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Original article

Changes in smoking habits and behaviors following the introduction and spread of heated tobacco products in Japan and its effect on FEV₁ decline: a longitudinal cohort study

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1 **ABSTRACT**

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3 Background: Heated tobacco product (HTP) use in Japan has rapidly increased. Despite this
4 rapid spread, little is known about the health effects of HTP use. We conducted a longitudinal
5 cohort study to investigate the change in smoking habits following the spread of HTP use and
6 its effect on forced expiratory volume in one second (FEV₁) decline.

7

8 Methods: Participants consisted of a resident population (n=2,612, aged 67.7) with FEV₁
9 measurement in 2012-2014 and 2018-2019, and a worksite population (n=722, aged 49.3)
10 without FEV₁ data. Participants were categorized as never, past and combustible cigarette-only
11 smokers, and HTP-only and dual users. The association between smoking group and the change
12 in smoking consumption for 5.6 years was examined. Differences in annual FEV₁ change
13 between smoking groups were examined in the resident population.

14

15 Results: Prevalence of HTP-only and dual users in 2018-2019 was 0.8% and 0.6% in the
16 resident population, and 5.0% and 1.9% in the worksite population, respectively. The overall
17 number of tobacco products smoked/used increased in dual users compared to baseline, but not
18 in others. Annual FEV₁ decline in dual users tended to be greater than that in cigarette-only
19 smokers (16 mL/yr [95% CI: -34, 2] after full adjustment). Participants switching to HTP-only

20 use 1.7 years before had a similar FEV₁ decline as cigarette-only smokers.

21

22 Conclusions: HTP use, including dual use, is prevalent even in a rural region of Japan. Dual
23 users appear to smoke/use tobacco products more and have a greater FEV₁ decline. Tobacco
24 policy should consider dual use as high-risk.

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28 Keywords: Heated tobacco products, Electronic nicotine delivery devices, Prevention,

29 Smoking Caused Disease

30

31 INTRODUCTION

32

33 Heated tobacco product (HTP) use is rapidly increasing in Japan. Sales of HTPs
34 commenced in 2014, ahead of the world, and 7.2% of Japanese men and 1.4% of women were
35 reported to be users in 2018, versus 22.0% of men and 7.5% of women who used combustible
36 cigarettes.¹ Most HTP users previously smoked combustible cigarettes.² This drastic change in
37 the smoking habits of Japanese following the spread of HTPs should be appropriately reflected
38 in tobacco control policies, including dual using. Given the now gradual adoption of HTPs in
39 other countries,^{3,4} information on the effect of HTP spread will be valuable worldwide.

40 While some populations use HTP and combustible cigarettes concurrently, the actual
41 number of such dual users is unclear, as studies have produced conflicting data. JASTIS^{5,6} and
42 ITC Japan^{2,7} have shown that the majority of HTP users were concurrent cigarette smokers. On
43 the other hand, the Japanese National Health and Nutrition Survey has reported the opposite.⁸
44 Therefore, providing data from an independent cohort study using face-to-face interviews
45 would be of great significance. Moreover, the smoking behavior of HTP users, including dual
46 users, is little known. From the perspective of tobacco control policy, an understanding of
47 trends in smoking behavior is essential, including both nicotine dependence and stages in the
48 transtheoretical model of smoking cessation.⁹

49 A second important issue in HTPs is their effect on health. Although levels of some

50 toxic substances in combustible cigarette mainstream smoke are reported to be decreased in
51 HTP aerosol,^{10 11} few studies have evaluated the effect of these changes in HTP users, and thus,
52 the health effects of HTPs remain unclear. Furthermore, even if HTPs reduce some of the
53 harmful effects of combustible cigarettes when used alone, the health effects of dual use should
54 also be considered.

55 Nevertheless, evaluation of the health effects of newly introduced smoking products
56 is challenging. Long-term evaluation is required to determine whether the increases in cancer,
57 cardiovascular disease, stroke and COPD seen with combustible cigarette smoking¹² can be
58 replicated with HTPs. However, an adverse effect of smoking that is consistently observed over
59 a relatively short period is a decrease in forced expiratory volume in one second (FEV₁)¹³. To
60 our knowledge, studies of the effect of HTP use on FEV₁ are scarce.

61 The Tsuruoka Metabolomics Cohort Study, a population-based cohort study in Japan,
62 has collected longitudinal data on smoking habits and FEV₁ from baseline in 2012, before
63 HTPs were sold, to follow-up in 2018, after HTPs became popular. Here, we used these data
64 to investigate the change in smoking habits following the introduction and spread of HTPs, to
65 evaluate the behavior of HTP users, including dual users, and to examine the effect of HTP use
66 on FEV₁ decline.

