Cigarettes, heated tobacco products and dual use: exhaled carbon monoxide, saliva cotinine and total tobacco consumed by Hong Kong tobacco users

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ABSTRACT

Background Independent studies on exhaled carbon monoxide (CO) and saliva cotinine levels in regular heated tobacco product (HTP) users, and how they compare with conventional cigarette (CC) smokers, are lacking.

Methods A total of 3294 current users of CCs, HTPs or electronic cigarettes (ECs) from a household survey and a smoking hotspot survey were classified into seven groups: exclusive users of CCs, HTPs, ECs; dual users of CCs and HTPs, CCs and ECs, HTPs and ECs; and triple users. We measured exhaled CO level using the piCo Smokerlyzer (n=780) and saliva cotinine using NicAlert cotinine test strips (n=620). Among the seven groups, the differences in (1) CO and cotinine levels were examined using Kruskal-Wallis test, and (2) the average daily tobacco consumption in the past 30 days was examined using multivariable linear regression.

Results Both exclusive and dual users of CCs had a higher CO level than exclusive HTP or EC users ($p<0.05$). Exhaled CO levels were similar between HTP and EC users, as were saliva cotinine levels among the seven groups. Compared with exclusive CC users, those who also used HTPs or ECs smoked fewer CCs (CCs+HTPs: adjusted coefficient −2.79, 95% CI −3.90 to −1.69; CCs+ECs: −1.34, 95% CI −2.34 to −0.34), but consumed more tobacco sticks equivalent in total (2.79 (95% CI 1.61 to 3.96); 1.95 (95% CI 0.79 to 3.12)).

Conclusions HTP or EC use showed lower exhaled CO but similar saliva cotinine levels compared with CC use. Dual users of CCs and HTPs/ECs smoked fewer CCs than exclusive CC users, but consumed more tobacco in total.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Manufacturer-funded studies found that conventional cigarette (CC) smokers switching to heated tobacco products (HTPs) had lower exposure to most harmful and potentially harmful constituents but similar exposure to nicotine compared with continued CC smokers. A few independent studies showed a lower level of exhaled carbon monoxide (CO) in inexperienced HTP users who had just switched from cigarette to HTP use. The use pattern of regular users may differ, hence the need to measure exposure levels in regular HTP users.

WHAT THIS STUDY ADDS

⇒ The study presented exhaled CO and saliva cotinine levels from regular HTP users in a real-life setting, and found a lower level of exhaled CO in exclusive HTP users than CC users (either used exclusively or concurrently) but similar levels of saliva cotinine. Dual users of CCs and HTPs smoked fewer cigarettes per day than exclusive CC users, but consumed more tobacco in total.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results suggest that CC users who want to reduce harm should quit all tobacco use rather than switching to HTPs or using them concurrently.

INTRODUCTION

Tobacco causes over 8 million deaths per year, with conventional cigarettes (CCs) most commonly consumed.[1] A total of 93 harmful and potentially harmful constituents (HPHCs) from burning tobacco leaves have been identified by the US Food and Drug Administration (FDA) to date.[2] Touted as less harmful, tobacco companies are aggressively promoting alternative tobacco products, such as heated tobacco products (HTPs).

Several randomised controlled trials (RCTs) supported by tobacco companies found that CC smokers switching to HTPs had lower exposure to most HPHCs than continued CC smokers.[3–5] Based on reduced exposure, the claim of reduced risk and harm was made. However, WHO found insufficient evidence for the 'less harmful' claim, as some other toxicants are higher in HTPs with unclear adverse health effects.[6] The reliability of manufacturer-funded findings is questionable due to conflicts of interest, but independent evidence of exposure and harm reduction is scarce. To date, only five small studies have examined exhaled carbon monoxide (CO) level after HTP use.[7–11] Furthermore, participants in previous trials were inexperienced HTP users who had just switched from cigarettes to HTPs, and their use pattern may differ from regular users. On average, regular HTP users consumed about 10 sticks (approximately 120–140 puffs) per day,[12] exceeding those of inexperienced HTP users in laboratory studies (up to 60 puffs).[7–9] It is therefore necessary to measure exposure levels in regular HTP users.

