models (asthma attacks/asthma-like symptoms: PR 1.49, 95% CI 1.21–1.85, $P<0.001$; persistent cough: PR 1.44, 95% CI 1.21–1.72, $P<0.001$) (**Table 3**).

Table 3 Multivariable weighted Poisson regression analysis for respiratory symptoms among non-smokers

Characteristics	N = 18,839	Asthma attacks/asthma-like symptoms				Persistent cough		
		PR	95% CI	*P* value		PR	95% CI	*P* value
Exposure to secondhand aerosols	Absent	Reference				Reference		
	Present	1.49	1.21–1.85	<0.001		1.44	1.21–1.72	<0.001
Age	15–29	1.35	1.01–1.79	0.04		1.02	0.79–1.31	0.87
	30–44	1.14	0.89–1.46	0.30		1.15	0.96–1.38	0.14
	45–59	Reference				Reference		
	60–80	0.85	0.64–1.14	0.27		1.13	0.91–1.39	0.27
Sex	Male	Reference				Reference		
	Female	0.92	0.74–1.15	0.45		1.12	0.93–1.36	0.24
Education status	High school or less	Reference				Reference		
	College or more	1.04	0.86–1.26	0.69		0.92	0.74–1.15	0.47
Marital status	Married	Reference				Reference		
	Not married	1.02	0.81–1.29	0.87		0.97	0.77–1.22	0.78
	Widowed/divorced	1.60	1.03–2.46	0.04		1.39	0.93–2.08	0.11
Household size	Living alone	Reference				Reference		
	Living with others	0.85	0.61–1.19	0.34		1.14	0.8–1.61	0.47
Equivalent household income	1st quartile	Reference				Reference		
	2nd quartile	0.81	0.61–1.07	0.14		0.90	0.67–1.21	0.49
	3rd quartile	0.88	0.62–1.24	0.47		0.77	0.56–1.06	0.11
	4th quartile	0.87	0.65–1.17	0.35		0.92	0.69–1.23	0.58
	Unknown/declined to answer	0.72	0.53–0.97	0.03		0.81	0.6–1.09	0.16
Combustible cigarette use	Never	Reference				Reference		
	Past	0.93	0.71–1.22	0.60		1.17	0.88–1.55	0.28
HTP use	Never	Reference				Reference		
	Past	1.71	1.19–2.44	0.003		1.34	1.05–1.72	0.02
Other tobacco product use	Never	Reference				Reference		
	Past	1.35	0.96–1.90	0.09		1.42	1.09–1.85	0.01
Exposure to secondhand smoke over the past month	Absent	Reference				Reference		

	Present	0.86	0.67–1.11	0.26		0.97	0.78–1.21	0.80
Asthma	Absent	Reference				Reference		
	Present	12.39	9.75–15.75	<0.001		4.12	3.13–5.42	<0.001
Bronchitis or pneumonia	Absent	Reference				Reference		
	Present	1.68	1.20–2.35	0.003		2.04	1.46–2.85	<0.001

Note. PR: prevalence ratio, CI: confidence interval, HTP: heated tobacco product.
The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting.

When examining the association of ordinal exposure variables with the outcomes, the same associations were observed (**Figure 1, Table S1**). Notably, all outcomes exhibited a nearly monotonic relationship with the frequency of exposure to secondhand aerosols (both $P<0.001$ with the linear trend test). The maximum variance inflation factor was 2.01, suggesting that there was no problematic multicollinearity in the regression models (**Table S2**).

The results of the sensitivity analysis were shown in **Table 4**. Consistent associations between exposure to secondhand aerosols from HTPs and two outcomes were observed (Asthma attacks/asthma-like symptoms, PR 1.64, 95% CI 1.31–2.04, $P<0.001$; persistent cough, PR 1.48, 95% CI 1.22–1.79, $P<0.001$).