67 **METHODS**

68

69 **Study participants**

70 This study was based on the Tsuruoka Metabolomics Cohort Study (TMCS), a
71 prospective cohort study conducted in Tsuruoka City, located in the rural area of Yamagata
72 Prefecture, Japan. The baseline survey of TMCS was conducted from fiscal year (April-March)
73 2012 to 2015 and enrolled 11,002 participants aged 35-74 years. Details on the cohort study
74 are available elsewhere.¹⁴⁻¹⁷ Briefly, two different populations exist in TMCS, a resident
75 population, and a worksite population. The resident population consists of participants
76 attending a municipal health check-up, and the worksite population of those from an
77 occupational health check-up. The follow-up survey from the fiscal year 2018 to 2021 is
78 currently ongoing for both populations. In this study, individuals from both the resident and
79 worksite cohorts who participated in the follow-up survey at Shonai Health Management
80 Center from April 2018 to June 2019 including detailed questionnaire for HTP use were
81 selected for analysis (Supplementary Figure 1). To be precise, for resident population, a total
82 of 4,760 participants were enrolled at the baseline surveys conducted in the fiscal years 2012
83 and 2014 at Shonai Health Management Center, and of these, 2,612 individuals who
84 participated in the follow-up survey between April 2018 and March 2019 at the same facility
85 were included in the present analysis. For the worksite population, 767 employees from three

86 different workplaces in Tsuruoka City participated in the baseline survey between January 2013
87 and July 2014, of which 676 people participated in the follow-up survey between January and
88 June 2019, and were subject to the present analysis. As an add-on to the worksite population,
89 we recruited an additional 46 individuals under the age of 40 from the same worksites between
90 March and June of 2019 to investigate the prevalence of smoking habits in younger generations
91 after the market introduction of HTP. In total, the number of participants in the present study
92 was 2,612 for the resident population, and 722 for the worksite population including 46
93 additional younger participants. The demographics at baseline were comparable between those
94 who participated in the 2018-2019 survey and those who did not (Supplementary Table 1).

95 The study was approved by the Medical Ethics Committee of the Keio University
96 School of Medicine, Tokyo, Japan (Approval Nos. 20110264 and 20180336). All individual
97 participants in this study provided written informed consent.

98 99 **Data collection**

100 All data were obtained in the TMCS baseline survey from April 2012 to March 2015
101 and the follow-up survey from April 2018 to June 2019. Information on smoking habits,
102 education, medical history and medication was collected through a standardized self-
103 administered questionnaire and face-to-face interview by trained interviewers in both the
104 baseline and follow-up surveys. Information on HTPs and e-cigarette smoking, nicotine

dependence and stage of behavioral change in smoking cessation was also collected at the follow-up survey.

Numbers of combustible cigarettes smoked and HTPs used daily were collected by product type (IQOS, Philip Morris Inter National Inc., NY; glo, British American Tobacco Plc., U.K.; and Ploom TECH, Japan Tobacco Inc.). Photographs of each HTP type were shown to each participant by an interviewer to confirm one's use of a particular product. The tobacco-containing insert of IQOS and glo is a stick, while Ploom TECH is a capsule.² The use of one stick of IQOS or glo was considered equivalent to smoking one combustible cigarette. As for Ploom TECH, a single use was defined as using the device for 10 minutes or less, since smoking one cigarette typically lasts less than ten minutes. Respondents were asked how many times a day they used their device based on this interpretation, and we assessed that single use of Ploom TECH device was equivalent to smoking one cigarette. Smoking history was also collected, namely age at starting and quitting smoking. Smoking habits were categorized into the following five groups according to information from the follow-up survey: combustible cigarette-only smokers, HTP-only users, dual users, past smokers, and never smokers. No participant used electric nicotine delivery systems other than HTPs, such as e-cigarettes. Combustible cigarette-only smokers were identified as smokers who smoked at least one combustible cigarette per day, but no HTPs; and HTP-only users as participants who used HTPs

at least once per day, but no combustible cigarettes. Participants with daily use of both a cigarette and an HTP were classified as dual users. All smokers at follow-up had started smoking before baseline; accordingly, the HTP-only and dual users had all smoked combustible cigarettes exclusively at baseline.

Nicotine dependence was evaluated using the Fagerstrom test for nicotine dependence (FTND).^{18 19} We classified an FTND score of 7-10 as high dependence, 3-6 as normal dependence, and 0-2 as low dependence. Stage of behavioral change in quitting smoking was assessed using the following stages: (1) pre-contemplation stage without interest in cessation (a smoker who answered “I am not interested in cessation”), (2) pre-contemplation stage with interest in cessation (“I am interested in cessation, but am not considering quitting within six months”), (3) contemplation stage (“I am considering quitting smoking within six months but am not ready to do so within one month”), and (4) preparation stage (“I am ready to quit smoking within one month”).^{9 20}

Respiratory function was repeatedly tested in the resident population at the baseline and follow-up surveys. Of the 2,612 participants in the resident population, 2,475 were tested at both baseline and follow-up. Forced expiratory volume in one second (FEV₁) was measured by a trained clinical laboratory technician using an electric spirometer (Aurospiro AS7, Minato Medical Science, Japan). FEV₁ change per year was calculated by subtracting FEV₁ at baseline

from FEV₁ at follow-up, then dividing it by the individual's follow-up period (5.7 (0.8) years).

Statistical analysis

A linear regression model was used to examine the differences among smoking groups in change of the total number of tobacco products smoked or used per day from baseline to follow-up. This model included a dummy variable for the smoking group (combustible cigarette only smokers (reference category), HTP only users, and dual users) as the independent variable, and the number of tobacco products smoked/used per day at follow-up minus the number of those at baseline was used as the outcome variable. This analysis was conducted using the two populations combined. We used two models: Model 1 was crude, and Model 2 was adjusted for sex, age, population (resident or worksite) and the number of combustible cigarettes smoked per day at baseline (equal to total smoking of tobacco products per day at baseline). Sensitivity analysis which excluded Ploom TECH users (n=8) was also conducted. A linear regression model was then developed to examine the differences between smoking groups in annual FEV₁ change in the resident population. This model included a dummy variable for the smoking group (combustible cigarette only smokers (reference category), HTP only users, dual users, past smokers and never smokers) as the independent variable, and FEV₁ change per year was used as the outcome variable. Participants who quit daily smoking before the baseline survey were defined as past smokers in the analysis for FEV₁ change. Participants

162 who quit daily smoking after baseline were excluded from this particular analysis (n=143).