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In Hong Kong, daily smoking has dropped from 23.3% in 1982 to 9.5% in 2021, among the lowest in the world.[13] However, the decline has slowed in the past decade, while alternative tobacco products gained popularity. The present study aimed to measure exhaled CO and saliva cotinine levels of regular tobacco users in a real-life setting in Hong Kong, and determine how such exposures vary across subgroups (eg, exclusive HTP users, dual users of CCs and HTPs). CO is one of the HPHCs, and exhaled CO can be measured non-invasively to assess cigarette consumption.[14,15] We measured exhaled CO to facilitate comparison with previous independent studies.[7–11] Cotinine is a primary metabolite of nicotine, and has a longer half life of about 17 hours than that of 2–3 hours for nicotine.[16] Therefore, cotinine is commonly used as a marker of tobacco exposure.[17] We also measured such exposures for electronic cigarettes (ECs), another popular alternative tobacco product. Self-reported consumption of tobacco products was included as a secondary outcome to compare the amount of tobacco consumed among users of different tobacco products.

METHODS

Study design

Current tobacco users were recruited from two surveys. One was a territory-wide survey conducted in 5000 households from October 2019 to November 2020 through an established survey agency. These included 3800 households (948 households had tobacco users) randomly selected from all 18 districts and 1200 households with tobacco users oversampled through referral by the random households or from the agency's panel of households. Trained interviewers conducted face-to-face household interviews initially and switched to telephone interviews since July 2020 due to the outbreak of COVID-19. In each household, all current and ex-tobacco users, and one never tobacco user aged 15+ who would have their next birthday soonest were selected. A unique survey link was generated for each eligible household member. They completed an online questionnaire via the link on a smartphone or tablet by themselves or with help from the interviewers. A small number of interviewer-administered telephone interviews were also conducted on request. Current tobacco users were invited to have their saliva cotinine tested after the face-to-face interviews, but the exhaled CO test was not required due to the short half life (2–6 hours) of CO.[18]

The other was a hotspot survey conducted at outdoor smoking hotspots from July 2019 to December 2020.[19] Outdoor smoking hotpots are public places where tobacco users gather to smoke or use tobacco products, such as exits of mass transit railway stations, entrances of shopping plazas and transport hubs, typically with a rubbish bin for collecting cigarette butts. Participants were asked to complete a short questionnaire using a provided smartphone and were invited to have their exhaled CO and saliva cotinine tested on-site by trained interviewers. These tests were discontinued from July 2020 due to COVID-19 and participants were given a leaflet with a QR code to complete the questionnaire using their own smartphones. Each participant received a voucher of HK$20 (US$2.56) for the CO test and HK$50 (US$6.41) for the saliva test. Figure 1 details the flow chart for sample collection.

Measurements

In the present study, 'smoking' refers to CC smoking, and 'tobacco use' refers to the use of any tobacco products. Each participant was asked 'Have you ever used the following tobacco products?' with a list of products provided. Those who answered yes were further asked 'In how many of the past 30 days have you used the following tobacco products?'. We focused on three types of tobacco products: CCs, HTPs and ECs. Those who had used CCs or HTPs or ECs at least 1 day in the past 30 days were defined as respective current users and classified into seven groups: (1) exclusive CC users; (2) exclusive HTP users; (3) exclusive EC users; (4) dual users of CCs and HTPs; (5) dual users of CCs and ECs; (6) dual users of HTPs and ECs; and (7) triple users. Thus, participants who last used tobacco over 30 days ago were not considered. For example, those who used CC currently and used HTPs over 30 days ago were classified as exclusive CC users. Other tobacco products (eg, waterpipe, cigar, smokeless tobacco products) were asked but not considered in the main analysis due to their small numbers.

We also recorded the type of tobacco products that participants were using at the smoking hotspots since a few months into the survey.