Table 4 Multivariable Poisson regression analysis based on a parsimonious model

Characteristics	N = 18,839	Asthma attacks/asthma-like symptoms			Persistent cough		
		PR	(95% CI)	*P* value	PR	(95% CI)	*P* value
Exposure to secondhand aerosols from HTPs	Absent	Reference			Reference		
	Present	1.64	(1.31–2.04)	<0.001	1.48	(1.22–1.79)	<0.001
Age	15–29	1.30	(1.04–1.64)	0.02	0.89	(0.74–1.08)	0.23
	30–80	Reference			Reference		
Sex	Male	Reference			Reference		
	Female	0.88	(0.70–1.11)	0.29	1.06	(0.84–1.34)	0.60
Education status	High school or less	Reference			Reference		
	College or more	0.99	(0.81–1.22)	0.96	0.89	(0.71–1.12)	0.33
Equivalent household income	Lower half	Reference			Reference		
	Upper half	0.93	(0.72–1.19)	0.56	0.81	(0.64–1.03)	0.09
	Unknown/declined to answer	0.76	(0.58–0.99)	0.04	0.80	(0.62–1.03)	0.08
Combustible cigarette use	Never	Reference			Reference		
	Past	0.94	(0.71–1.26)	0.69	1.26	(0.93–1.71)	0.13
HTP use	Never	Reference			Reference		
	Past	2.05	(1.48–2.84)	<0.001	1.54	(1.17–2.02)	<0.001
Exposure to secondhand smoke over the past month	Absent	Reference			Reference		
	Present	0.84	(0.64–1.11)	0.22	0.99	(0.79–1.24)	0.92
Asthma	Absent	Reference			Reference		
	Present	14.64	(11.63–18.42)	<0.001	5.23	(4.05–6.76)	<0.001

Note. PR: prevalence ratio, CI: confidence interval, HTP: heated tobacco product.

The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting.

DISCUSSION

Using data from a large-scale, nationwide survey conducted in February 2021 in Japan, we discovered a cross-sectional association between secondhand-aerosol exposure and two respiratory symptoms (asthma attacks/asthma-like symptoms and persistent cough) after adjusting for 12 potential confounding factors. The PRs of respiratory symptoms increased as the frequency of exposure to secondhand aerosols from HTPs increased. Furthermore, the weighted prevalence of secondhand-aerosol exposure over the past month was approximately 20%, and, similar to those of SHS from combustible cigarettes and secondhand aerosols from e-cigarettes [1,6]. Given these findings, many current nonsmokers in Japan may be exposed to secondhand aerosols from HTPs, which may have detrimental effects on their respiratory systems.

There are several potential mechanisms by which secondhand aerosols may cause respiratory symptoms. First, in the biochemical context, aerosols from HTPs contain substantial amounts of chemical compounds such as carbonyl compounds and polycyclic aromatic hydrocarbons [22]. These chemicals damage human bronchial epithelial cells [23], inducing asthma attacks or asthma-like symptoms. Second, in the physiological context, inhalation of the chemical compounds in aerosols from HTPs impairs respiratory function (forced expiratory volume in one second, both absolute and as a percentage of the predicted value) [24], resulting in respiratory symptoms. Finally, in the indoor environmental context, secondhand aerosols contain concentrations of harmful chemical compounds, such as nicotine and fine particulate matter, greater than the upper limits of the range of tolerable concentrations [25]. Consequently, even current nonsmokers may experience asthma attacks/asthma-like symptoms or persistent cough via the above-

mentioned biochemical and physiological mechanisms after inhalation of secondhand aerosols emitted by others, especially indoors.

Secondhand aerosols from e-cigarettes have already been an emerging public health threat. A study by Bayly *et al.* presented a cross-sectional association between exposure to secondhand aerosol from e-cigarettes and asthma attacks in youth aged 11–17 years (n = 11,830) in the United States [10]. In the study, both secondhand aerosol from e-cigarettes and SHS were associated with asthma attacks in the multivariable logistic regression model; however, the estimated odds ratio in SHS was smaller than that in secondhand aerosols (SHS, odds ratio [OR] 1.19, 95% CI 1.05–1.35; and secondhand aerosol rom e-cigarettes, OR 1.27, 95% CI 1.11–1.47). Although the study adjusted for numerous confounding factors including various patterns of tobacco product use, there was an important limitation regarding inconsistent time frames of the measurements, *i.e.*, the time frame of the exposure was past 30 days and that of the outcome was 12 months. Such an inconsistent time frame may imply an increased risk of the reverse relationship between exposure to secondhand aerosol from e-cigarettes and asthma attacks. Another study by Alnajem *et al.* also showed a cross-sectional association between secondhand aerosol exposure from e-cigarettes in the past 7 days and respiratory symptoms in the past 12 months among schoolchildren aged 16–19 years in Kuwait [11]. In that study, frequent secondhand aerosol exposure was associated with an increased risk of wheeze (PR 1.30, 95% CI 1.04–1.59), asthma (PR 1.56, 95% CI 1.13–2.16), and uncontrolled asthma symptoms (PR 1.88, 95% CI 1.35–2.62). However, like the study by Bayly *et al.*, the same limitation for time frame was observed (7 days for the exposure and 12 months for the outcome). A. recent study by Islam *et al.* showed the longitudinal association between