163 Three models were used for this analysis. Model 1 was crude, model 2 was adjusted for sex

164 and age, and model 3 was adjusted for sex, age, height, FEV₁ at baseline and the number of

165 combustible cigarettes smoked per day at baseline. For past and never smokers, model 3 was

166 conducted without adjustment for the number of combustible cigarettes. We also conducted a

167 sensitivity analysis as model 4 that included the number of tobacco products smoked/used per

168 day at follow-up instead of the number of combustible cigarettes smoked per day at baseline.

169 All statistical analyses were performed using R.3.6.2 (R Core Team 2019, R

170 Foundation for Statistical Computing, Vienna, Austria.).

171

RESULTS

HTP usage and change in smoking habits

Prevalence of HTP only and dual users in 2018 was 0.8% and 0.6% in the resident population (67.7 (7.1) years), and 5.0% and 1.9% in the worksite population (49.3 (7.3) years), respectively (Tables 1 and 2, Supplementary Tables 2 and 3). The prevalence of combustible cigarette-only smokers was 8.9% in the resident and 8.6% in the worksite population. HTP-only users had switched from combustible cigarettes to HTPs 1.66 (0.86) years before the follow-up survey, whereas dual users had started combining HTPs 1.21 (1.01) years prior to follow-up. In both populations, HTP only and dual users were younger than the other groups. HTP use was more frequent in the younger population (Table 3), and HTP users were accordingly much more prevalent in the worksite than the resident population. Dual users accounted for 29.2% of HTP users aged 40-49 years and over 40% of those aged 50-79 years in males. Among women using HTPs, 28.6% in their 40s and 33.3% in their 50s were dual users. IQOS was the most popular HTP brand. None of the participants were daily users of electronic nicotine delivery systems other than HTPs in either population.

For combustible cigarette-only smokers and HTP-only users, the number of combustible cigarettes smoked per day at baseline and the number of tobacco products used

per day at follow-up were comparable with a decreasing trend. Using combustible cigarette-only smokers as the reference group, -0.96 [95% confidence interval: -2.58, 0.67] change was observed in HTP-only users after adjustment (Table 4). In contrast, in dual users, the total number of tobacco products (combustible cigarettes and HTPs) smoked and used per day increased, with a 3.12 [1.18, 5.07] change compared with combustible cigarette-only smokers after adjustment. Results were consistent after the exclusion of Ploom TECH users (-0.93 [-2.57, 0.70] change in HTP only users and 3.18 [0.99, 5.37] in dual users). Although the number of combustible cigarettes smoked also decreased in dual users, the added number of HTPs led to an increase in the use of total number of smoking tobacco products.

Nicotine dependence and stage of behavioral change in quitting smoking

For nicotine dependence, no difference was found between smoking groups in the resident population (χ^2 test; $p = 0.79$). FTND score seemed to be marginally different in the worksite population (χ^2 test; $p = 0.05$). With regard to the stage of behavioral change in quitting smoking, there were no obvious differences between smoking groups.

FEV₁

A linear regression model was used to examine the differences in annual FEV₁ decline between smoking group (Table 5). Compared with combustible cigarette smokers,

210 dual users showed greater FEV₁ decline per year (-18 mL/yr [95%CI: -35 to -1] in model 2,
211 and -16 [-34, 2] in model 3), whereas HTP-only users had a similar reduction (1 mL/yr
212 [95%CI: -14 to 16] in model 2, and 6 mL/yr [-11 to 23] in model 3). Smaller FEV₁ decline
213 was observed for never and past smokers as compared to cigarette smokers. A sensitivity
214 analysis was conducted by including the number of tobacco products smoked/used per day at
215 follow-up as an adjusting covariate (model 4). Dual users still demonstrated a greater annual
216 FEV₁ decline than cigarette-only smokers, but their difference in the magnitude of the decline
217 was smaller than observed in model 3.

DISCUSSION

This study showed that HTP use was prevalent even in the rural area of Japan. Among our participants, a prevalence of HTP use for men in the 40s, 50s, 60s, and 70s were 16.7%, 9.5%, 3.4%, and 0.4%, respectively, whereas for women, 2.6% in their 40s, 0.9% in the 50s, and 0% in the 60s and 70s. These prevalence were similar to other surveys which likely were heavily weighted towards urban areas.¹⁸ A population-based study conducted in Japan in 2018¹ reported a prevalence of HTP use within the preceding 30 days of 13.3% of men and 2.5% of women aged 40-49 years, 7.7% and 2.3% in those aged 50-59, 5.6% and 0.2% in those aged 60-69, and 0.7% and 0% in those aged 70-79, respectively.¹ The prevalence of HTP users in our study was largely consistent with this previous study, albeit higher in males and lower in females. This indicates that HTP use is prevalent in Japan, not only in urban areas but also in rural area, suggesting the need for nationwide measures for the spread of HTPs.