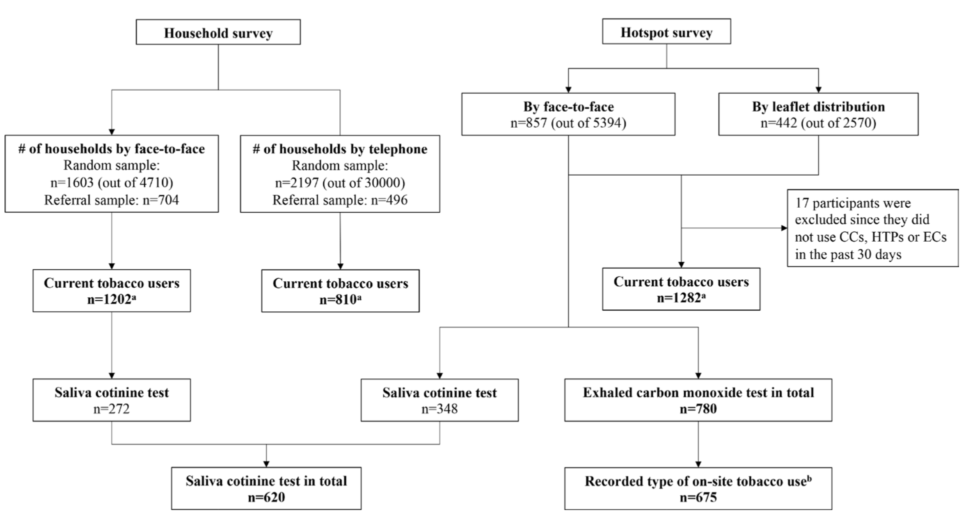

Figure 1 Flow chart for sample collection. [a]Current tobacco users were defined as those who were currently using conventional cigarettes (CCs), heated tobacco products (HTPs) or electronic cigarettes (ECs) in the past 30 days. [b]The type of tobacco products used on-site at the hotspots was recorded since a few months into the survey.

For each tobacco product, participants reported the number of days it was used in the past 30 days and the number of sticks of CCs/HTPs or sessions of ECs used on a typical day of use. One session of EC use is typically defined as 15 puffs or 10 min of use by previous studies.[20 21] As for HTPs, our data in 150 current HTP users showed that IQOS (78.6%) was most popular, followed by Lil (7.3%), Ploom (2.7%) and Glo (2.7%). Each IQOS HEETS stick lasts about 6 min or 14 puffs, and each Lil Fiit stick about 5 min or 14 puffs, similar to a cigarette.[22 23] Therefore, based on the number of puffs, we assumed a similar amount of tobacco smoke consumed for one session of EC use, one stick of HTPs and one cigarette. The average daily consumption of each product was estimated by multiplying the number of days by the number of tobacco sticks equivalent of that product used and then divided by 30 (days). The average daily total tobacco consumed was estimated by the sum of CCs, ECs and HTPs consumed daily. Missing data or outliers on tobacco consumption were excluded from the analysis.

Sample collection

Saliva cotinine was tested using NicAlert cotinine test strips, which is a rapid and cost-effective method for verifying smoking status.[24] The test strip has seven levels (0–6), representing different cotinine levels, with level 0 equivalent to 0–10 ng/mL (non-users of tobacco products) and level 6 indicating >1000 ng/mL of cotinine.[25]

CO level was tested using the piCo Smokerlyzer at the smoking hotspots immediately after the participants finished using the tobacco products.[26] The breath CO, measured in parts per million (ppm), was recorded with a reading of 0–6 ppm indicating no smoking and >6 ppm smoking.[26]

Statistical analysis

Sociodemographic characteristics were analysed using χ^2 test. The differences in exhaled CO and saliva cotinine levels among the seven groups were tested using Kruskal-Wallis test, as the variables were not normally distributed as shown by the Shapiro-Wilk test. The Dunn's test was conducted to correct for multiple comparisons in the presence of significant differences. The results were plotted using GraphPad V.9.0.2. We also used multivariable linear regression models to compare the average daily consumption of cigarettes and total tobacco products among the seven groups, adjusting for sex, age, marital status, education level and household income. The correlation between the amount of each tobacco used and exhaled CO or saliva cotinine levels in exclusive users was assessed using Spearman correlation. P values <0.05 are considered statistically significant. Data were analysed using R V.4.0.2.

Sensitivity analysis

In the main analysis, some participants may concurrently use tobacco products other than CCs, HTPs and ECs in the past 30 days. These participants were excluded in the sensitivity analysis to better compare exhaled CO and saliva cotinine levels across groups.

Since CO has a short half life,[18] we did another sensitivity analysis to test the level of exhaled CO among the three products used on-site during the interview.

RESULTS

Table 1 shows that of the 3294 current tobacco users (2012 from the household survey and 1282 from the hotspot survey), exclusive CC users were most common (80.5%), followed by dual users of CCs and ECs (6.4%), and dual users of CCs and HTPs (5.0%). Only 2.1% were triple users. The proportion of females was greater among dual users of HTPs and ECs (40.0%), triple users (38.6%) and exclusive HTP users (37.1%) than other tobacco users. Young people aged 15–29 were most common among dual users of CCs and ECs (53.3%), triple users (48.6%) and exclusive EC users (45.7%) than other tobacco users. Exclusive HTP or EC users had higher education level and higher household income than exclusive CC users.

Exhaled CO was tested in a total of 780 participants and the type of on-site tobacco use was recorded from 675 participants in the hotspot survey; saliva cotinine was tested in a total of 620 participants from the household (n=272) and hotspot (n=348) surveys. The most common reasons for refusal were 'lack of interest' and 'no time'.