exposure to e-cigarette secondhand aerosols and bronchitic symptoms (OR 1.40, 95% CI 1.06–1.84) and shortness of breath (OR 1.53, 95% CI 1.06–2.21) among young adults (average age, 17.3 years; n = 2,090) in the United States [12]. Although these studies are informative, they commonly focus on e-cigarettes and a specific population (adolescents and young adults). There have been few studies on the association of exposure to secondhand aerosol from HTPs with respiratory outcomes. To date, we could find only one study by Imura and Tabuchi, via an internet survey conducted in 2019, which examined the cross-sectional association between exposure to secondhand aerosols and symptoms directly induced by such exposure [13]. They revealed that asthma-like attacks and chest pain were more prevalent in those who were exposed to secondhand aerosols from HTPs than to SHS from combustible cigarettes. Although this study is informative, evaluation of its association with subacute to chronic respiratory symptoms remains limited. Thus, we examined the association between exposure to secondhand aerosols from HTPs and asthma attacks/asthma-like symptoms and persistent cough. When designing this study, we used the same frame for the measurement of the exposure and outcomes (past 12 months) to compensate for the previous cross-sectional studies. The associations were mostly consistent with the previous studies regarding secondhand aerosols from e-cigarettes. However, there were some inconsistent estimates, *e.g.*, the association between SHS and respiratory outcomes was not observed. Nevertheless, as noted above, a previous study showed that the odds ratio of SHS for asthma was smaller than that of secondhand aerosols from e-cigarettes [10]. The phenomenon that the odds or prevalence ratios in SHS were lower than those in secondhand aerosols from HTPs might be induced by the different time frames of measurements for SHS (30 days) and outcomes (12 months) both in this study and a previous study. Moreover, when stratified

by exposure to SHS, the associations of exposure to secondhand aerosol from HTPs with both asthma attacks/asthma-like symptoms and persistent cough were consistently observed among the exposure to SHS group in our data (asthma attacks/asthma-like symptoms, PR 1.53, 95% CI 1.21–1.93; persistent cough, PR 1.44, 95% CI 1.19–1.74). Therefore, we believe that our results were not discrepant from the previous studies. Notably, the strength of this study is that we focused on current nonsmokers whom most policymakers have interested [1], and used consistent time frames for the measurements of the exposure and outcomes. To our knowledge, this is the first study in which the environments in which people were exposed to secondhand aerosols from HTPs were clarified and the association between such exposure and respiratory symptoms was evaluated among current nonsmokers, by using nationally representative, large-scale survey data. As the number of HTP users is growing in Europe and the United States [26,27], as well as in Japan, the threat to current nonsmokers' health due to secondhand-aerosol exposure from HTPs will increase globally. Thus, our findings provide policymakers with meaningful information in regulating HTP use for the protection of current nonsmokers. In addition, we believe our results will contribute to longitudinal epidemiological studies, biological studies for the relationship between respiratory systems and toxic effects of aerosols from HTPs, environmental studies that examined the chemical pounds from HTP aerosols, and so on.