In this study, the proportion of dual use was 20-30% in HTP users aged 34-49, while it was nearly half among those aged 50 and above. An internet survey conducted in Japan in 2017 reported that the prevalence of HTP or e-cigarette use within the preceding 30 days was 4.7%. The dual use of combustible cigarettes and HTPs/e-cigarettes was 3.4%.²¹ The prevalence of dual users without e-cigarettes was not clear, but the proportion of dual users in HTP users was higher than in our study, at over 75% among participants aged 30 years and

237 older. In that report, the prevalence of e-cigarette use appeared high, at 1.9%, despite the
238 prohibition on the sale of e-cigarettes with nicotine by governmental regulation in Japan,
239 indicating that participants likely misclassified these two new tobacco products, as noted by
240 the authors. Such misclassification of HTP use is a major concern and has not been sufficiently
241 addressed in the previous studies.^{22 23}

242 Other surveys in Japan also showed a high proportion of dual users among HTP users²
243 ⁵⁻⁷, while that of the Japan National Health and Nutrition Survey in 2018 was similar to or
244 slightly lower than our study.⁸ This conflict may be due to differences in sampling methods and
245 questioning methods. In the Japan National Health and Nutrition Survey, random selection was
246 conducted nationwide, but the questionnaire was limited in that the section on HTP use was
247 not separated. Other nationwide surveys focused on HTP use, had detailed questionnaires on
248 HTP use, but were conducted mainly through internet surveys.

249 The strength of this study is that misclassification was reduced as much as possible.
250 We asked product-specific questions about HTP use, separate from the questionnaire for
251 cigarette use, and confirmed each response through careful face-to-face interviews using
252 photographs of the devices. Since the study was conducted in one rural region of Japan, the
253 results are primarily generalizable for elderly residents and middle-aged workers in rural
254 regions of Japan.

255

The number of smoking tobacco products used per day decreased over the six years of the observation period for both combustible cigarette smokers and HTP users, and the degree of reduction was comparable. This finding suggests that the shift to HTPs did not affect the number of tobacco products smoked. However, some combustible cigarette smokers started to use both combustible cigarettes and HTPs. These dual users tended to smoke a greater number of products than at baseline, and showed a greater decline in FEV₁ over the observation period compared to either the combustible cigarette only or HTP-only users. Considering many dual users among HTP users, the adverse health effects of HTP use and those of dual use should be considered when HTPs control policies are established.

It remains unclear whether switching from combustible cigarettes to HTPs causes a decrease in smoking consumption. In our study, smokers who switched to HTPs used a closely similar number of tobacco products to smokers who continued to smoke combustible cigarettes from baseline to follow-up. This result suggests that switching to HTPs does not contribute to a reduction in the number of products smoked, and therefore, provides new insight into changing the habit of smoking. Further, our results also suggest that dual users tend to smoke more than they did prior to initiating the use of HTPs. One likely explanation for this is that HTP use might lead to a decrease in hesitation to smoke in public spaces, given that tobacco companies tend to emphasize the lower possibility of secondhand smoke exposure with HTP use. Indeed, 16 of our 30 dual users reported that they initially began to use HTPs because they

would not bother the people around them (data not shown). It is possible that dual users smoked either combustible cigarettes or HTPs depending on the situation, resulting in more opportunities for the use of tobacco products than before. A second possibility is that dual users oversmoked to compensate for the lower nicotine concentration delivered by HTPs. It is well known that lower nicotine cigarettes can produce compensatory smoking.²⁴⁻²⁶ Given that nicotine concentration in IQOS aerosol is reportedly only 84%¹⁰ or 71%¹¹ of that in mainstream smoke of combustible cigarettes, compensatory smoking behavior might have occurred. A randomized controlled trial conducted by Philip Morris International of combustible cigarette smokers versus HTP-dominant users who used an almost equal number of tobacco products reported that urinary levels of nicotine metabolites after the six-month trial were closely similar.²⁷ If so, it can be considered that HTP users compensate for the reduced nicotine by using HTPs for longer or deeper than combustible cigarettes.

Nicotine dependence was closely consistent between combustible cigarette smokers and HTP-only users in this study. Switching to HTP use alone was not associated with nicotine dependence. It is possible that dual users had higher nicotine dependence than other smokers in the worksite population, but careful interpretation is needed because the sample size is small. Stages of behavioral change in quitting smoking did not differ among the three smoking groups. Only 5% of smokers were at the preparation stage, and most had little intention to quit, indicating that a shift to HTPs did not lead to smoking cessation. Further studies are needed to

clarify effective interventions to quit HTP use.

We compared annual FEV₁ change between combustible cigarette only, HTP only and dual users to examine the health effect of daily HTP use during the few years after introduction to the market. Annual FEV₁ change between combustible cigarette-only smokers and HTP-only users was comparable. This suggests that switch to HTP may not have affected respiratory function in the participants of this study. However, this should be interpreted carefully since the duration of HTP use was only 1.7 (0.9) years. In contrast, FEV₁ declined substantially in dual users compared with combustible cigarette smokers or HTP-only users, in which the mean duration and S.D. of dual using was 1.1 (0.8) years. Evidence for the health effects of smoking HTPs is markedly limited. Some toxic substances such as tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons are reportedly reduced in IQOS aerosol, whereas other compounds such as formaldehyde and nicotine remain.^{10 11 28} Given the paucity of evaluation, it is not clear whether HTPs have fewer harmful effects than combustible cigarettes. A decline in FEV₁ has been established as a short-term effect of the adverse effect of smoking cigarettes.¹³