The median exhaled CO level was highest in exclusive CC users (18.0 ppm), and lowest in exclusive EC users (3.0 ppm) (table 1). Figure 2A shows significant differences in exhaled CO levels among the seven groups (p<0.001). Compared with exclusive CC users, the other groups showed significantly lower levels of exhaled CO. In addition, exclusive CC use or concurrent use with HTPs or ECs showed a higher exhaled CO level than exclusive HTP or EC use. Exhaled CO levels were similar between HTP and EC users, either used exclusively or concurrently with CCs. Consistently, the sensitivity analysis based on the on-site tobacco product used during the interview at smoking hotspots also found significant differences in exhaled CO levels among on-site CC, HTP and EC users. The median exhaled CO level was much higher for CCs (17.0 ppm) than HTPs (4.0 ppm) and ECs (3.0 ppm) (p<0.001, online supplemental table 1).

The median saliva cotinine level was 3.0 (equivalent to 100–200 ng/mL) in exclusive CC and HTP users, 3.5 in exclusive EC users and 4.0 (equivalent to 200–500 ng/mL) in triple users, but these differences were not statistically significant (figure 2B).

Consistent with our main findings, the sensitivity analysis of tobacco users who did not use products other than CCs, HTPs or ECs showed significant differences in exhaled CO levels but not in saliva cotinine levels among the seven groups (online supplemental table 2).

Table 2 shows that compared with exclusive CC users, fewer cigarettes were smoked on average by dual users of CCs and HTPs (adjusted coefficient −2.79, 95% CI −3.90 to −1.69) and dual users of CCs and ECs (−1.34, 95% CI −2.34 to –0.34); however, the total tobacco consumed daily on average was greater in dual users (CCs+HTPs: 2.79, 95% CI 1.61 to 3.96; CCs+ECs: 1.95, 95% CI 0.79 to 3.12) and triple users (4.54, 95% CI 2.49 to 6.60). Dual users of HTPs and ECs also consumed more tobacco than exclusive CC smokers, although the difference was non-significant probably due to small numbers (3.97, 95% CI −0.36 to 8.29, p=0.06). In exclusive users, HTP users consumed less tobacco than CC smokers (−2.23, 95% CI −3.49 to −0.97), and EC users consumed marginally significantly less tobacco than CC smokers (−1.78, 95% CI −3.62 to 0.07, p=0.07).

Exhaled CO level correlated with the average daily consumption of cigarettes (r=0.53, p<0.001) in exclusive CC users, but not with consumption of HTPs or ECs in exclusive HTP or EC users. Saliva cotinine correlated with cigarette consumption (r=0.20, p<0.001) and HTP consumption (r=0.33, p=0.03), but not with EC consumption in exclusive users.