Our study has several limitations. First, because of this study's cross-sectional design, the temporal relationship between secondhand-aerosol exposure and respiratory symptoms was unclear, and our results cannot be used to infer causality. However, the results from this study implied a nearly monotonic relationship between the frequency of exposure to

secondhand aerosols and the PR for each respiratory symptom under assessment, which is a key component in explaining causality [28]. Second, this study was based on self-report questionnaires and not all variables were measured with validated questionnaires; therefore, measurement errors may exist. However, we developed an algorithm for exclusion of responses that were unreliable or invalid, and excluded such respondents *a priori*. Moreover, our questionnaire for exposure variables clearly assumed that someone used HTPs in the respondents' presence. In combination with the high prevalence of HTP use in 2020 Japan [29], we believe that our questionnaire for exposure had substantial sensitivity. Third, this study is based on an internet survey; the composition of study participants may have differed from that of the general Japanese public. However, to minimize such differences, we adjusted for demographic, socioeconomic, and health-related differences between respondents in the present study and the Japanese general public by using nationally representative survey data. Finally, this study was conducted in Japan, where HTPs are more popular than in other countries [30]; therefore, our findings may not be generalizable to other countries.

In conclusion, by using data from a nationally representative survey, this study revealed that exposure to secondhand aerosols from HTPs were prevalent in 2021 in Japan. This study clarified the association between such exposure and asthma attacks/asthma-like symptoms and persistent cough among current nonsmokers. Our results will provide policymakers with meaningful information for a smoke-free policy. Also, we can provide good evidence to make progress in future research in relation to respiratory diseases induced by secondhand aerosol from HTPs.

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Author contributions: TY, TS, AH, KN, SO and TT contributed to the conceptualization of this study. TY and TT collected data, and TY, TS, and TT developed the plan for analysis. TY analyzed the data. TY wrote the original manuscript, and TS, AH, KN, SO, and TT reviewed, interpreted, critically appraised, and revised the original manuscript. TY, TS, AH, KN, SO, and TT reviewed the final version of the manuscript and approved its submission. TY takes responsibility for the content of the manuscript, including the data and analysis.

Funding/Support: This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI grants (grant numbers 17H03589, 19K10671, 19K10446, 18H03107, 18H03062, 19H03860), the JSPS Grant-in-Aid for Young Scientists (grant number 19K19439), the Research Support Program to Apply the Wisdom of the University to tackle COVID-19 Related Emergency Problems, University of Tsukuba, and Health Labour Sciences Research Grant (grant numbers 19FA1005, 19FG2001, 19FA1012) and the Japan Agency for Medical Research and Development (AMED; grant number 2033648). We acknowledge the support by National Institute of Public Health for the article publishing charge.

Disclaimer: The funders had no role in the study design, data collection, statistical analysis, decision to publish, or preparation of the manuscript, except for conducting the internet survey, language editing of the manuscript, and the article publishing charge.

Competing interests: None to declare.

Data availability statement: The data used in this study are not available in a public repository because they contain personally identifiable or potentially sensitive participants' information. Based on the regulations for ethical guidelines in Japan, the Institutional Review Board of the Osaka International Cancer Institute has imposed restrictions on the dissemination of the data collected in this study. All data inquiries will be channeled through Takahiro Tabuchi (tabuchitak@gmail.com) to Osaka Cancer Institute Institutional Ethics Committee.

Ethics Approval

All procedures were conducted according to the ethical standards of the Declaration of Helsinki. We obtained web-based informed consent from all the respondents for use of their data from the JASTIS study in our research. A credit point known as "Epoints," which could be used for internet shopping and cash conversion, was provided to the participants as an incentive. This study was approved by the Institutional Review Board of Osaka International Cancer Institute (Number: 20084). The internet research group fully respected the Act on the Protection of Personal Information in Japan. This study followed the STROBE guidelines for cross-sectional studies.

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Figure Legends

Figure 1 Prevalence ratios of ordinal exposure variables for the outcomes

A: asthma attacks/asthma-like symptoms, B: persistent cough.