²⁹ This effect was also confirmed in our study. The annual decline in FEV₁ among cigarette only smokers were 13 mL/year higher than never smokers, and comparable to previous studies. The results of a systematic review of 47 studies on the annual decline in FEV₁ due to smoking showed that the annual decline in FEV₁ was over 10 mL/year greater than in smokers compared with non-smokers.¹³ Although the sample size was small, our results showing that the decline

in dual users was 18 mL/year greater than in cigarette-only smokers suggests that the adverse effects of smoking are more enhanced in elderly dual users. The differences in the magnitude of the FEV₁ decline between cigarette-only smokers and dual users decreased by adjusting for the number of tobacco products smoked/used at follow-up. This result may suggest the more rapid decline in FEV₁ observed in the dual users could be explained by the increase in smoking/using tobacco products after they started to use HTPs. Our present results were in contrast to those from a study conducted by Phillip Morris International, which reported that the use of HTPs improved lung function as measured by FEV₁ compared to continuous use of combustible cigarettes for six months.²⁷ Our study is significant in examining the association of dual use with respiratory function decline in a longitudinal cohort independent of the tobacco industry.

One of the limitations of this study is that it was conducted in a single rural area of Japan, primarily among elderly residents and middle-aged workers. The results should be generalized carefully. Another important limitation is that the analysis of respiratory function was conducted only among the resident population, thus included mainly elderly participants and a small number of HTP users. It should be noted that even when the number of HTP users was small and the duration of exposure was short, dual users showed a greater decline in respiratory function. Nevertheless, a longer follow-up study with a larger age group is needed for a more accurate discussion.

332

333 **CONCLUSIONS**

334 HTP users are prevalent in Japan, particularly among younger generations and even
335 in the rural area. In this study, around 30-50% of HTP users were dual users of both combustible
336 cigarettes and HTPs among older adults and middle-aged workers in Japan. Dual users tended
337 to smoke/use tobacco products more after they started to use HTPs. FEV₁ appears to have
338 declined more strongly in these dual users than in the combustible cigarette-only smokers and
339 HTP-only users. Individuals who switched to HTP-only use a mean of 1.7 years before had a
340 similar reduction in FEV₁ as those who had exclusively smoked cigarettes. Although the
341 adverse health effects of HTPs remain controversial, dual users should be marked as a high-
342 risk group when tobacco policies for HTPs are considered.

343

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COMPETING INTERESTS:

The authors have no conflicts of interest to declare.

REFERENCES

1. Kinjo A, Kuwabara Y, Fujii M, et al. Heated tobacco product smokers in Japan identified by a population-based survey. *J Epidemiol* 2020;**30**(12):547-555. doi: 10.2188/jea.JE20190199
2. Sutanto E, Miller C, Smith DM, et al. Prevalence, Use Behaviors, and Preferences among Users of Heated Tobacco Products: Findings from the 2018 ITC Japan Survey. *Int J Environ Res Public Health* 2019;**16**(23): 4630. doi: 10.3390/ijerph16234630
3. Liu X, Lugo A, Spizzichino L, et al. Heat-Not-Burn Tobacco Products Are Getting Hot in Italy. *J Epidemiol* 2018;**28**(5):274-75. doi: 10.2188/jea.JE20180040
4. Wu YS, Wang MP, Ho SY, et al. Heated tobacco products use in Chinese adults in Hong Kong: a population-based cross-sectional study. *Tob Control* 2020;**29**(3):277-281 doi: 10.1136/tobaccocontrol-2018-054719
5. Sugiyama T, Tabuchi T. Use of Multiple Tobacco and Tobacco-Like Products Including Heated Tobacco and E-Cigarettes in Japan: A Cross-Sectional Assessment of the 2017 JASTIS Study. *Int J Environ Res Public Health* 2020;**17**(6) doi: 10.3390/ijerph17062161
6. Yoshioka T, Tabuchi T. Combustible cigarettes, heated tobacco products, combined product use, and periodontal disease: A cross-sectional JASTIS study. *PLoS One* 2021;**16**(3):e0248989. doi: 10.1371/journal.pone.0248989

7. Sutanto E, Miller C, Smith DM, et al. Concurrent Daily and Non-Daily Use of Heated Tobacco Products with Combustible Cigarettes: Findings from the 2018 ITC Japan Survey. *Int J Environ Res Public Health* 2020;**17**(6):2098.
8. Ministry of Health LaW, Japan. The Japan National Health and Nutrition Survey in 2018 2020 [updated April 17 2020; cited 2021 June 23 2021]. Available from: <https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450171&tstat=000001041744&cycle=7&tclass1=000001139646&tclass2val=0> accessed June 23 2021.
9. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. *Am Psychol* 1992;**47**(9):1102-14. doi: 10.1037//0003-066x.47.9.1102
10. Auer R, Concha-Lozano N, Jacot-Sadowski I, et al. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA Internal Medicine* 2017;**177**(7):1050-52. doi: 10.1001/jamainternmed.2017.1419
11. Bekki K, Inaba Y, Uchiyama S, et al. Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes. *Journal of UOEH* 2017;**39**(3):201-07. doi: 10.7888/juoeh.39.201
12. National Center for Chronic Disease P, Health Promotion Office on S, Health. Reports of the Surgeon General. The Health Consequences of Smoking-50 Years of Progress: A

Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US) 2014.