Table 1 Characteristics of tobacco users

		Type of tobacco products used							
	Total	CC only	HTP only	EC only	CC+HTP	CC+EC	HTP+EC	Triple	P value*
N	3294 (100.0)	2652 (80.5)	116 (3.5)	70 (2.1)	164 (5.0)	212 (6.4)	10 (0.3)	70 (2.1)	
Sex									0.002
Male	2415 (73.3)	1986 (74.9)	73 (62.9)	49 (70.0)	116 (70.7)	142 (67.0)	6 (60.0)	43 (61.4)	
Female	879 (26.7)	666 (25.1)	43 (37.1)	21 (30.0)	48 (29.3)	70 (33.0)	4 (40.0)	27 (38.6)	
Age (years)									<0.001
15–29	695 (21.1)	461 (17.4)	14 (12.1)	32 (45.7)	39 (23.8)	113 (53.3)	2 (20.0)	34 (48.6)	
30–39	952 (28.9)	695 (26.2)	61 (52.6)	25 (35.7)	80 (48.8)	61 (28.8)	5 (50.0)	25 (35.7)	
40–49	810 (24.6)	698 (26.3)	30 (25.9)	9 (12.9)	36 (22.0)	27 (12.7)	1 (10.0)	9 (12.9)	
50 or more	837 (25.4)	798 (30.1)	11 (9.5)	4 (5.7)	9 (5.5)	11 (5.2)	2 (20.0)	2 (2.9)	
Education									<0.001
Secondary or below	1952 (59.3)	1700 (64.1)	48 (41.4)	30 (42.9)	54 (32.9)	87 (41.0)	6 (60.0)	27 (38.6)	
Tertiary	1342 (40.7)	952 (35.9)	68 (58.6)	40 (57.1)	110 (67.1)	125 (59.0)	4 (40.0)	43 (61.4)	
Marital status									<0.001
Single	1260 (38.3)	910 (34.3)	46 (39.7)	43 (61.4)	78 (47.6)	133 (62.7)	3 (30.0)	47 (67.1)	
Married	1793 (54.4)	1523 (57.4)	64 (55.2)	25 (35.7)	81 (49.4)	73 (34.4)	6 (60.0)	21 (30.0)	
Divorced/widowed	241 (7.3)	219 (8.3)	6 (5.2)	2 (2.9)	5 (3.0)	6 (2.8)	1 (10.0)	2 (2.9)	
Household income (HK$)									<0.001
<20 000	580 (18.6)	515 (20.5)	8 (7.1)	4 (6.2)	14 (8.9)	31 (15.6)	2 (20.0)	6 (9.2)	
20 000–39 999	1190 (38.1)	975 (38.8)	46 (40.7)	22 (33.8)	51 (32.5)	69 (34.7)	2 (20.0)	25 (38.5)	
≥40 000	1350 (43.3)	1021 (40.7)	59 (52.2)	39 (60.0)	92 (58.6)	99 (49.7)	6 (60.0)	34 (52.3)	
Exhaled carbon monoxide levels (ppm)†									<0.001
Sample size (n)	780	491	70	15	97	60	7	40	
Median (25th, 75th centiles)	14.0 (6.0, 22.0)	18.0 (12.0, 26.0)	3.5 (2.8, 5.0)	3.0 (2.0, 3.0)	6.0 (3.0, 15.0)	11.0 (5.3, 17.0)	4.0 (2.0, 5.0)	8.5 (3.3, 18.5)	
Saliva cotinine level‡									0.81
Sample size (n)	620	426	44	8	68	50	4	20	
Median (25th, 75th centiles)	3.0 (2.0, 4.0)	3.0 (3.0, 4.0)	3.0 (2.0, 4.0)	3.5 (2.3, 4.0)	4.0 (2.0, 4.0)	3.5 (2.0, 4.0)	4.0 (1.8, 4.8)	4.0 (2.0, 4.0)	

US$1=HK$7.8.
*P value was based on χ^2 test.
†The exhaled carbon monoxide levels are expressed in ppm, with 0–6 ppm indicating no smoking and >6 ppm suggesting smoking (7–9 ppm: borderline; 10–15 ppm: mild addiction; 16–25 ppm: moderate addiction; 26+ ppm: heavy addiction).
‡The saliva cotinine levels of 0–6 correspond to saliva cotinine concentrations of 0–10 (indicating non-users of tobacco products), 10–30, 30–100, 100–200, 200–500, 500–1000 and 1000+ ng/mL, respectively.
CC, conventional cigarette; EC, electronic cigarette; HTP, heated tobacco product.

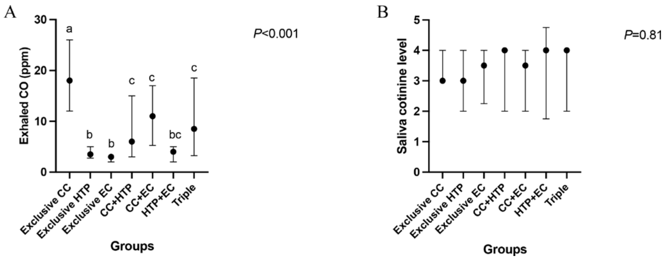

Figure 2 (A) Exhaled CO (ppm), shown as median and IQR, according to different tobacco product use. Multiple comparison analysis of Kruskal-Wallis test (Dunn's test) was used. Medians denoted by a letter (a, b, c) in common are not significantly different, while medians not denoted by a letter in common are significantly different by the Dunn's test at the 5% level of significance. (B) Saliva cotinine level, shown as median and IQR, according to different tobacco product use. Kruskal-Wallis test was used. CC, conventional cigarette; CO, carbon monoxide; EC, electronic cigarette; HTP, heated tobacco product.