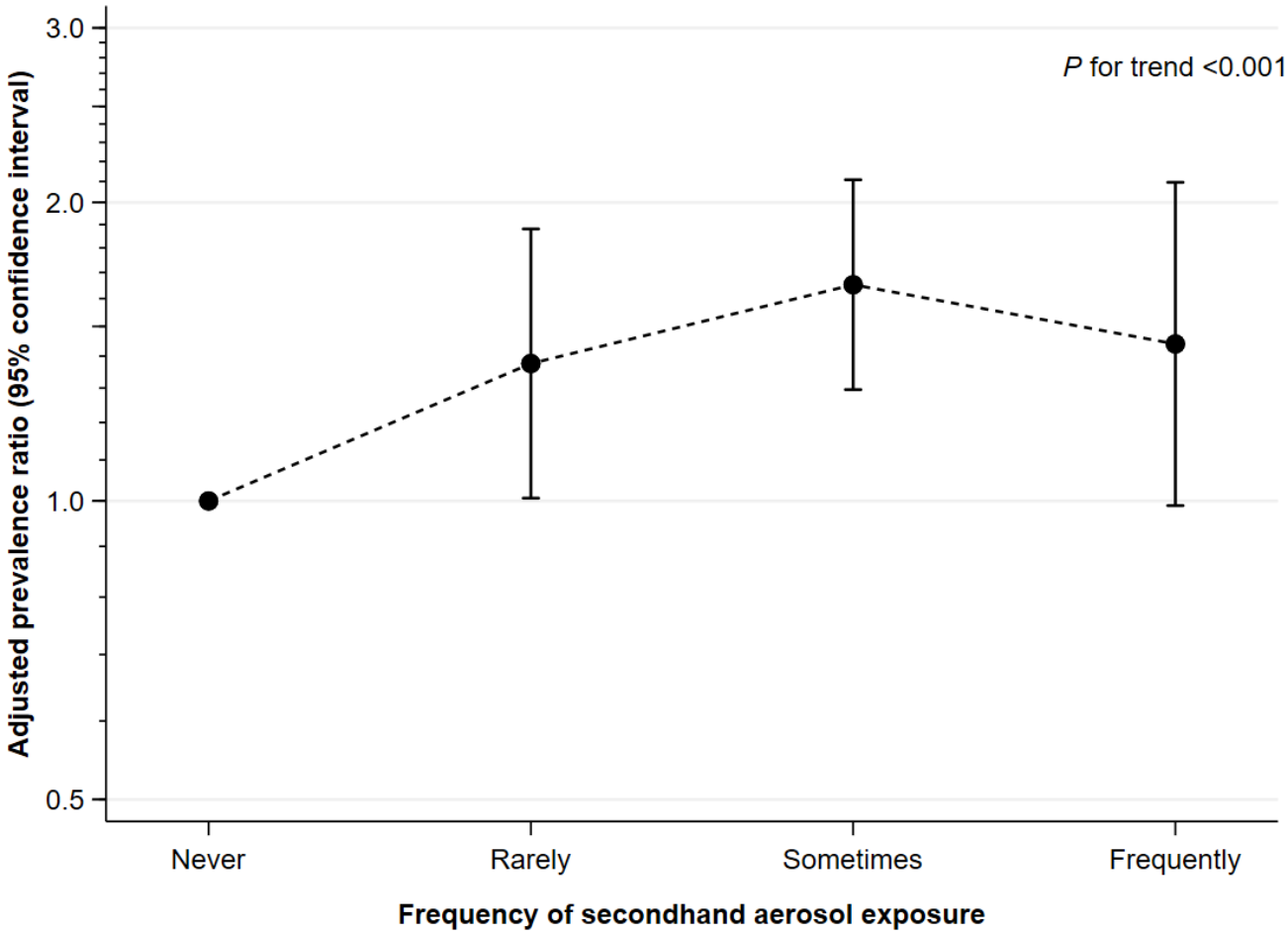
Supplemental materials:

Table S1 Multivariable Poisson regression analysis using ordinal exposure variables