13. Lee PN, Fry JS. Systematic review of the evidence relating FEV1 decline to giving up smoking. *BMC Med* 2010;**8**:84. doi: 10.1186/1741-7015-8-84
14. Harada S, Takebayashi T, Kurihara A, et al. Metabolomic profiling reveals novel biomarkers of alcohol intake and alcohol-induced liver injury in community-dwelling men. *Environ Health Prev Med* 2016;**21**(1):18-26. doi: 10.1007/s12199-015-0494-y
15. Iida M, Harada S, Kurihara A, et al. Profiling of plasma metabolites in postmenopausal women with metabolic syndrome. *Menopause* 2016;**23**(7):749-58. doi: 10.1097/GME.0000000000000630
16. Fukai K, Harada S, Iida M, et al. Metabolic Profiling of Total Physical Activity and Sedentary Behavior in Community-Dwelling Men. *PLoS One* 2016;**11**(10):e0164877. doi: 10.1371/journal.pone.0164877
17. Kuwabara K, Harada S, Sugiyama D, et al. Relationship between Non-High-Density Lipoprotein Cholesterol and Low-Density Lipoprotein Cholesterol in the General Population. *Journal of atherosclerosis and thrombosis* 2016;**23**(4):477-90. doi: 10.5551/jat.33100
18. Heatherton TF, Kozlowski LT, Frecker RC, et al. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*

- 1991;**86**(9):1119-27. doi: 10.1111/j.1360-0443.1991.tb01879.x
19. Mikami I, Akechi T, Kugaya A, et al. Screening for nicotine dependence among smoking-related cancer patients. *Jpn J Cancer Res* 1999;**90**(10):1071-5. doi: 10.1111/j.1349-7006.1999.tb00679.x
20. Hanioka T, Ojima M, Hamajima N, et al. Patient feedback as a motivating force to quit smoking. *Community Dent Oral Epidemiol* 2007;**35**(4):310-7. doi: 10.1111/j.1600-0528.2006.00338.x
21. Tabuchi T, Gallus S, Shinozaki T, et al. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. *Tob Control* 2018;**27**(e1):e25-e33. doi: 10.1136/tobaccocontrol-2017-053947
22. Lee C, Shin H, Kim S, et al. Are Self-Reported Surveys Accurate for Assessing the Use of Novel Tobacco Products Such as Electronic Cigarettes and Heated Tobacco Products? *JKSRNT* 2019;**10**(2):106-11. doi: 10.25055/JKSRNT.2019.10.2.106
23. Brose LS, Simonavicius E, Cheeseman H. Awareness and Use of 'Heat-not-burn' Tobacco Products in Great Britain. *Tobacco Regulatory Science* 2018;**4**(2):44-50. doi: 10.18001/TRS.4.2.4
24. Hammond D, Fong GT, Cummings KM, et al. Smoking topography, brand switching, and nicotine delivery: results from an in vivo study. *Cancer Epidemiol Biomarkers Prev*

2005;**14**(6):1370-5. doi: 10.1158/1055-9965.Epi-04-0498

25. Matsumoto M, Inaba Y, Yamaguchi I, et al. Smoking topography and biomarkers of exposure among Japanese smokers: associations with cigarette emissions obtained using machine smoking protocols. *Environ Health Prev Med* 2013;**18**(2):95-103. doi: 10.1007/s12199-012-0293-7
26. Ueda K, Kawachi I, Nakamura M, et al. Cigarette nicotine yields and nicotine intake among Japanese male workers. *Tob Control* 2002;**11**(1):55-60. doi: 10.1136/tc.11.1.55
27. Ludicke F, Ansari SM, Lama N, et al. Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically Relevant Biomarkers to Assess a Candidate Modified Risk Tobacco Product: A Randomized Trial. *Cancer Epidemiol Biomarkers Prev* 2019;**28**(11):1934-43. doi: 10.1158/1055-9965.EPI-18-0915
28. Bentley MC, Almstetter M, Arndt D, et al. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. *Anal Bioanal Chem* 2020 doi: 10.1007/s00216-020-02502-1
29. Omori H, Nonami Y, Morimoto Y. Effect of smoking on FEV decline in a cross-sectional and longitudinal study of a large cohort of Japanese males. *Respirology* 2005;**10**(4):464-9. doi: 10.1111/j.1440-1843.2005.00727.x