DISCUSSION

This study showed for the first time that exclusive HTP users had a lower exhaled CO level than CC users (either used exclusively or concurrently with HTPs), but saliva cotinine levels were similar between the three groups in a real-world setting. Previous laboratory studies from independent and manufacturer-funded studies also showed lower level of CO in mainstream HTP aerosol than in CC smoke.[27–30] However, our result on saliva cotinine level differed from laboratory results which showed nicotine in mainstream HTPs was about 57%–83% of that in CCs.[31] It should be noted that laboratory studies rely on machine-generated emissions, and cannot accurately replicate human exposure.[32] All but five trials on HTPs in humans were manufacturer funded.[7–11] The manufacturer-funded RCTs consistently found that switching to HTPs reduced HPHC exposure, and delivered a similar level of nicotine compared with continued CC smoking.[3–5]

The findings of five independent trials were controversial. Two independent randomised cross-over trials on 15 and 12 smokers, respectively, found that exhaled CO level increased significantly after CC use but did not increase after HTP use, and one further found that plasma nicotine level increased significantly both after CC and HTP use.[7 8] However, a cross-over trial on 30 smokers and a quasi-experimental trial on 45 smokers showed a small but significant increase in exhaled CO level after HTP use.[9 10] Such contradiction was attributed to the small sample sizes of 15 and 12 in the former two trials. These trials were short and limited to the controlled laboratory setting, and may not reflect real-world use. Only one independent clinical trial on 40 Italian smokers showed that switching to HTPs/ECs for 6 months lowered CO levels considerably.[11]

Previous studies focused on inexperienced HTP users who had just switched from cigarette to HTP use, and were mostly Caucasians. We presented exhaled CO and saliva cotinine levels from regular HTP users in a real-life setting. The median exhaled CO level in exclusive HTP users was lower than 6 ppm, the cut-off level for distinguishing non-smokers from smokers.[26] Our results indicate that HTPs may produce very low levels of exhaled CO, equivalent to those in non-smokers. However, our study did not evaluate the presence of other toxins generated by HTPs. In fact, HTPs contain many other constituents that have not been recognised as HPHC by the FDA but are potentially toxic.[6] The overall toxicity or harms of such constituents are unknown. Acute eosinophilic pneumonia was reported in HTP users[33] and associations of HTP use with asthma, allergic rhinitis, atopic dermatitis and other respiratory symptoms have also been found in adolescents.[34 35] Some independent studies found that rats exposed to HTPs developed pulmonary inflammation and immunomodulatory toxicities,[36] and that HTPs potentially led to hepatotoxicity not previously associated with CCs.[37] Another concern is that the irregular cleaning of heating device of HTPs will increase the charring of tobacco particles and emission of unexpected toxicants.[38]

Table 2 Average daily consumption of tobacco products in the past 30 days according to different tobacco product use

	n	Number of CCs or sticks equivalent consumed* Mean (SD)	Crude coefficient (95% CI)†	Adjusted coefficient (95% CI)†‡
CCs consumed on average daily (n=2939)§				
CC	2542	11.5 (6.6)	Ref	Ref
CC+HTP	147	7.7 (5.6)	−3.78 (−4.88 to −2.68)***	−2.79 (−3.90 to −1.69)***
CC+EC	189	8.8 (6.7)	−2.64 (−3.62 to −1.67)***	−1.34 (−2.34 to −0.34)**
Triple	61	9.2 (6.9)	−2.24 (−3.92 to −0.56)**	−1.29 (−3.00 to 0.41)
Sticks equivalent total tobacco consumed on average daily (n=3040)§				
CC	2542	11.5 (6.6)	Ref	Ref
HTP	115	8.3 (4.5)	−3.14 (−4.41 to −1.87)***	−2.23 (−3.49 to −0.97)***
EC	54	9.1 (8.6)	−2.35 (−4.18 to −0.51)*	−1.78 (−3.62 to 0.07)¶
CC+HTP	137	13.3 (7.4)	1.85 (0.69 to 3.02)**	2.79 (1.61 to 3.96)***
CC+EC	141	12.1 (8.4)	0.67 (−0.48 to 1.83)	1.95 (0.79 to 3.12)**
HTP+EC	9	14.8 (12.1)	3.38 (−1.07 to 7.83)	3.97 (−0.36 to 8.29)¶
Triple	42	14.6 (9.2)	3.19 (1.12 to 5.27)**	4.54 (2.49 to 6.60)***

*P<0.05; **p<0.01; ***p<0.001.
*One session of EC use was defined as 15 puffs or 10 min of use, which was assumed to be equivalent to one stick of cigarette. One tobacco stick of HTPs was assumed to be equivalent to one cigarette based on the number of puffs.
†Linear regression model was used.
‡Adjusted for sex, age, marital status, education level and household income.
§The numbers in some groups were smaller in the latter analyses due to missing information on consumption of alternative tobacco products.
¶P<0.1.
CC, conventional cigarette; EC, electronic cigarette; HTP, heated tobacco product.