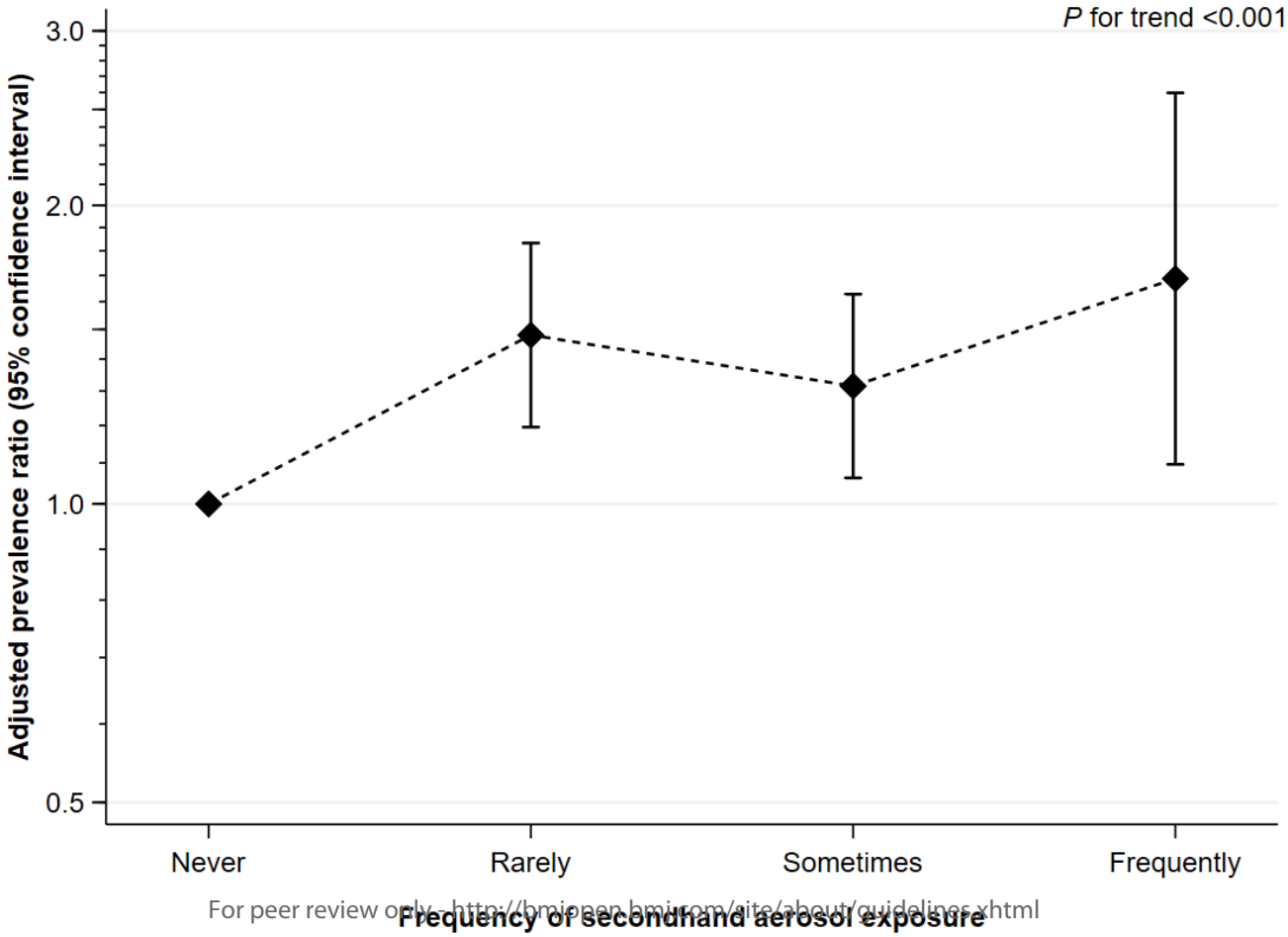
Table S2 Variance inflation factors for the evaluation of multicollinearity

Figure S1 Flow diagram of the study

A



B



Supplemental materials

Yoshioka T, Shinozaki T, Hori A, Okawa S, Nakashima K, Tabuchi T. Association between exposure to secondhand-aerosol from heated tobacco products and respiratory symptoms among current nonsmokers in Japan: a cross-sectional study

Table S1 Multivariable Poisson regression analysis using ordinal exposure variables