Table 1. Characteristics of the resident population in the follow-up survey

		Combustible					
		cigarette-only		HTP-only			
		Overall	smoker	user	Dual user	Past smoker ^a	Never smoker
N (%)		2612 (100)	233 (8.9)	20 (0.8)	16 (0.6)	808 (30.9)	1535 (58.8)
Sex (%)	male	1177 (45.1)	205 (88.0)	18 (90.0)	15 (93.8)	715 (88.5)	224 (14.6)
	female	1435 (54.9)	28 (12.0)	2 (10.0)	1 (6.2)	93 (11.5)	1311 (85.4)
Age—yr (SD)		67.7 (7.1)	65.1 (7.1)	57.7 (9.2)	58.1 (8.5)	67.6 (7.5)	68.3 (6.7)
Total tobacco products number per day (SD)		16.9 (6.8)	16.6 (6.6)	15.7 (6.1)	23.4 (8.3)	-	-
Cigarette number per day		16.6 (6.7)	16.6 (6.6)	-	16.1 (8.4)	-	-
IQOS number per day		10.1 (8.0)	-	13.9 (7.7)	5.3 (5.5)	-	-
glo number per day		1.0 (3.6)	-	1.0 (4.5)	0.9 (2.1)	-	-
Ploom number per day		0.9 (3.5)	-	0.8 (3.3)	1.1 (3.8)	-	-
Cigarette number per day at baseline (SD)		18.4 (7.2)	18.2 (7.1)	18.3 (8.0)	21.8 (9.1)	-	-
Years of smoking (SD)		30.0 (14.8)	43.8 (8.1)	36.3 (9.1)	38.1 (8.7)	25.7 (14.0)	-
Years of using HTPs		1.5 (0.9)	-	1.7 (0.9)	1.1 (0.8)	-	-
FTND score (%)							
High (7-10)		21 (12.1)	16 (11.0)	3 (20.0)	2 (16.7)	-	-
Normal (3-6)		115 (66.5)	97 (66.9)	10 (66.7)	8 (66.7)	-	-
Low (0-2)		37 (21.4)	32 (22.1)	2 (13.3)	2 (16.7)	-	-
Stage of behavioral change in quitting smoking (%)							
pre-contemplation stage without interest		43 (24.3)	37 (24.7)	4 (26.7)	2 (16.7)	-	-
pre-contemplation stage with interest		93 (46.5)	77 (51.3)	8 (53.3)	8 (66.7)	-	-
contemplation stage		31 (15.5)	28 (18.7)	2 (13.3)	1 (8.3)	-	-
preparation stage		10 (5.6)	8 (5.3)	1 (6.7)	1 (8.3)	-	-
Educated (%)							
-9 years		448 (17.3)	28 (12.1)	3 (15.8)	2 (12.5)	126 (15.8)	289 (19.0)
10-12 years		1567 (60.6)	149 (64.2)	7 (36.8)	10 (62.5)	481 (60.1)	920 (60.5)
13-15 years		419 (16.2)	36 (15.5)	8 (42.1)	4 (25.0)	122 (15.2)	249 (16.4)
16- years		153 (5.9)	19 (8.2)	1 (5.3)	0 (0.0)	71 (8.9)	62 (4.1)
Height—cm (SD)		158.4 (8.8)	165.3 (7.1)	169.2 (8.8)	165.7 (7.4)	164.2 (7.0)	154.1 (7.2)
FEV ₁ —L (SD)		2.20 (0.55)	2.42 (0.58)	2.90 (0.67)	2.69 (0.62)	2.49 (0.55)	2.00 (0.45)

FEV ₁ at baseline—L (SD)	2.38 (0.58)	2.65 (0.60)	3.14 (0.60)	3.04 (0.62)	2.68 (0.57)	2.17 (0.47)
Follow-up period—yr (SD)	5.6 (0.7)	5.5 (0.9)	5.7 (0.9)	5.6 (0.8)	5.6 (0.8)	5.6 (0.8)

FEV₁; forced expiratory volume in one second, FTND; Fagerstrom test for nicotine dependence, HTP; heated tobacco product

a. Of the 808 past smokers, all had smoked cigarettes, and three had smoked/used both cigarettes and HTPs.

Table 2. Characteristics of the worksite population in the follow-up survey

		Combustible				
		cigarette-only		HTP-only		
		Overall	smoker	user	Dual user	Past smoker ^a Never smoker
N (%)		722 (100)	62 (8.6)	36 (5.0)	14 (1.9)	168 (23.3) 442 (61.2)
Sex (%)	male	250 (34.6)	38 (61.3)	28 (77.8)	11 (78.6)	104 (61.9) 69 (15.6)
	female	472 (65.4)	24 (38.7)	8 (22.2)	3 (21.4)	64 (38.1) 373 (84.4)
Age—yr (SD)		49.3 (7.3)	49.6 (7.4)	44.8 (8.3)	46.1 (9.0)	50.0 (7.2) 49.5 (7.0)
Total tobacco products number per day (SD)		12.6 (7.0)	12.3 (8.0)	12.2 (4.4)	14.8 (8.0)	- -
Cigarette number per day		11.6 (7.6)	12.3 (8.0)	-	8.6 (4.4)	- -
IQOS number per day		8.2 (6.6)	-	10.0 (6.0)	3.6 (6.0)	- -
glo number per day		2.0 (5.0)	-	2.2 (5.3)	1.5 (4.1)	- -
Ploom number per day		0.3 (1.1)	-	0 (0.0)	1.1 (1.9)	- -
Cigarette number per day at baseline (SD)		14.4 (6.5)	13.4 (6.6)	14.5 (5.2)	14.0 (6.4)	- -
Years of smoking (SD)		19.2 (11.1)	27.8 (9.1)	22.9 (8.8)	26.1 (9.8)	14.6 (9.8) -
Years of using HTPs		1.52 (0.98)		1.6 (0.9)	1.3 (1.2)	- -
FTND score (%)			-	-	-	- -
	High (7-10)	8 (7.3)	3 (5.0)	2 (5.6)	3 (21.4)	- -
	Normal (3-6)	49 (44.5)	22 (36.7)	20 (55.6)	7 (50.0)	- -
	Low (0-2)	53 (48.2)	35 (58.3)	14 (38.9)	4 (28.6)	- -
Stage of behavioral change in quitting smoking (%)						
	pre-contemplation stage without interest	21 (19.1)	9 (15.0)	9 (25.0)	3 (21.4)	- -
	pre-contemplation stage with interest	67 (60.9)	40 (66.7)	18 (50.0)	9 (64.3)	- -
	contemplation stage	15 (13.6)	6 (10.0)	7 (19.4)	2 (14.3)	- -
	preparation stage	7 (6.4)	5 (8.3)	2 (5.6)	0 (0.0)	- -
Educated (%)						
	-9 years	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0) 1 (0.2)
	10-12 years	214 (29.9)	21 (33.9)	16 (44.4)	5 (35.7)	48 (28.7) 124 (28.4)
	13-15 years	349 (48.7)	23 (37.1)	13 (36.1)	7 (50.0)	66 (39.5) 240 (54.9)
	16- years	152 (21.2)	18 (29.0)	7 (19.4)	2 (14.3)	53 (31.7) 72 (16.5)