Our results showed that exclusive HTP use resulted in a similar level of saliva cotinine as other tobacco use, suggesting similar risks of nicotine addiction in never tobacco users who start to use HTPs or cigarettes, for example. Prolonged nicotine exposure would potentially lead to adverse health effects on haemostasis, sleep, memory, mood stability and neurocognitive skills.[39 40]

Similar results were also found for EC use (lower exhaled CO and similar saliva cotinine level), which were in line with previous studies.[41 42] A population-based study also showed that saliva cotinine levels were similar in CC smokers and regular EC users.[43] However, such studies were conducted in Western countries, where nicotine-containing EC products are preferred or promoted. It is worth noting that ECs containing nicotine must be registered as pharmaceutical products before sale or distribution in Hong Kong at the time of the study, but none has registered to date.[44] Our results that exclusive EC users had a similar level of saliva cotinine as the other product users provide direct evidence of the widespread usage of illegal nicotine-containing ECs in Hong Kong.

Compared with exclusive CC smokers, those who also used HTPs smoked fewer cigarettes but consumed more tobacco in total, indicating a compensatory consumption of HTPs in dual users. Specifically, tobacco users consumed more HTPs to compensate for reduced CC use. Furthermore, triple users also had extra consumption of HTPs and ECs. Previous studies have shown that HTPs may not bring the same sensory and psychological satisfaction as CCs,[3 45] and thus dual users may increase HTP consumption to get satisfaction.

Such consumption pattern in dual users and triple users raises several concerns. First, as our results have shown, dual use of CCs and HTPs did not reduce emissions of CO to the same level as exclusive HTP users. Thus, the harm from HPHCs, at least from CO, could not be eliminated. Second, short-term and long-term adverse health effects of HTPs are unclear, and hence dual or triple users may be at greater health risks than exclusive CC smokers. Third, the effectiveness of HTPs for smoking cessation is in doubt.[46] In 2020, the FDA authorised the marketing of IQOS (one of HTPs) as modified risk tobacco products, with the claim that IQOS may help reduce tobacco-related harms if smokers fully switch from regular cigarettes to IQOS.[47] However, our prospective study in Hong Kong showed that in smokers with an intention to quit or to reduce smoking, HTP use at baseline was not associated with smoking cessation at 6-month follow-up, while the use of smoking cessation services increased smoking cessation.[48]

Our study had several limitations. First, the period between the last episode of tobacco use and saliva test was not measured in the household survey, and participants might have metabolised the biomarkers to different extent before testing. Second, although our study had a larger sample size to test biomarkers in a real-world setting than previous studies, small numbers in subgroups may produce less precise estimates. Third, patterns of tobacco use were different in different users, and thus it is difficult to quantify and convert EC/HTP consumption into cigarette equivalent amount, although we assumed 15 puffs or 10 min of EC use, or one stick of HTPs was equivalent to one cigarette. Furthermore, we relied on self-reported information on tobacco use status and the amount consumed, which might result in reporting bias. To validate the data, we assessed exhaled CO and saliva cotinine levels in relation to the amount of each tobacco used on average. Exhaled CO level correlated with the average daily consumption of cigarettes; saliva cotinine correlated with CC consumption and HTP consumption. Exhaled CO level and HTP or EC consumption were not correlated, which may be attributed to the low levels of exhaled CO in HTPs and ECs. No correlation was observed between saliva cotinine and EC consumption, possibly because we did not and could not distinguish whether the ECs used contained nicotine or not. Such results were reasonable and in line with expectations, which supported the validity of our data. Fifth, tobacco users at the hotspots may not represent tobacco users in general. Nevertheless, we reanalysed the results of the average daily consumption in the household sample, and found no difference in cigarette consumption between exclusive CC users and dual users of CCs and HTPs (possibly due to smaller sample size), but the total tobacco consumption was also greater in dual users (4.18, 95% CI 1.75 to 6.61), again raising the concern on dual use. The sample sizes for primary outcome analyses (n=780 in CO test and n=620 in saliva cotinine test) were much smaller than that for secondary outcome analysis (n=3294) (online supplemental table 3). Future studies based on representative data are needed to confirm the results. Finally, we did not collect information about other toxicants, and cannot conclude whether HTPs/ECs are more or less harmful than CCs.