Characteristics	N = 18,839	Asthma/asthma-like attacks			Persistent cough		
		PR	95% CI	*P* value	PR	95% CI	*P* value
Exposure to secondhand aerosols	Never		Reference			Reference	
	Rarely	1.38	1.01–1.88	0.05	1.48	1.20–1.83	<0.001
	Sometimes	1.65	1.30–2.11	<0.001	1.31	1.06–1.63	0.01
	Frequently	1.44	0.99–2.10	0.06	1.69	1.10–2.60	0.02
Age	15–29	1.36	1.02–1.82	0.04	1.01	0.78–1.30	0.94
	30–44	1.14	0.89–1.47	0.28	1.15	0.96–1.38	0.14
	45–59		Reference			Reference	
	60–80	0.86	0.64–1.15	0.31	1.13	0.91–1.40	0.28
Sex	Male		Reference			Reference	
	Female	0.92	0.74–1.15	0.46	1.11	0.92–1.35	0.27
Education status	High school or less		Reference			Reference	
	College or more	1.04	0.85–1.27	0.70	0.93	0.74–1.16	0.50
Marital status	Married		Reference			Reference	
	Not married	1.03	0.81–1.30	0.82	0.97	0.77–1.21	0.77
	Widowed/divorced	1.61	1.04–2.48	0.03	1.39	0.93–2.07	0.11
Household size	Living alone		Reference			Reference	
	Living with others	0.84	0.60–1.19	0.33	1.14	0.81–1.61	0.47
Household-equivalent income	1st quartile		Reference			Reference	
	2nd quartile	0.81	0.62–1.07	0.14	0.89	0.66–1.21	0.46
	3rd quartile	0.89	0.63–1.26	0.51	0.76	0.56–1.05	0.10
	4th quartile	0.87	0.65–1.18	0.38	0.92	0.69–1.22	0.56
	Unknown/declined to answer	0.72	0.53–0.98	0.03	0.80	0.60–1.08	0.14
Combustible cigarette use	Never		Reference			Reference	
	Past	0.94	0.71–1.22	0.63	1.17	0.88–1.55	0.29
HTP use	Never		Reference			Reference	
	Past	1.70	1.19–2.43	0.004	1.35	1.05–1.73	0.02
Other tobacco product use	Never		Reference			Reference	
	Past	1.35	0.96–1.91	0.08	1.41	1.08–1.85	0.01
Exposure to secondhand smoke over the past month	Absent		Reference			Reference	
	Present	0.86	0.67–1.11	0.25	0.97	0.78–1.21	0.81
Asthma	Absent		Reference			Reference	
	Present	12.31	9.68–15.65	<0.001	4.13	3.14–5.42	<0.001
Bronchitis or pneumonia	Absent		Reference			Reference	
	Present	1.68	1.20–2.36	0.002	2.04	1.46–2.84	<0.001

Note. PR: prevalence ratio, CI: confidence interval, HTP: heated tobacco product.