FTND; Fagerstrom test for nicotine dependence, HTP; heated tobacco product

a. Of the 168 past smokers, all had smoked cigarettes, and none had used HTPs.

Table 3. HTP use stratified by sex and age

	Combustible cigarette-only smoker	HTP-only user	Dual user	Past smoker	Never smoker	Dual/HTP users ^a
N (%)						
Overall						
34-39	2 (4.3)	10 (21.7)	3 (6.5)	5 (10.9)	26 (56.5)	23.1%
40-49	42 (10.2)	22 (5.4)	9 (2.2)	101 (24.6)	237 (57.7)	29.0%
50-59	54 (10.2)	13 (2.5)	10 (1.9)	161 (30.5)	290 (54.9)	43.5%
60-69	128 (10.6)	10 (0.8)	7 (0.6)	335 (27.6)	732 (60.4)	41.2%
70-79	69 (6.1)	1 (0.1)	1 (0.1)	371 (32.9)	685 (60.8)	50.0%
80	0 (0)	0 (0)	0 (0)	3 (30.0)	7 (70.0)	-
Male						
34-39	0 (0.0)	7 (25.9)	2 (7.4)	4 (14.8)	14 (51.9)	22.2%
40-49	27 (18.8)	17 (11.8)	7 (4.9)	55 (38.2)	38 (26.4)	29.2%
50-59	38 (18.1)	11 (5.2)	9 (4.3)	109 (51.9)	43 (20.5)	45.0%
60-69	112 (22.7)	10 (2.0)	7 (1.4)	290 (58.8)	74 (15.0)	41.2%
70-79	66 (12.0)	1 (0.2)	1 (0.2)	358 (65.3)	122 (22.3)	50.0%
80	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	2 (40.0)	-
Female						
34-39	2 (10.5)	3 (15.8)	1 (5.3)	1 (5.3)	12 (63.2)	25.0%
40-49	15 (5.6)	5 (1.9)	2 (0.7)	46 (17.2)	199 (74.5)	28.6%
50-59	16 (5.0)	2 (0.6)	1 (0.3)	52 (16.4)	247 (77.7)	33.3%
60-69	16 (2.2)	0 (0.0)	0 (0.0)	45 (6.3)	658 (91.5)	-
70-79	3 (0.5)	0 (0.0)	0 (0.0)	13 (2.2)	563 (97.2)	-
80	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (100.0)	-

HTP; heated tobacco product

a. Proportion of dual users among all HTP users

Table 4. Differences between smoking groups in change of the total number of tobacco products smoked/used per day from baseline to follow-up (overall population)

	Differences in change of the total number of tobacco products smoked/used per day [95% CI]	
	Crude	Adjusted ^a
Combustible cigarette-only smoker	Ref	Ref
HTP only user	-0.79 [-2.39 to 0.81]	-0.96 [-2.58 to 0.67]
Dual user	2.71 [0.66 to 4.76]	3.12 [1.18 to 5.07]

CI; confidence interval, HTP; heated tobacco product
a. adjusted for sex, age, number of cigarettes per day at baseline, and population
The differences from cigarette-only smokers in change of the total number of tobacco products smoked/used per day from baseline to follow-up were estimated in the overall population.

Table 5. Differences between smoking groups in annual FEV₁ change (mL/yr) from baseline to follow-up (resident population only)

	Differences in annual FEV ₁ change—mL/yr [95% CI]				Annual FEV ₁ change mL/yr (SD)
	model 1 (crude)	model 2 ^a	model 3	model 4	
Cigarette-only smoker	ref	Ref	ref	ref	-44 (45)
HTP-only user	2 [-14 to 17]	1 [-14 to 16]	6 [-11 to 23] ^b	4 [-15 to 24] ^d	-43 (32)
Dual user	-18 [-36 to -1]	-18 [-35 to -1]	-16 [-34 to 2] ^b	-11 [-33 to 11] ^d	-63 (32)
Past smoker	10 [5 to 15]	10 [5 to 15]	14 [9 to 19] ^c	-	-34 (35)
Never smoker	13 [8 to 18]	3 [-2 to 9]	8 [3 to 14] ^c	-	-31 (32)

CI; confidence interval, FEV₁; forced expiratory volume in one second, HTP; heated tobacco product

a. adjusted for sex and age

b. adjusted for sex, age, height, FEV₁ at baseline and number of cigarettes per day at baseline

c. adjusted for sex, age, height and FEV₁ at baseline

d. adjusted for sex, age, height, FEV₁ at baseline and number of tobacco products per day at follow-up

The differences from cigarette-only smokers in FEV₁ change per year (mL/yr) were estimated in the resident population.