Nevertheless, our study has the largest sample with both CO and cotinine data in HTP users to date. It is also the first to our knowledge to report these biomarkers and their correlates with the amount of average daily consumption in regular HTP users in a real-world setting. In conclusion, HTP and EC use showed lower levels of exhaled CO and similar levels of saliva cotinine compared with CC use. Dual users of CCs and HTPs smoked fewer cigarettes in the past 30 days, but consumed more tobacco in total. Similar cotinine levels across the seven groups suggested that CC users switching to HTPs or using them concurrently did not reduce overall nicotine intake, hence tobacco consumption. With insufficient evidence that HTPs are less harmful than CCs, consuming HTPs exclusively or concurrently may not reduce harm. Our results suggest that CC users who want to reduce harm should quit all tobacco use rather than switching to HTPs or using them concurrently.

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Patient consent for publication Not applicable.

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Supplementary Table 1. Carbon monoxide levels according to different types of tobacco products used on site just before the interview.

	Total	CC	HTP	EC	*P*-value
Exhaled carbon monoxide levels (ppm)					
Type of on-site tobacco use (n)[a]	675	525	108	42	
Median (25th, 75th centiles)	14.0 (6.0, 22.0)	17.0 (11.0, 25.0)[a]	4.0 (2.5, 5.0)[b]	3.0 (2.0, 4.0)[b]	<0.001

CC: conventional cigarette; HTP: heated tobacco product; EC: electronic cigarette.

P-value was based on Kruskal-Wallis test; Medians denoted by a letter (a, b) in common are not significantly different, while medians not denoted by a letter in common are significantly different by the Dunn's test at the 5% level of significance.

[a] The type of tobacco products used on site at the hotspots were recorded since a few months into the survey.

Supplementary Table 2. Carbon monoxide and saliva cotinine levels in tobacco users who did not use products other than CCs, HTPs or ECs in the past 30 days.

	Total	CC only	HTP only	EC only	CC+HTP	CC+EC	HTP+EC	Triple	*P*-value
Exhaled carbon monoxide levels (ppm)									
Sample size (n)	639	419	64	13	82	35	6	20	
Median (25th, 75th centiles)	14.0 (6.0, 23.0)	18.0 (12.0, 26.0)[a]	3.0 (2.0, 5.0)[b]	2.0 (1.5, 3.0)[bc]	5.5 (3.0, 15.0)[cd]	12.0 (7.0, 20.0)[d]	4.5 (2.5, 5.8)[bcd]	11.0 (3.0, 22.8)[ad]	<0.001
Saliva cotinine level									
Sample size (n)	537	384	39	7	60	33	4	10	
Median (25th, 75th centiles)	3.0 (2.0, 4.0)	3.0 (3.0, 4.0)	3.0 (2.0, 4.0)	4.0 (3.0, 4.0)	4.0 (2.0, 4.0)	3.0 (2.0, 4.0)	4.0 (1.8, 4.8)	3.0 (2.0, 4.0)	0.90

CC: conventional cigarette; HTP: heated tobacco product; EC: electronic cigarette.

P-value was based on Kruskal-Wallis test; Medians denoted by a letter (a, b) in common are not significantly different, while medians not denoted by a letter in common are significantly different by the Dunn's test at the 5% level of significance.

Supplementary Table 3. Characteristics of tobacco users across three analytic samples.

	Total **n (%)**		**Samples with CO test** **n (%)**		**Samples with saliva cotinine test** **n (%)**
N	3294 (100.0)		780 (23.7)		620 (18.8)
Sex					
Male	2415 (73.3)		551 (70.6)		415 (66.9)
Female	879 (26.7)		229 (29.4)		205 (33.1)
Age, years					
15-29	695 (21.1)		229 (29.4)		167 (26.9)
30-39	952 (28.9)		298 (38.2)		204 (32.9)
40-49	810 (24.6)		168 (21.5)		153 (24.7)
50 or more	837 (25.4)		85 (10.9)		96 (15.5)
Education					
Secondary or below	1952 (59.3)		322 (41.3)		306 (49.4)
Tertiary	1342 (40.7)		458 (58.7)		314 (50.6)
Marital status					
Single	1260 (38.3)		414 (53.1)		290 (46.8)
Married	1793 (54.4)		330 (42.3)		284 (45.8)
Divorced/widowed	241 (7.3)		36 (4.6)		46 (7.4)
Household income (HK$)					
<20,000	580 (18.6)		72 (9.6)		93 (15.5)
20,000-39,999	1190 (38.1)		257 (34.3)		211 (35.1)
>=40,000	1350 (43.3)		421 (56.1)		297 (49.4)

CO: carbon monoxide; US$1=HK$7.8.