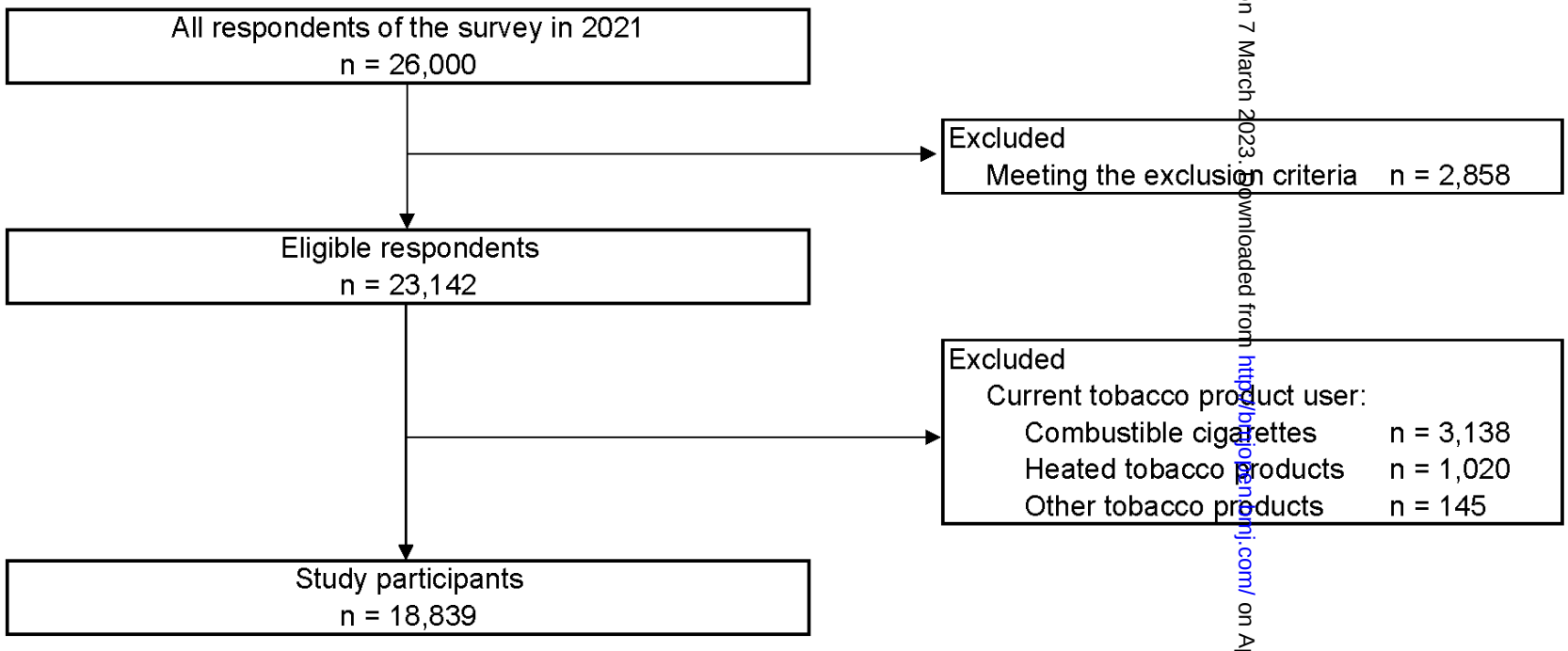
The sampling weights, which were scaled such that the total amounted to 26,000 (the original number of respondents), were predicted from a logistic model in which we adjusted for area of residence, marital status, education status, home-ownership status, self-rated health, and smoking status in individuals aged 20–80 years; and area of residence, education status, home-ownership status, and self-rated health (omitting marital and smoking status) in individuals aged 15–19 years, to adjust for the difference in respondents between the current internet survey and the 2016 Comprehensive Survey of Living Conditions in Japan. All CIs and *P* values were based on the robust variance estimator to account for the inverse-probability weighting.

Table S2 Variance inflation factors for the evaluation of multicollinearity

Characteristics	N = 18,839	VIF
Exposure to secondhand aerosols	Absent	Reference
	Present	1.07
Age	15–29	1.78
	30–44	1.49
	45–59	Reference
	60–80	1.68
Sex	Male	Reference
	Female	1.19
Education status	High school or less	Reference
	College or more	1.06
Marital status	Married	Reference
	Not married	2.01
	Widowed/divorced	1.31
Household size	Living alone	Reference
	Living with others	1.48
Household-equivalent income	1st quartile	Reference
	2nd quartile	1.63
	3rd quartile	1.65
	4th quartile	1.68
	Unanswered	1.66
Combustible cigarette use	Never	Reference
	Past	1.40
HTP use	Never	Reference
	Past	1.19
Other tobacco product use	Never	Reference
	Past	1.31
Exposure to secondhand smoke over the past month	Absent	Reference
	Present	1.03
Asthma	Absent	Reference
	Present	1.09
Bronchitis or pneumonia	Absent	Reference
	Present	1.10
Mean		1.41

Note. VIF: variance inflation factor, CI: confidence interval, HTP: heated tobacco products.

Figure S1 Flow diagram of the study



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	#1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	#3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	#5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	#6
Methods			
Study design	4	Present key elements of study design early in the paper	#7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	#7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	#8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	#8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	#7-10
Bias	9	Describe any efforts to address potential sources of bias	#11
Study size	10	Explain how the study size was arrived at	#7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	#10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	#10-11
		(*b*) Describe any methods used to examine subgroups and interactions	#10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	#7
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	#12
		(b) Give reasons for non-participation at each stage	#12, Figure S1
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	#12
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	#15, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	#17, Table 1-3
		(*b*) Report category boundaries when continuous variables were categorized	#17, Table 1-3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figure 1, #19, Table 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	#21
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	#24,25
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	#22-24
Generalisability	21	Discuss the generalisability (external validity) of the study results	#25
Other information			
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	#26

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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.